# BIOMEDICINSKA ISTRAŽIVANJA

Časopis Medicinskog fakulteta Foča,
Univerzitet u Istočnom Sarajevu

**Godište 14, broj 1, jun 2023.**

Journal of the Faculty of Medicine Foča,
University of East Sarajevo

**Volume 14, No 1, June 2023**

# BIOMEDICINSKA ISTRAŽIVANJA

Časopis
Medicinskog fakulteta Foča,
Univerzitet u Istočnom Sarajevu

ISSN 1986-8529 (Print)
ISSN 1986-8537 (Online)
UDK 57+61

**Izdavač**
Medicinski fakultet Foča
Univerzitet u Istočnom Sarajevu
Studentska 5,
73 300 Foča

**Za izdavača**
Prof. dr Dejan Bokonjić, dekan

**Adresa uredništva**
Medicinski fakultet Foča
Studentska 5,
73 300 Foča
Telefon: 058/210-420
Fax: 058/210-007
E-mail: biomedicinskaistrazivanja@yahoo.com

Članci su u cjelosti dostupni na interent stranici:
http://biomedicinskaistrazivanja.mef.ues.rs.ba

**Prelom teksta i priprema za štampu**
Vedrana Krsmanović

**Štamparija**
„Kopikomerc", Istočno Sarajevo

**Tiraž**
300 primjeraka

Časopis "Biomedicinska istraživanja" je indeksiran u Directory of Open Access Journals, Google Scholar, Directory of Research Journal Indexing, CrossRef, DOI Srpska.

Ustanove članova Izdavačkog saveta i Uređivačkog odbora navedene su u online izdanju časopisa.

**BIOMEDICINSKA ISTRAŽIVANJA**

Journal of the Faculty of Medicine Foča, University of East Sarajevo

ISSN 1986-8529 (Print)
ISSN 1986-8537 (Online)
UDC 57+61

**Published by**
Faculty of Medicine Foča University of East Sarajevo Studentska 5, 73 300 Foča

**On behalf of the publisher**
Prof. Dejan Bokonjić, MD, PhD, Dean

**Editorial office**
Medicinski fakultet Foča
Studentska 5,
73 300 Foča
Telephone: 058/210-420
Fax: 058/210-007
E-mail:
biomedicinskaistrazivanja@yahoo.com

All articles are available on the following website:
http://biomedicinskaistrazivanja.mef.ues.rs.ba

**Text capture and processing**
Vedrana Krsmanović

**Print**
„Kopikomerc", Istočno Sarajevo

**Printing**
300 copies

The journal "Biomedicinska istraživanja" is indexed in Directory of Open Access Journals, Google Scholar, Directory of Research Journal Indexing, CrossRef, DOI Srpska.

The affiliations of the members of the Publishing Council and the Editorial Board are listed in the online edition of the journal.

# Sadržaj

## ORIGINALNI RADOVI



## PRIKAZ BOLESNIKA



## PREGLEDNI RADOVI

# Contents

## ORIGINAL ARTICLES



## CASE REPORT



## REVIEW

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):1–12

UDK: 004.738.5:[616.98COVID-19]-053.2
DOI: 10.59137/BII202301304V

*Original article*

# Screen time in children and adolescents during the COVID-19 pandemic

**Bojana Vuković,**
**Sanja Živanović,**
**Bojana Mastilo,**
**Ivana Zečević**

University of East Sarajevo,
Faculty of Medicine Foca,
Republic of Srpska,
Bosnia and Herzegovina

Primljen – Received: 15/02/2023
Prihvaćen – Accepted: 20/03/2023

**Corresponding author:**
*Bojana Vuković, MD*
*Nemanjina 1, 73300 Foča*
*bvukovic75@gmail.comm*



**Summary**

**Introduction**. With the beginning of the pandemic caused by the COVID-19 virus, restrictions on movement, the so-called "lockdown" were applied by many governments. As a result of these actions taken against the transmission of the COVID-19 virus, the use of digital devices has increased, i.e. the time spent in front of screens has increased.

**Methods**. This paper dealt with a bibliometric analysis of scientific publications on the topic of screen time in children and adolescents during the COVID-19 pandemic. The Dimensions database was chosen as the data source. No time frame is given, but given the topic, publications from 2020-2023 are included in the analysis. The data were analyzed in the VOSviewer program, specified for bibliometric and visual data analysis.

**Results**. Map of word co-occurrence show that there are three different clusters. In the red cluster, consisting of 53 terms, the most frequent terms are sleep (124), lifestyle (103) and restriction (83), while in the green cluster, consisting of 41 terms, family (126), education (88), relationship (86) are the most represented. The blue cluster consists of significantly fewer terms, 12 of them, of which anxiety (91), symptom (81), depression (58) are the most represented.

**Conclusion**. Based on the bibliometric analysis, we can conclude that the scientists were mostly concerned with the impact of the screen time phenomenon on the physical health of children and adolescents. In addition, screen time has been linked to mental health, education and socio-emotional relationships.

**Keywords**: COVID-19, screen time, children, adolescents

## Introduction

Since the initial outbreak in China in December 2019, the COVID-19 has spread around the world and on March 11, 2020, the World Health Organization declared the Covid-19 virus a global pandemic. So far, 760,360,956 cases of the disease have been confirmed, of which 6,873,477 cases have resulted in death [1]. However, even though death is the worst consequence of the pandemic, three years after the declaration of the pandemic, the world is also facing other consequences, including those caused by lifestyle changes. After the World Health Organization (WHO) declared a pandemic, governments took different measures to manage

the risk associated with COVID-19, including the closure of educational and cultural institutions, sports facilities and other public places [2]. Since the beginning of the pandemic caused by COVID-19, more than 100 countries have taken measures of isolation or social distancing (known as "lockdown"), all with the aim of reducing the rate of virus transmission. More precisely, with the pandemic restrictions, bans and orders to stay at home came, which were the cause of excessive use of screens among children and adolescents [3]. Thus, while physical distance was the key to reducing virus transmission, prolonged physical constraint reduced opportunities for outdoor activities [4] and increased anxiety and depression [5]. As a result of these actions taken against the transmission of the COVID-19 virus, the use of digital devices, i.e. the time spent in front of screens (screen time) has increased worldwide. The results of a comprehensive study examining changes in the length of screen time during the pandemic speak in favor of this. Namely, a review of 31 studies with data from over 20 countries found an increase in screen time among adolescents during the pandemic compared to the period before the pandemic [6]. These increases ranged from 55 min per day to 2.9 h per day [7]. Screen time refers to the amount of time spent and various activities performed online through digital devices [8]. For example, screen time includes the use of digital devices for work purposes (or educational purposes) as well as for leisure and entertainment. Kanekar and Sharma found that during the COVID-19 pandemic, digital platforms were the only way for people to maintain socioeconomic ties [9]. However, at the same time, prolonged time on the screen has caused various concerns related to its negative impact on the physical and mental health of the individual [10]. Several authors have confirmed that regulated use of digital devices is associated with well-being, excessive use is associated with a whole range of mental problems [11, 12]. Also, some authors believe that excessive use of screens is associated with risks for cardiovascular diseases, such as obesity, high blood pressure and insulin resistance because sedentary behavior is increased, which is associated with "snacking" [3]. Sedentary behavior is defined as any awake behavior characterized by an energy expenditure of ≤1.5 metabolic equivalents (MET) while in a sitting, semi-recumbent, or supine position [13]. Although excessive screen use is associated with potential health risks, including poor sleep and more sedentary time [14], given laws and policies during the pandemic, increased screen time may be inevitable and may even be beneficial for education and socialization [3]. As previously mentioned, sedentary behavior and snacking are usually associated with screen time, although screen time does not have to be sedentary. While in one place, screen time can be used to promote physical activity [15] on various platforms such as online physical activity classes, mobile exercise apps, or video games that have physical activity components [16]. Children and adolescents could also use virtual games and online activities to maintain social connection during the COVID-19 pandemic. Also, during this period social media was used as a platform to play and connect with friends and family. This was some kind of way to maintain social contact. During school closures, many schools as well as universities were forced to switch to virtual or online curricula, which require students to use the screen. Although prolonged screen time may have educational benefits, it may also exacerbate the risk of depression, anxiety, suicide, and attention deficits in children and adolescents [14]. However, during the COVID-19 pandemic, many educational resources and mental health support services were available through online platforms that required the use of screen time [17]. Furthermore, mental health practices offered counseling and therapy sessions exclusively via telehealth, which involved screen time [18]. The

first reports from China, i.e. regions affected by the pandemic, indicate that media entertainment was the most popular tool used by parents to deal with their children's problems and mitigate the consequences [19]. Moreover, it was a striking finding that a record number of people, from all age categories, turned to online video games [20]. When implemented as a coping strategy in the midst of the COVID-19 pandemic, screen time may be associated with certain negative risks, both among children and adolescents. Considering the change in lifestyle reflected in the excessive use of screens, which was imposed during this global problem that we faced, the aim of our work was to examine the trend in the scientific literature dealing with the phenomenon of screen time during the pandemic caused by COVID-19. As we have already mentioned, scientists immediately recognized some advantages and disadvantages of screen use during COVID-19, however some consequences are also long-term, which we as a society are yet to face. Therefore, we believe it is useful to identify topics that researchers have associated with screen time during the COVID-19 pandemic. The main goal of this research is to determine the most relevant sources, countries and research areas, as well as to create a map of keywords in the field of screen time among children and adolescents during COVID-19.

## Methods

This paper deals with the bibliometric analysis of scientific publications on the topic of screen time in children and adolescents during the COVID-19 pandemic. PRISMA protocol was applied for dataset extraction (Figure 1). The Dimensions database is chosen as the data source. No time frame is given, but given the topic, publications from 2020-2023 are included in the analysis. The data have been analyzed in the VOSviewer program, which is intended for bibliometric and visual data analysis.

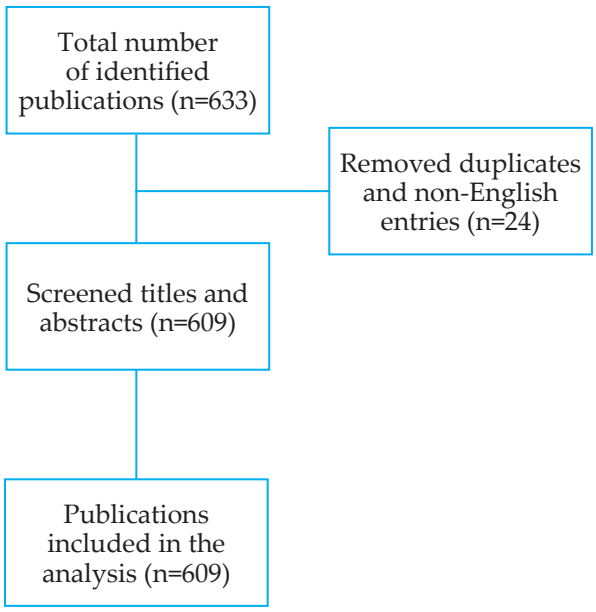


**Figure 1.** Flowchart according to PRISMA

Bibliometric and visual analyses was used to map the scientific literature in the researched area. The Dimensions database was used for the search. After many attempts to search for different combinations of words, the final search strategy according to the Boolean algorithm included the following: (covid-19 OR Coronavirus) AND ("screen time" OR "digital screen time") AND (children OR adolescent). Raw data was extracted from the Dimensions database in CSV format. The CSV file was processed in the VOSviewer program, in order to determine the national cooperation network, the co-citation network of authors, countries and the network of repeating words. Journal citation reports (JCR) Science Edition 2020 were used to determine the journal's impact factor (IF), JCR, and SCImago journal rank (SJR). The search was conducted in March 2023 and a total of 609 scientific publications were found. Scientific publications with keywords in the title or abstract in all research categories are included. The research included all citation databases, all types of publications and all research categories.

## Results

Figure 2 shows the evolution of scientific production on the topic of screen time among children and adolescents during the COVID-19 pandemic. Our search included 609 articles, of which there were the total of 523 scientific articles, 67 preprint versions, 11 chapters and 8 proceedings with the total of 11000 citations and 16.75 citations per document. In 2021, scientific production on this topic had a peak (267 publications), which made up almost half of the scientific literature (43.84%) with a number of 4000 citations. The number of scientific publications in the year 2022 was 235, however with much fewer citations, in total 790.

Figure 3 shows which research categories according to the Australian and New Zealand Standard Research Classification (ANZSRC, 2000) have the most scientific publications on the researched topic. The five most represented research categories are biomedical and clinical sciences, health sciences, psychology, education and human society. It is important to note that one document appears in several research categories.

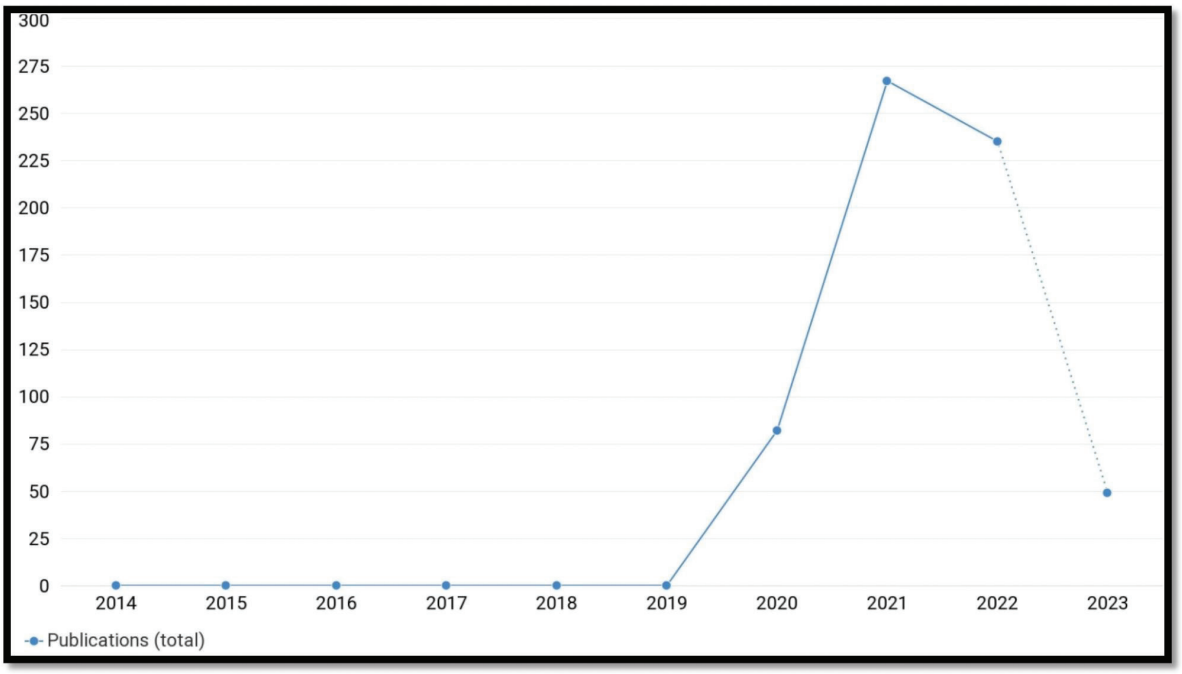


**Figure 2.** Evolution of scientific production

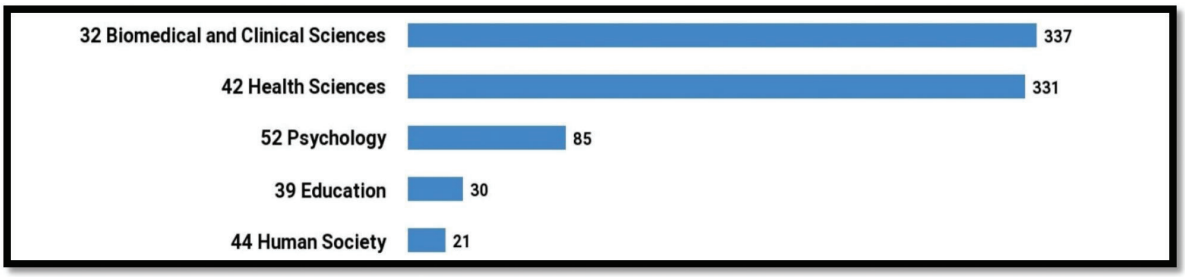


**Figure 3.** The most represented research categories

**Table 1.** The most prominent journals

| Journals | n | IF | SJR | JCR |
|---|---|---|---|---|
| International journal of environmental research and public health | 41 | 4.61 | 0.81 | Q1 |
| Children | 13 | 2.83 | 0.65 | Q2 |
| Nutrients | 11 | 5.71 | 1.29 | Q1 |
| Frontiers in psychiatry | 11 | 5.43 | 1.28 | Q1 |

Table 1 shows the most prominent journals with criteria (obtained by the criterion: minimum 10 documents per journal and minimum 10 citations), in which articles dealing with screen time in children and adolescents during the COVID-19 pandemic were published. The JCR database was searched for impact factors and quartiles. Three of the four top journals are in JCR Q1, which indicates the high quality of the articles they publish in these journals.

In order to determine the potential partnership between the journals, a co-citation analysis was conducted. It is the method used to determine the similarity between two documents. Two articles are said to be co-cited when they both appear in the reference list of a third document. If documents A and B are cited in paper C, they can be said to be related, even though they are not directly cited. If articles A and B are both cited in many other articles, they have a stronger connection. The more articles citing them together, the stronger their connection. Co-citation frequency is defined as the frequency with which two articles are cited together. The minimum number of citations was set to 100, which resulted in the inclusion of 29 articles. The journal co-citation map shown in figure 4 gives us an overview of the structure of the scientific world. Journal clusters can be identified on the map. Clusters that are closer to each other on the map indicate a close connection, and three large clusters can be seen in figure 4. Interpretation of the map is quite simple. The map contains a green, red and blue cluster. Each node represents a magazine and the larger the nodes and the thicker the connection lines, the stronger the collaboration. Thus, we see that the most prominent node in the green cluster is the journal *Pediatrics* with a total of 398 citations, which means that other journals from the green cluster are most often cited together with this journal. In the red cluster, the most prominent node is the journal *International journal of environmental research and public health* with 635 citations, which means that this journal is the most cited journal with the others in the green cluster (most often with journals which nodes are more prominent, see figure 4). The blue cluster consists of one journal, *The Journal of the American Medical Association-JAMA*, which is not particularly related to the journals in the green and red clusters.

Table 2 shows the three most cited scientific articles from the total unit of analysis consisting of a total of 609 articles. All three

**Table 2.** The most cited articles

| | |
|---|---|
| Pietrobelli A, Pecoraro L, Ferruzzi A, Heo M, Faith M, Zoller T, et al. Effects of COVID-19 lockdown on lifestyle behaviors in children with obesity living in Verona, Italy: a longitudinal study. Obesity 2020;28(8):1382–5. | 683 |
| Moore SA, Faulkner G, Rhodes RE, Brussoni M, Chulak-Bozzer T, Ferguson LJ, et al. Impact of the COVID-19 virus outbreak on movement and play behaviours of Canadian children and youth: a national survey. Int J Behav Nutr Phys Act 2020;17(1):85. | 600 |
| Xiang M, Zhang Z, Kuwahara K. Impact of COVID-19 pandemic on children and adolescents' lifestyle behavior larger than expected. Prog Cardiovasc Dis 2020;63(4):531–2. | 473 |

articles were published in 2020. The most cited article is by Pietrobelli et al. published in the journal Obesity. The second most cited article is by Moore and colleagues from 2020, which was published in the International journal of behavioral nutrition and physical activity. Xiang et al. was published in Progress in cardiovascular diseases with a total of 473 citations and is the third most cited.

The analysis of the most influential authors included the analysis of the most productive authors. The most productive authors are shown in the table with the number of publications and citations. Australia's Anthony Okely from the University of Wollongong is the most prolific author with a total of 239 citations in the field and an H-index of 87. The H-index is an author-level metric that measures both the productivity and citation impact of publications. Other authors have fewer publications, but they are cited almost three times more (Table 3).

**Table 3.** The most productive authors

| Authors | N | Citations |
|---|---|---|
| Okely, Anthony | 13 | 239 |
| Faulkner, Guy | 9 | 857 |
| Tremplay, Mark S | 7 | 876 |
| Moore, Sarah A. | 6 | 842 |

Figure 5 shows the bibliographic coupling map of the countries (according to criteria: minimum five documents per country and minimum 100 citations). The map shows two larger (green and red) and two smaller clusters (blue and yellow). The most prominent node in the red cluster is the USA, which means that articles from the USA are most often found in the bibliographies of articles from other countries from the red cluster (UK, Brazil, India, Italy, Portugal etc.). In the

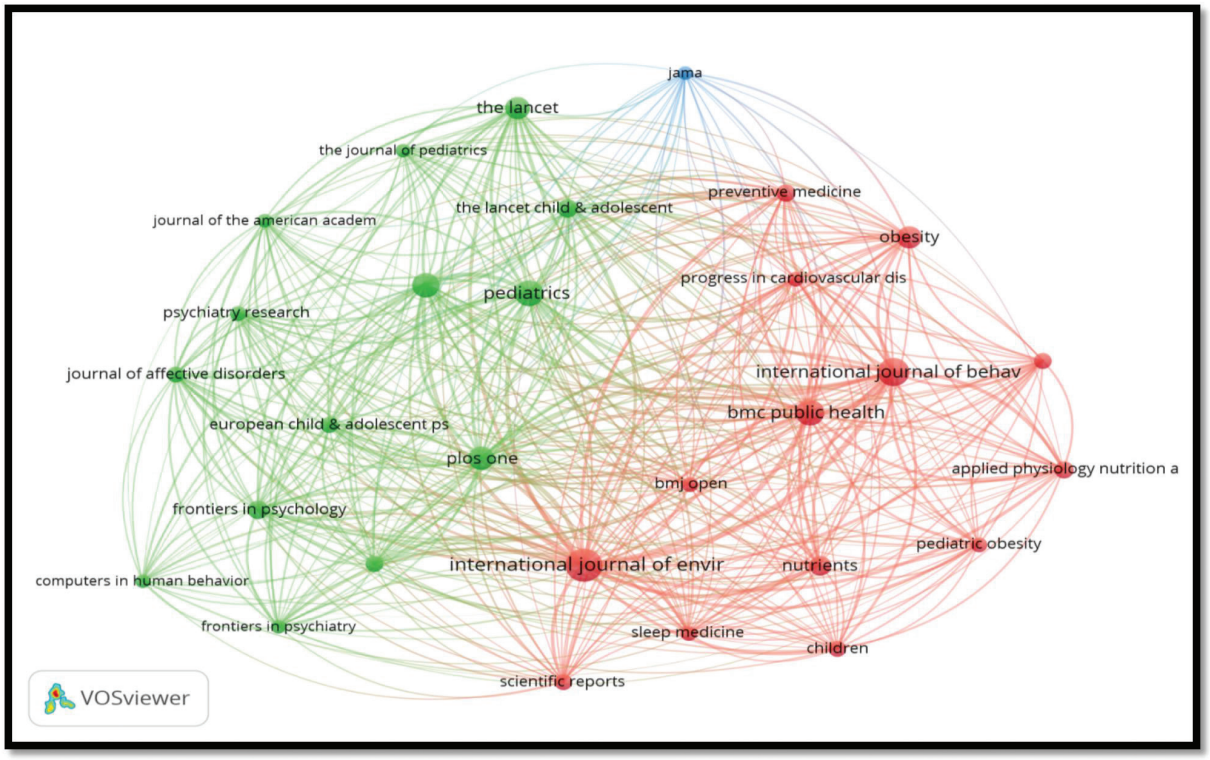


**Figure 4.** Journal co-citation map

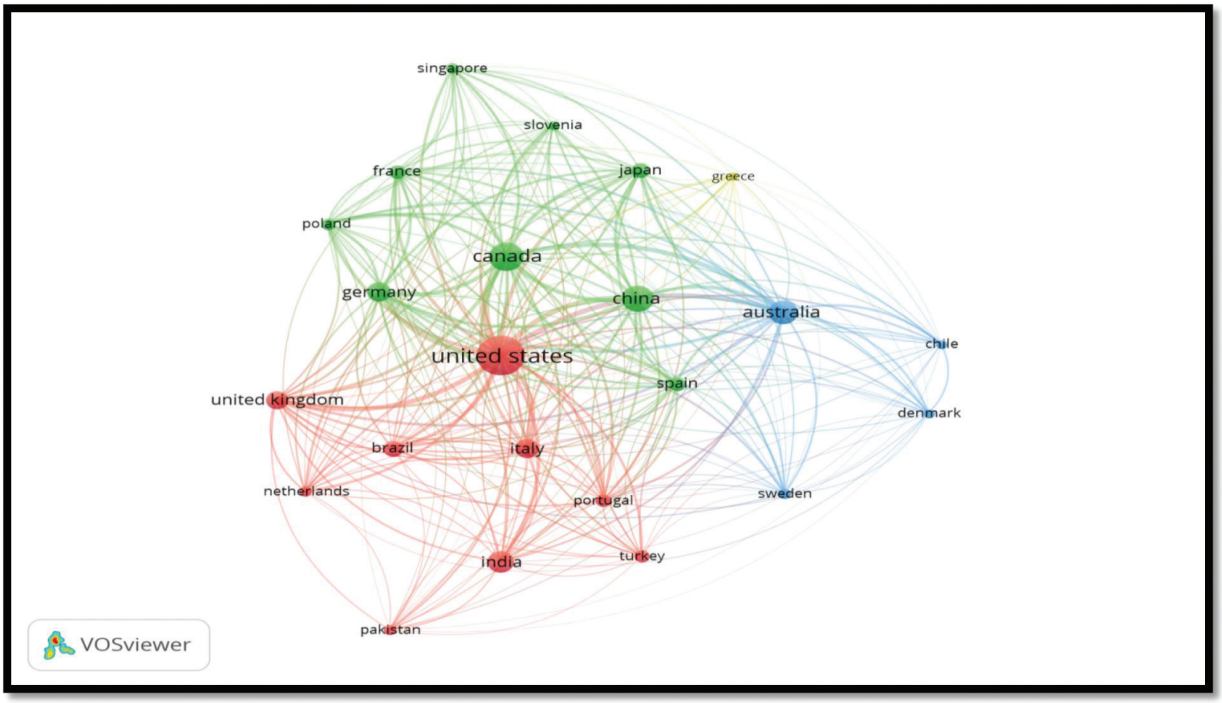


**Figure 5.** Bibliographic coupling of countries

green cluster, the most prominent nodes are those representing Canada and China, which means that bibliographies of articles from other countries most often cite articles created in these countries (Canada and China). The blue cluster is small and includes four countries Australia, Denmark, Chile and Sweden. The yellow cluster consists only of Greece.

In order to examine current topics covered by scientific publications in the field of screen time in children and adolescents during the COVID-19 pandemic, a map was created based on textual data, i.e. by extracting words from titles and abstracts from a total of 609 scientific publications. Out of a total of 14353 terms, 478 of them were singled out according to the minimum repetition criterion of 20 times. For each of the 212 terms, the program calculated a relevant score based on which the most relevant terms were selected. The default was to select 60% (127) of relevant terms. In figure 6 we see three clusters, red, blue and green. In the red cluster, which consisted of 53 terms, the most frequent terms are sleep (124), lifestyle (103) and restriction (83), while in the green cluster, which consisted of 41 terms, family (126), education (88), relationship (86) were the most represented. The blue cluster consisted of significantly fewer terms, 12 of them, of which anxiety (91), symptom (81), depression (58) were the most represented. By looking at the map, we can see more detailed terms that most often appear together. The larger the nodes the word is repeated more often. Nodes of the same color represent words appearing together most often.

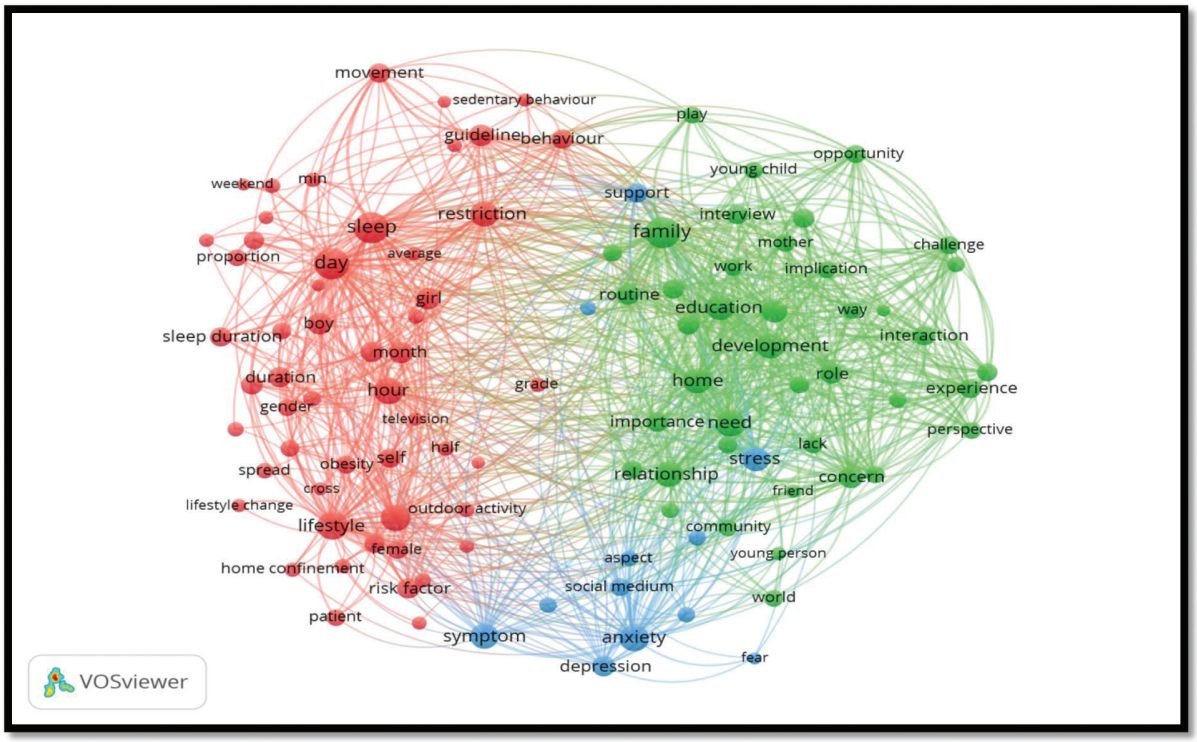


**Figure 6.** Map of word co-occurrence

## Discussion

The main goal of this research was to determine the most relevant sources, countries and research areas, as well as to create the map of key words in the field of screen time among children and adolescents during the pandemic caused by the COVID-19 virus. The phenomenon of "screen time" was the subject of interest to the scientific public even before the pandemic. However, most of the existing studies on screen time were cross-sectional studies and examined screen time among different cohorts of people before and during the pandemic. The few prospective studies to date have been limited to the early phase of the pandemic. Given Hedderson's results that excessive screen use was present, even after many health warnings, it remained unclear what happened during the pandemic and what the impact of screen time was on children and adolescents, as well as what connections the researchers made with screen time during and in the post-covid period [21]. A search of the Dimensions database found a total of 609 scientific publications in the period from 2020-2023, where the most publications were during 2021-2022. Considering the large number of scientific works dealing with this topic in the past three years, we conclude that this topic was recognized by scientific authorities as a current field that requires answers to many questions. By reviewing the research categories dealing with this topic, we see that the majority of publications were created within two research categories: biomedical and clinical sciences, and health sciences. Bearing in mind these results of the bibliometric analysis, we must conclude that science in this period was mostly concerned

with the relationship between screen time and health during COVID-19. One of the best-researched connections between screen time in young people is the connection between the length of screen time and physical activity [22]. Indeed, many studies conducted before the pandemic showed support for the view that excessive screen time led to less physical activity in children and adolescents [14, 23]. Bearing in mind the fact that screen time during COVID-19 is a global phenomenon that the world was faced with and still is facing, it is not surprising that the most prominent journal dealing with this topic is the International journal of environmental research and public health. It covers environmental sciences and engineering, public health, environmental health, occupational hygiene, economic health and global health research. The journal has a high impact factor in JCR Q1 as well, which indicates the high quality of the articles published in this journal.

The most cited article on this topic is Pietrobelli et al. 2020, which dealt with the effects of the pandemic lockdown on the lifestyle of children and adolescents with obesity in Verona. The authors found that screen time increased by 4.85h/day in this examined population during that period [24]. The most productive author exploring this topic is Anthony Okely from the University of Wollongong whose research areas are physical health, sedentary behavior and children's health. Other authors with the largest number of articles are from Canada. It may be surprising that there are no authors from China in the list of the most productive who have dealt with this topic. The analysis of the bibliographic coupling of the countries showed four clusters in which the most prominent nodes were the USA, Australia, and Canada. The term bibliographic coupling refers to a similar linkage as in co-citations only in reverse order. A bibliographic link is considered when two articles refer to the common third article in their bibliographies. The strength of bibliographic coupling increases with the increase in the number of common references. In this case, it means that in the bibliographies of articles from other countries, articles from these three mentioned countries were most often found. Given that these countries adopted the "zero community transmission" model by introducing serious restrictions in terms of movement bans, questions arose about the possible negative effect of excessive screen time that occurred as a consequence of the aforementioned restrictions. Scientists sought to answer questions that arose about the potential negative impact of screen time during COVID-19 on children and adolescents. By creating the map of repeating words, we got three clusters, which means that the words within one cluster most often appear together. In the red cluster we have the words: day, sleep, movement, restriction, outdoor activity, lifestyle, obesity, risk factor, so we conclude that scientists looked at the impact of screen time on the physical health of children and adolescents during COVID-19 pandemics. This cluster is also the largest, which means that this, as previously mentioned, is one of the best-researched connections [22]. In the blue cluster, the most frequently repeated words are: symptom, anxiety, depression, fear, support, stress. Considering the words in this cluster, we can conclude that the subject of interest of the scientific public was also the mental health of children and adolescents. Considering the size of the cluster, this topic is the least researched. The green cluster is also large and the most common words in this cluster are those related to education, family, need, relationship. By reviewing the most frequently recurring key terms in this cluster, we assume that this researched part refers to education and socio-emotional relationships of children and adolescents during COVID-19. Other studies have shown that physical health, sleep and socio-emotional well-being are most often linked to screen time [25].

## Conclusion

Despite the mitigating of restrictions in terms of movement, the average screen time in the third quarter of 2021 was still more present than in the third quarter of 2020 by 1.0% [26]. While the debate over whether screen time is always harmful remains, many studies suggest that increased screen time is often positively correlated with other behaviors that are detrimental to overall well-being [27]. Even now, three years after the declaration of the pandemic, the world is facing long-term consequences for the well-being of children and adolescents. Undoubtedly, this topic preoccupied researchers during the pandemic, and it definitely opened up some new questions about the long-term consequences of screen time that still need to be explored. This research can be a good starting point for future researchers as a cross-section of the state of scientific literature in this area.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** This article does not contain any studies with human participants performed by any of the authors.

**Conflicts of interest.** The authors declare no conflict of interest.

### References:

1. World Health Organization. WHO Coronovirus Disease (COVID19) Dashboard. Accessed March, 2023. https://covid19.who.int
2. Ozturk Eyimaya A, Yalçin Irmak A. Relationship Between Parenting Practices and Children's Screen Time During the COVID-19 Pandemic in Turkey. J Pediatr Nurs 2021;56:24–9.
3. Nagata JM, Magid HS, Gabriel KP. Screen time for children and adolescents during the coronavirus disease 2019 pandemic. Obesity (Silver Spring) 2020;28(9):1582–3.
4. Chen P, Mao L, Nassis GP, Harmer P, Ainsworth BE, Li F. Coronavirus disease (COVID-19): The need to maintain regular physical activity while taking precautions. J Sport Health Sci 2020;9(2):103–4.
5. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020;395(10227):912–20.
6. Kharel M, Sakamoto JL, Carandang RR, Ulambayar S, Shibanuma A, Yarotskaya E, et al. Impact of COVID-19 Pandemic Lockdown on Movement Behaviours of Children and Adolescents: A Systematic Review. BMJ Glob Health 2022;7(1):e007190.
7. Lua VYQ, Chua TBK, Chia MYH. A Narrative Review of Screen Time and Wellbeing among Adolescents before and during the COVID-19 Pandemic: Implications for the Future. Sports (Basel) 2023;11(2):38.
8. Data Reportal. Digital: 2023 Global Digital Overview [Internet]. Accessed March, 2023. https://datareportal.com/reports/digital-2023-global-overview-report
9. Kanekar A, Sharma M. COVID-19 and Mental Well-Being: Guidance on the Application of Behavioral and Positive Well-Being Strategies. Healthcare (Basel) 2020;8(3):336.
10. Pandya A, Lodha P. Social connectedness, excessive screen time during COVID-19 and mental health: a review of current evidence. Front Hum Dyn 2021;3:684137.

11. Allen MS, Walter EE, Swann C. Sedentary behaviour and risk of anxiety: A systematic review and meta-analysis. J Affect Disord 2019;242:5–13.

12. Rahman MA, Hoque N, Alif SM, Salehin M, Islam SMS, Banik B, et al. Factors associated with psychological distress, fear and coping strategies during the COVID-19 pandemic in Australia. Global Health 2020;16(1):95.

13. Sedentary behavior Network. Accessed February, 2023. https://www.sedentarybehaviour.org/what-is-sedentary-behaviour/

14. Lissak G. Adverse physiological and psychological effects of screen time on children and adolescents: literature review and case study. Environ Res 2018;164:149–57.

15. World Health Organization. Stay physically active during self-quarantine. Published 2020. Accessed February, 2023. http://www.euro.who.int/en/health-topics/healthemergencies/coronavirus-covid-19/novel-coronavirus-2019-ncov-technical-guidance/ stay-physically-active-during-self-quarantine

16. Rose T, Barker M, Maria Jacob C, Morrison L, Lawrence W, Strömmer S, et al. A systematic review of digital interventions for improving the diet and physical activity behaviors of adolescents. J Adolesc Health 2017;61(6):669–77.

17. Liu S, Yang L, Zhang C, Xiang YT, Liu Z, Hu S, et al. Online mental health services in China during the COVID-19 outbreak. Lancet Psychiatry 2020;7(4):e17–e18.

18. Nagata JM. Rapid Scale-Up of Telehealth During the COVID-19 Pandemic and Implications for Subspecialty Care in Rural Areas. J Rural Health 2021;37(1):145.

19. Jiao WY, Wang LN, Liu J, Fang SF, Jiao FY, Pettoello-Mantovani M, et al. Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic. J Pediatr 2020;221:264–266.e1.

20. Wilde T. Online gaming surge: steam breaks concurrent user record amid socail distancing mandates. Accessed March, 202. https://www.geekwire.com/2020/online-gaming-surge-steam-breaks-concurrent-user-record-amid-social-distancing-mandates/

21. Hedderson MM, Bekelman TA, Li M, Knapp EA, Palmore M, Dong Y, et al. Environmental Influences on Child Health Outcomes Program. Trends in Screen Time Use Among Children During the COVID-19 Pandemic, July 2019 Through August 2021. JAMA Netw Open 2023;6(2):e2256157.

22. Lua VYQ, Chua TBK, Chia MYH. A Narrative Review of Screen Time and Wellbeing among Adolescents before and during the COVID-19 Pandemic: Implications for the Future. Sports (Basel) 2023;11(2):38.

23. Stiglic N, Viner RM. Effects of screen time on the health and well-being of children and adolescents: a systematic review of reviews. BMJ Open 2019;9(1):e023191.

24. Pietrobelli A, Pecoraro L, Ferruzzi A, Heo M, Faith M, Zoller T, et al. Effects of COVID-19 lockdown on lifestyle behaviors in children with obesity living in Verona, Italy: a longitudinal study. Obesity (Silver Spring) 2020;28(8):1382–5.

25. Belton S, Issartel J, Behan S, Goss H, Peers C. The Differential Impact of Screen Time on Children's Wellbeing. Int J Environ Res Public Health 2021;18(17):9143.

26. Kemp, S. Digital 2022: Time Spent Using Connected Tech Continues to Rise; Data Reportal: 2022. Accessed February, 2023. https: //datareportal.com/reports/digital-2022-time-spent-with-connected-tech.

27. Fang K, Mu M, Liu K, He Y. Screen time and childhood overweight/obesity: A systematic review and meta-analysis. Child Care Health Dev 2019;45(5):744–53.

# "Screen time" kod djece i adolescenata tokom pandemije COVID-19

Bojana Vuković, Sanja Živanović, Bojana Mastilo, Ivana Zečević

Univerzitet u Istočnom Sarajevu, Medicinski fakultet Foča, Republika Srpska, Bosna i Hercegovina

**Uvod.** Sa početkom pandemije izazvane virusom COVID-19 na snagu su stupila ograničenja kretanja, tzv. "lockdown". Kao rezultat ovih preduzetih akcija protiv transmisije virusa COVID-19 porasla je upotreba digitalnih uređaja, odnosno produženo je vrijeme provedeno pred ekranima ("screen time").

**Metode.** Ovaj rad se bavio bibliometrijskom analizom naučnih publikacija na temu "screen time" kod djece i adolescenata tokom pandemije COVID-19. Kao izvor podataka birana je Dimensions baza podataka. Nije zadat vremenski okvir, ali s obzirom na temu, publikacije od 2020. do 2023. godine su uključene u analizu. Podaci su analizirani u program VOSviewer, koji je namijenjen bibliometrijskoj i vizuelnoj analizi podataka.

**Rezultati.** Mapa koincidencije riječi pokazuje da postoje tri različita klastera. U crvenom klasteru, koji se sastojao od 53 pojma, najčešći pojmovi su spavanje (sleep) (124), životni stil (lifestyle) (103) i ograničenje (restriction) (83), dok su u zelenom klasteru, koji se sastojao od 41 termina najzastupljeniji pojmovi porodica (family) (126), obrazovanje (education) (88) i odnosi (relationship) (86). Plavi klaster se sastojao od znatno manje pojmova, njih 12, od kojih su najzastupljeniji anksioznost (anxiety) (91), simptom (symptom) (81), depresija (depression) (58).

**Zaključak.** Na osnovu bibliometrijske analize možemo da utvrdimo da su se naučnici najviše bavili uticajem "screen time" fenomena na fizičko zdravlje djece i adolescenata. Pored toga, "screen time" je dovođen u vezu sa mentalnim zdravljem, edukacijom i socio-emocionalnim odnosima.

**Ključne riječi:** Covid-19, "screen time", djeca, adolescenti

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):13–20

UDK: 616.833-009.7-055.1
DOI: 10.59137/BII202301306S

*Original article*

# Idiopathic carpal tunnel syndrome in male patients

**Igor Sladojević[1], Tatjana Bućma[2], Ostoja Savić[3]**

[1]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina
[2]Institute for Physical Medicine and Rehabilitation "Dr Miroslav Zotović", Banja Luka, Republic of Srpska, Bosnia and Herzegovina
[3]University Clinical Center of Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Primljen – Received: 19/03/2023
Prihvaćen – Accepted: 15/05/2023

**Corresponding author:**
*Igor Sladojević, PhD*
*Save Mrkalja 14,*
*78000 Banja Luka*
*igor.sladojevic@med.unibl.org*



**Summary**

**Introduction**. The carpal tunnel syndrome (CTS) in male patients, due to anatomical characteristics and the perception of CTS-related symptoms, remains undetected for a long time. Men respond less well to CTS treatment, and early detection enables conservative treatment of mild and moderate CTS. The aim of this paper was to examine the average age, the frequency of bilateral CTS and its correlation with the age, and to determine the grade of electrophysiological damage of the median nerve in male patients with idiopathic CTS diagnosed by electromyoneurography.

**Methods**. The retrospective study included 83 male patients, aged from 32 to 81 years, with complaints of unilateral CTS on the right, dominant hand. All patients underwent EMNG for confirmation of CTS and the degree of median nerve damage. Statistical analysis was performed by methods of descriptive statistics, t-test, Wilcoxon signed rank test, and Pearson's correlation coefficient. The value of $p < 0.05$ was considered statistically significant.

**Results**. The average age of patients was 55.84 years. The bilateral CTS was confirmed in 88.4%, most often of a moderate degree and more pronounced on the right, dominant hand (p=0.001). In cases of bilateral CTS, age did not correlate with the grade of CTS changes in both hands. The changes in the dominant hand were more pronounced in patients older than 51 years.

**Conclusion**. Male patients with idiopathic CTS usually have bilateral CTS, with more pronounced changes on dominant hand. Bilaterality of CTS and the degree of median nerve damage are not connected with age.

**Keywords**: carpal tunnel syndrome, median nerve, men

## Introduction

Carpal tunnel syndrome (CTS) is the most common nerve entrapment syndrome. While other nerve entrapment syndromes are more frequent in older adults and men, CTS is more common in women [1, 2]. Women are more likely to experience carpal tunnel syndrome even though they have no comorbidities, because of a narrower wrist and tendon diameter similar to men's

[3], with greater differences between men and women at the outlet and the middle portions of the carpal tunnel and lesser differences at the inlet [4]. There are numerous risk factors for CTS among which are age, pregnancy (mostly during the third trimester), menopause, obesity, renal failure, diabetes mellitus, rheumatoid arthritis, hypothyroidism, exposure to vibration and activities that require forceful gripping and repetitive movements in the wrist [5, 6]. Also, there are some studies about possible genetic causes of CTS, but the results are not conclusive [7]. Since none of these factors is confirmed as primary, the etiology of CTS remains idiopathic [8].

The frequency of CTS differs from study to study- some report that CTS is four times higher in women, while others show a similar ratio between men and women [2, 9, 10]. Women may have a finer perception of CTS-related symptoms than men, who attend their first examination when the CTS symptoms become more severe [9]. A neurophysiological study by Padua et al found that men had more severe nerve impairment than women, although initially, men had complained of just minor discomfort and pain [9]. Possible explanation for this could be the loss of function of sensory nerve fibers. A study by Cirakli et al. found no statistically significant association between CTS and gender [11]. CTS appears to be more severe in the elderly [12] and occurs more frequently in the dominant hand [13]. Due to stronger hands, male patients show less impairment than females.

Bilateral CTS is more frequent than unilateral and there is a wide range of CTS frequency (between 22-87 %), but most studies cite a rate of about 60 % [9]. A study by Bagatur and Zorer suggests that CTS is a bilateral disorder and there is a correlation between the duration of symptoms and the bilateral occurrence of CTS [14]. The results of this study point out that patients with unilateral symptoms should be closely monitored due to the development of this median nerve mononeuropathy in asymptomatic hands. Also, mononeuropathy may start as a bilateral condition or begin as a unilateral condition and progress to bilateral neuropathy [15].

Many clinicians report that men with CTS respond less well to treatment [16]. In cases where a surgical treatment is needed, men have a worse post-surgical outcome than women [17]. Since the conservative treatment is still possible only in mild and moderate cases of CTS, the aim of our study was to analyze the average age, unilateral or bilateral presentation of CTS on the electromyoneurographic study, and grade of severity of symptoms in male patients with idiopathic CTS on their first examination in electromyoneurography cabinet.

## Methods

A total of 126 male patients were referred to the Cabinet for electromyoneurography of the Department for neurorehabilitation IIA, Institute for physical medicine and rehabilitation "Dr. Miroslav Zotović", Banja Luka, Bosnia and Herzegovina, in the period 2019–2021, to have their first electromyographical study due to complains on unilateral CTS. In all patients the right hand was dominant. The finding of electroneurography (ENG) was performed and interpreted in all patients on device Nicolet EDX (Natus Medical Inc.) by the same doctor. The diagnosis of CTS was based on the Clinical Diagnostic Criteria for CTS Research proposed by the American Association of Electro-Diagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation [19]. Inclusion criteria were: patients over 18 years of age, who underwent ENG on both hands and were diagnosed with idiopathic CTS. Excluding criteria were: the existence of a systemic disease of the peripheral nervous system, injury to the bone or soft tissue structures of the carpal tunnel area or

injury to the median nerve (which would be the basis of secondary CTS), C6-C8 cervical radiculopathy of brachial plexopathy, and any contraindication for ENG study.

The following data were used in this research: age, distal motor latency (DML) on both sides, and conduction velocity of sensory nerves on both sides. The obtained parameters were scored according to the Padua et al scale [19]:

1. Extreme CTS: absence of motor and sensory response (SNAP and CMP);
2. Severe CTS: absence of the sensory response (SNAP) – a segment of carpus-finger and abnormal DML;
3. Moderate CTS: slowing of digit-wrist conduction and abnormal DML;
4. Mild CTS: slowing of median digit-wrist conduction and normal DML;
5. Minimal CTS: standard negative hands with abnormal comparative or segmental (< 7–8 cm) tests;
6. Negative CTS: normal finding with all tests (including both comparative and segmental tests).

The software used for data processing was SPSS software (SPSS Inc), version 25, using methods of descriptive statistics, t-test, Wilcoxon signed rank test, and Pearson's correlation coefficient.

## Results

Out of 126 referred patients, 83 met the criteria for inclusion in the study. The average age of patients was 55.84 years (the youngest patient had 32, and the oldest was 81 years). Age distribution of patients showed the highest frequency in the age group 50–59 years (Figure 1).

Most patients (84.4 %) had bilateral CTS, and in 15.6 % of patients CTS was unilateral. There was no statistically significant difference in the age of patients with unilateral (M=53.15, SD=13.03) and bilateral CTS (M=56.06, SD=11.85; t(81)=-0.798, p=0.427). The magnitude of differences in the means (mean difference = -2.903, 95% CI -10.13 to 4.331) was very small (eta squared= 0.0078).

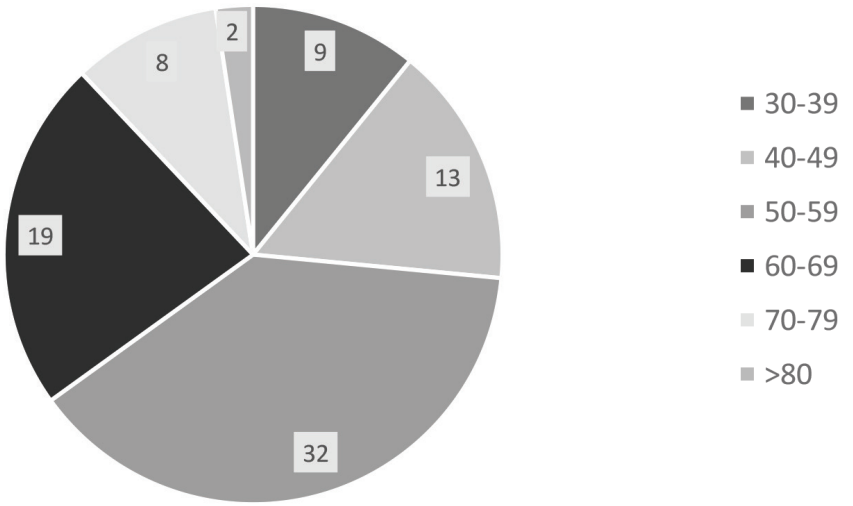


**Figure 1.** Age distribution of patients

The distribution of CTS grades in bilateral cases showed that, in both hands, changes had been most commonly moderate (grade 3) and rarely minimal (grade 5). In regard to the arm side, changes were more pronounced on the right hand (Figure 2).

In patients with bilateral CTS, Pearson's coefficient of correlation did not show significant correlations between CTS grade and age (right hand r=-0.211, p=0.055; left hand r=-0.096, p=0.389). Wilcoxon signed rank test showed a statistically significant difference between CTS grades on the left and right hand (Z= -3.416, p=0.001). Kruskal-Wallis test showed a statistically significant difference in the CTS grades in the right (dominant) hand among analyzed age groups of patients that had bilateral carpal tunnel (Group 1:30-39 years N=7, Group 1: 40-49 years N=9, Group 3: 50-59 N=28, Group 4: 60-69 years N=18, Group 5: 70 years and older N=8) $\chi 2$ (4, N=70)= 13.636, p=0.009). Post hoc test revealed that the cause of statistical difference was a comparisson between two groups: 51–60 years and older than 70, and 61–70 years and older than 70. On the left, non-dominant hand, the difference among age groups did not reach a statistical difference ($\chi 2$ (4, N=70)= 8.668, p=0.07).

## Discussion

CTS is a common disorder among women and people with known comorbidities. Damage to sensory fibers occurs first, as well as consequential sensory symptoms due to which patients report for examination. With time, the changes occur in motor fibers too, along with possible ascending degeneration of the nerve, causing irreversible changes in muscle structures. This all leads to hand dysfunctionality, a disorder of sensibility and proprioception, and with time weakness in muscle structures. Most studies describe such cases of CTS, while data on CTS among male patients are obscure. Also, studies on idiopathic CTS are very rare, especially those that describe bilateral CTS [15]. In this paper, we have analyzed only idiopathic male patients in our area. Authors worked on diagnosing this disease over many years and were concerned whether the patients in our area reported and were being sent to the diagnostic process in time, which influenced the timely treatment as well as the selection of treatment methods for this disease.

Idiopathic etiology of CTS in male patients has an incidence of 12.6% and 48.9% in female patients [20]. Although several studies

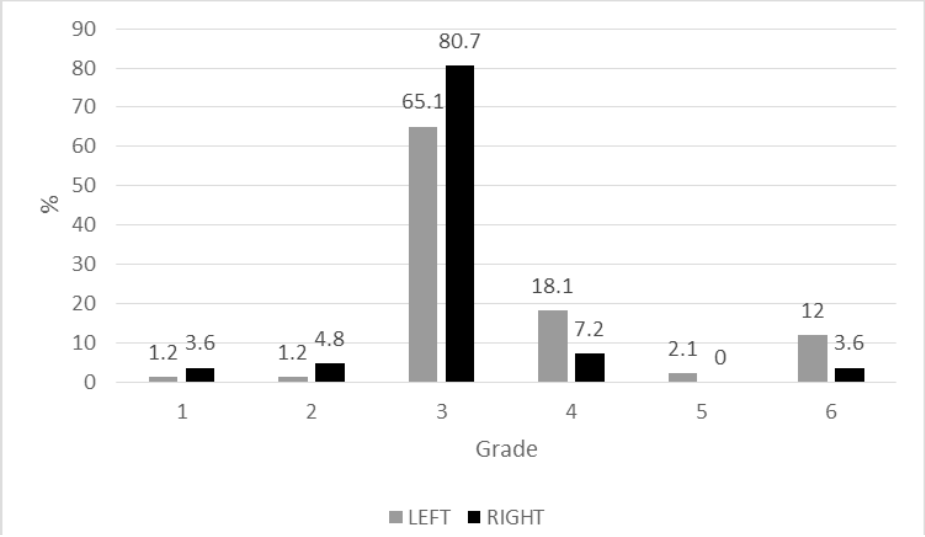


**Figure 2.** Distribution of CTS grades in bilateral cases in regard to arm side

show more prevalent CTS in female patients [10, 21], men have a greater tolerance to CTS symptoms than women and this could explain the difference in registered CTS prevalence [9].

In our sample, we have seen a peak incidence of CTS in the age group 50–59 years, while the lowest number of patients was in two age groups: 20–29 years and older than 80 years. Age distribution showed a gradually increasing incidence of CTS among male patients till the age of 59 and a gradual decrease in incidence after the age of 60. A South Korean study [22] also found the peak incidence in males aged 50–59 years, but in females the peak was at perimenopausal age- in the group 40–49 years. Bland and Rudolfer [12] report that the incidence is bimodal and has two peaks: at the age group 50–59, and over 80 years. We did not meet the second peak in this study, possibly because we had only two patients older than 80 years.

The patients report to the doctor after a shorter or longer presence of subjective difficulties, whereas the length of the presence of the difficulties does not necessarily have to be in line with the severity of the electrophysiological finding. It is a chronic insidious disease, which gives subjective difficulties when the motoric functional changes have already occurred. Most of our patients had a bilateral CTS and more severe symptoms in the dominant hand at first presentation in the electromyoneurography cabinet. Since mononeuropathies may start bilaterally or turn from unilateral to bilateral condition, electrophysiological studies tried to find if there was the asymmetry of nerve sensitivity thresholds between dominant and non-dominant hand [23], but the results did not find any difference in thresholds. Neurophysiological abnormalities tend to lateralize to the dominant hand [12], therefore symptoms begin on the dominant hand and are more severe due to the greater use of this hand [24]. The dominant hand is more affected in both unilateral and bilateral CTS [25], which was also noticed in our sample. Some studies report that CTS is more severe in idiopathic patients [26], which might explain such a high incidence of bilateral CTS in our sample (84.4%). Padua et al. studied patients with idiopathic CTS and found that 87% had bilateral neuropathy [19]. In a study by Lewanska [11] 74.3% of patients had bilateral idiopathic CTS. In our patients, the most common grade of changes on both the left and right sides was moderate. Cirakli et al also found that a moderate degree of median nerve compression was most frequent [11].

There was a statistically significant difference in electrophysiological findings on the median nerve in the carpal tunnel in different age groups on dominant, right hands in patients with bilateral CTS. Such a difference was not seen in the non-dominant left hand. This means that age, together with the more frequent use of the dominant hand, is a factor influencing the severity of changes on the median nerve and the consequential clinical presentation of CTS, but only on the dominant hand. It seems that there is a cumulative effect of repetitive movements in the wrist, which makes changes on tendons within the carpal tunnel. Such tendons can easily make compression to the median nerve and cause CTS.

The main limitations of this study were the absence of a control group and a small sample of patients older than 80 years.

## Conclusion

Although patients complain of unilateral symptoms, most develop bilateral CTS, with more pronounced changes on the dominant hand. The degree of median nerve damage in CTS, as well as the presence of bilateral symptoms, is not related to age. The patients most often report with a moderate degree of nerve damage, when there is still a possibility of conservative treatment.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** The Ethics Committee of the Department for Physical Medicine and Rehabilitation "Dr Miroslav Zotović", Banja Luka, Republic of Srpska, Bosnia and Herzegovina (No. 116-01-3108-2/22), approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

**Conflicts of interest.** The authors declare no conflict of interest.

## References:


7. Hanewinckel R, Ikram MA, Van Doorn PA. Peripheral neuropathies. Handb Clin Neurol 2016;138:263–82.
8. Mathew AE, John T. A Clinical and Neurophysiological Analysis of Idiopathic Carpal Tunnel Syndrome with Respect to Gender and Occupation. Ann Indian Acad Neurol 2021;24(6):865–72.
9. von Schroeder HP, Botte MJ. Carpal tunnel syndrome. Hand Clin 1996;12(4):643–55.
10. Rodríguez P, Casado A, Potau JM. Quantitative anatomical analysis of the carpal tunnel in women and men. Ann Anat 2022;243:151956.
11. Calandruccio JH, Thompson NG. Carpal Tunnel Syndrome Making Evidence-Based Treatment Decisions. Orthop Clin North Am 2018;49(2):223–9.
12. Duncan SFM, Bhate O, Mustaly H. Pathophysiology of carpal tunnel syndrome. In: Duncan S, Kakinoki R, editors. Carpal tunnel syndrome and related median neuropathies. Cham: Springer; 2017:13-29.
13. Żyluk A. The role of genetic factors in carpal tunnel syndrome etiology: A review. Adv Clin Exp Med 2020;29(5):623–28.
14. Uchiyama S, Itsubo T, Nakamura K, Kato H, Yasutomi T, Momose T. Current concepts of carpal tunnel syndrome: pathophysiology, treatment, and evaluation. J Orthop Sci 2010;15(1):1–13.
15. Padua L, Padua R, Aprile, Tonali P. Italian multicentre study of carpal tunnel syndrome. Differences in the clinical and neurophysiological features between male and female patients. J Hand Surg Br 1999;24(5):579–82.
16. Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosén I. Prevalence of carpal tunnel syndrome in a general population. JAMA 1999;282(2):153–8.
17. Cirakli A, Ulusoy EK, Ekinci Y. The role of electrophysiological examination in the diagnosis of carpal tunnel syndrome: Analysis of 2516 patients. Niger J Clin Pract 2018;21(6):731–4.
18. Bland JDP, Rudolfer SM. Clinical surveillance of carpal tunnel syndrome in two areas of the United Kingdom, 1991-2001. J Neurol Neurosurg Psychiatry 2003;74(12):1674–9.
19. Reinstein L. Hand dominance in carpal tunnel syndrome. Arch Phys Med Rehabil 1981;62(5):202–3.
20. Bagatur AE, Zorer G. The carpal tunnel syndrome is a bilateral disorder. J Bone Joint Surg Br 2001;83(5):655–8.
21. Lewańska M. The bilaterality of idiopathic carpal tunnel syndrome among manual workers.Int J Occup Med Environ Health 2020;33(2):151–61.
22. Watts AC, NcEachen J. Carpal tunnel syndrome in men. CurrOrthop 2006;20:294–8.
23. de Krom MC, Knipschild PG, Kester AD, Thijs CT, Boekkooi PF, Spaans F. Carpal tunnel syndrome: prevalence in the general population. J Clin Epidemiol 1992;45(4):373–6.
24. American Association of Electrodiagnostic Medicine, American Academy of Neurology, and American Academy of Physical Medicine and Rehabilitation. Practice parameter for electrodiagnostic studies in carpal tunnel syndrome: Summary statement. Muscle Nerve 2002;25(6):918–22.
25. Padua L, LoMonaco M, Gregori B, Valente EM, Padua R, Tonali P. Neurophysiological classification and sensitivity in 500 carpal tunnel syndrome hands. Acta Neurol Scand 1997;96(4):211–7.

26. Lee JK, Lee SH, Kim B, Jung K, Park I, Han SH. Risk Factors of Carpal Tunnel Syndrome for Male Patient Undergoing Carpal Tunnel Release. Handchir Mikrochir Plast Chir 2018 Sep;50(5):335-340.

27. Singjam A, Charoentanyarak K, Saengsuwan J. Prevalence and predictive factors for bilateral carpal tunnel syndrome by electrodiagnosis: A retrospective study. PLoS One 2021;16(12):e0260578.

28. Rhee SY, Cho HE, Kim JH, Kim HS. Incidence and Reappraisal of Known Risk Factors Associated with Carpal Tunnel Syndrome: A Nationwide, 11-Year, Population-Based Study in South Korea. J Clin Neurol 2021;17(4):524–33.

29. Tsuji Y, Noto Y, Shiga K, Yokota I, Nakagawa M, Mizuno T. Does hand dominance affect peripheral nerve excitability? Clin Neurophysiol 2016;127(4):1921–2.

30. Dec P, Zyluk A. Bilateral carpal tunnel syndrome - A review. Neurol Neurochir Pol 2018;52(1):79–83.

31. El-Magzoub MS, Mustafa ME, Abdalla SF. Neurophysiologic pattern and severity grading scale of carpal tunnel syndrome in Sudanese patients. J Neurol Neurosci 2017;8(4):213–21.

32. Tortland PD. Nonsurgical management of carpal tunnel syndrome. Tech Orthop 2003;18(1):23–9.

# Idiopatski sindrom karpalnog kanala kod muškaraca

Igor Sladojević[1], Tatjana Bućma[2], Ostoja Savić[3]

[1]Univerzitet u Banjoj Luci, Medicinski fakultet, Banja Luka, Republika Srpska, Bosna i Hercegovina

[2]Zavod za fizikalnu medicinu i rehabilitaciju "Dr Miroslav Zotović", Banja Luka, Republika Srpska, Bosna i Hercegovina

[3]Univerzitetski klinički centar Republike Srpske, Banja Luka, Republika Srpska, Bosna i Hercegovina

**Uvod.** Sindrom karpalnog tunela (CTS) kod muških pacijenata, zbog anatomskih karakteristika i percepcije simptoma povezanih sa CTS, ostaje dugo vremena neotkriven. Muškarci slabije reaguju na liječenje CTS, a rano otkrivanje omogućava konzervativno liječenje blagog i umjerenog CTS. Cilj ovog rada bio je da se ispita prosječna starost, učestalost bilateralnog CTS i korelacija sa godinama života, te da se utvrdi stepen elektrofiziološkog oštećenja nervus medianus kod pacijenata muškog pola sa idiopatskim CTS dijagnostikovanim elektromioneurografijom.

**Metode.** Retrospektivnom studijom obuhvaćena su 83 pacijenta muškog pola, starosti od 32 do 81 godine, sa žalbama na simptome unilateralnog CTS na desnoj, dominantnoj šaci. Svim pacijentima je urađen EMNG radi potvrde CTS i stepena oštećenja nervus medianus. Statistička analiza je izvršena metodama deskriptivne statistike, t-testom, Wilcoxon testom ranga i Pirsonovim koeficijentom korelacije. Vrijednost $p< 0,05$ smatrana je statistički značajnom.

**Rezultati.** Prosječna starost pacijenata bila je 55,84 godine. Bilateralni CTS je potvrđen u 88,4%, najčešće umjerenog stepena i izraženije na desnoj, dominantnoj ruci ($p=0,001$). U slučajevima bilateralne CTS, godine života nisu korelirale sa stepenom CTS promjena na obje ruke. Promjene u dominantnoj šaci bile su izraženije kod pacijenata starijih od 51 godine.

**Zaključak.** Muškarci sa idiopatskim CTS obično imaju bilateralni CTS sa izraženijim promjenama na dominantnoj ruci. Bilateralnost CTS i stepen oštećenja nervus medianus nisu povezani sa godinama života.

**Ključne riječi:** sindrom karpalnog tunela, nervus medianus, muškarci

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):21–28

UDK: 616-073:618.19-006
DOI: 10.59137/BII202301299M

*Original article*

# Could Apparent Diffusion coefficient (ADC) be used as an imaging marker for proliferative activity in breast carcinoma?

**Jelena Marić[1], Jasmina Boban[2,3], Tatjana Ivković-Kapicl[2,3], Dragana Djilas[2], Viktorija Vučaj-Ćirilović [2,3], Dragana Bogdanović-Stojanović[4]**

[1]General hospital "Sveti Vračevi", Bijeljina, Republic of Srpska, Bosnia and Herzegovina

[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

[3]Oncology Institute of Vojvodina, Center for Diagnostic Imaging, Sremska Kamenica, Serbia

[4]Health Medic Clinic, Novi Sad, Serbia

Primljen – Received: 24/11/2021
Prihvaćen – Accepted: 16/01/2023

**Corresponding author:**
*Jelena Marić, MD*
*Srpske vojske 53, 76300 Bijeljina*
*maric.jelena@live.com*



**Summary**

**Introduction**. Multiparametric magnetic resonance mammography (mMRM) has an important role in detection, evaluation and follow-up of breast lesions. The aim of this study was to explore whether imaging parameters, in particular ADC, can be used as a biomarker of cell proliferation in breast cancer.

**Methods**. This cohort-study included 67 lesions in 50 female patients who underwent mMRM on a 3T scanner. Percutaneous biopsies and surgical excisions were performed after imaging in period up to 3 weeks. The Ki67 index was assessed microscopically. Seven Ki67 categories were defined: 0–5%, 10–20%, 20–40%, 40–50%, 50–80% and over 80%. Methods of descriptive statistics were used; correlations were determined using Pearson's correlation test. ROC curve was constructed and analyzed for determination of "cut-off" values for diagnostic potential. Statistical significance was set at $p < 0.05$.

**Results**. Different subtypes of breast carcinomas were involved: ductal carcinoma (59.9%), lobular carcinoma (17.9%), metastatic carcinoma (10.5%), ductal carcinoma in situ (9%), and tubular carcinoma (3%). It was not possible to determine whether there was significant difference in values of ADC for histological subtypes of breast carcinoma because of small number of samples in some groups. The cut off value of ADC for breast carcinoma was 0.792 (sensitivity 98.6%, specificity 65.7%). There was no significant difference in values of ADC for categories of Ki67. There was no significant correlation between ADC mean and Ki67 for all histological subtypes of breast carcinomas ($r = 0.156$, $p = 0.243$).

**Conclusion**. ADC cannot be used as a reliable imaging marker for proliferative activity in breast cancer.

**Key words**: breast cancer, ADC, DWI, Ki67

## Introduction

Magnetic resonance mammography (MRM) is a novel diagnostic and screening modality based on morphology and kinetic features of the breast lesion [1]. It has an important role in follow-up, as well as in detection and evaluation of breast lesions. Diffusion-weighted

imaging (DWI) is a MRI technique based on Brown motion of water molecules reflecting tissue cellularity and integrity of cell membranes [2]. This diffusion of water in tissue can be quantified by apparent diffusion coefficient (ADC) [3, 4]. ADC can be divided in 3 sub-parameters: ADC mean, ADC minimum and ADC maximum [4]. Mean ADC is most frequently used in clinical and experimental investigations.

Usually, benign breast lesions show a decrease in DWI signal and higher apparent diffusion coefficient (ADC) values compared to breast cancers which have lower values [5–7]. This means that ADC values can discriminate malignant and benign breast lesions. Also, it has been shown that ADC correlated inversely with cell count of investigated lesions [8]. Association with proliferation, e.g. Ki67 receptor are very important because the fact that it predicts behavior of several tumors [4, 8]. According to the literature, breast carcinomas with high expression of Ki67 had lower ADC values in comparison to tumors with low Ki67 expression [8].

Utility ADC as a biomarker of tumor proliferation is controversial due to several issues. Firstly, wide spectrum of correlations coefficient between ADC and Ki67 was reported [9–13]. Secondly, most reports about association between ADC and Ki67 investigated small samples ranging from 11 to 50 patients/tumors [9, 12, 13]. There only few studies investigated collectives over 100 patients [10, 11, 14].

Some studies showed that $ADC_{min}$ had stronger correlations with Ki67 [15] and can better reflect proliferation potential of malignant lesions.

The aim of this study was to explore associations between the mean ADC values and Ki67 in different types of breast tumors, and whether imaging parameters, in particular ADC, can be used as a biomarker of cell proliferation in breast cancer.

## Methods

This randomized retrospective cohort-study included 67 lesions in 50 females who underwent MRM in period from January 2013 to January 2017. The study was approved by ethical committee. Percutaneous biopsies and surgical excisions were performed after imaging in period up to 3 weeks. The including criteria were age over 18 and female gender. The excluding criteria were absence of subsequent histological finding and contraindications for MRM.

All patients signed a fully informed written consent for taking part in the study.

*Magnetic Resonance Mammography (MRM)*

MRM in all patients was performed on 3T scanner (Siemens Trio Tim, Erlangen, Germany), using a dedicated 36-channel coil, in the prone position. DWI was integrated in conventional protocol that consisted of non-fat-suppressed T2-weigthed turbo spin echo transversal, non-fat-suppressed and fat suppressed T1-weighetd transversal sequences and STIR sagittal sequence, followed by dynamic contrast study (fat-suppressed 3D T1-weighted Fast Low Angle Shot (FLASH) transversal tomograms). Gadolinium contrast agent was injected in the dose of 0.1mmol/kg, at the rate 2.5 ml/s, followed by 25 ml saline injection. Parameters for dynamic contrast study were: time of repetition/ time of echo (TR/TE) 4.2 ms/1.6 ms, flip angle (FA) 15°, field of view (FOV) 340x340 mm, matrix size 512x410, slice thickness 2mm, time of acquisition 86s. Diffusion-weighted imaging was performed prior to contrast study, using echo-planar imaging (EPI) sequence in the axial plane, with b values of 750, 1000 and 1500 s/mm2. Parameters for this sequence were: TR/TE 8400 ms/98 ms, FOV 340x170 mm, matrix size 192x96, slice thickness 4 mm. Apparent diffusion coefficient (ADC) maps were created during the post-processing by using available software provided by the manufacturer (Syngo, Siemens Healthcare). The region of

interest (ROI) was selected manually including only solid parts of tumor.

Percutaneous biopsies or surgical excision obtained tissues samples that underwent histological examination. Core biopsy was performed using Bard Magnum biopsy instrument and needles of 14 G. Three to twelve tissue samples were taken and put into formalin. Histological report contained histological finding according to WHO Classification of the breast tumors [16]. The Ki67 index was assessed microscopically. In the „hot spot" within the tumor (area with highest number of positive nuclei) scoring was performed. The Ki67 index was expressed as the percentage of Ki-67 positive malignant cells in 1000 malignant cells. We defined seven Ki67 categories: 0–5%, 10–20%, 20–40%, 40–50%, 50–80% and over 80%.

Statistical analysis was performed using SPSS ver. 19.0 (IBM, Chicago, IL, USA). Methods of descriptive statistics were used (mean, standard deviation, minimum, maximum). Differences between variables were tested using chi-square test. Correlations were determined using Pearson's correlation test. For determination of cut off value for diagnostic and prognostic potential of variable, Receiver Operating Characteristic (ROC) curves were constructed. Statistical significance was set at value $p < 0.05$.

## Results

The study included 50 females with 67 detected breast lesions. Histologically, there were different subtypes of breast carcinomas involved. Most frequently, ductal carcinoma (59.9%), followed by lobular carcinoma (17.9%), metastatic carcinoma (10.5%), ductal carcinoma in situ (9%), and tubular carcinoma (3%) were reported. Mean ADC values and distribution of pathohistological subtypes of breast carcinoma are summarized in table 1. Since in category tubular carcinoma were only two cases, it was not possible to determine whether there was significant difference in values of ADC in different histological subtypes of breast carcinoma.

Mean values and standard deviations of ADC and defined groups of Ki67 are summarized in table 2 and shown in figure 1.

**Table 1.** Mean ADC values and distribution of histological subtypes of breast carcinoma

| Histological subtype of breast carcinoma | N (frequency) | ADC (x $10^{-3}$ mm2/s) (3rd–1st quartile) | max | min |
|---|---|---|---|---|
| Ductal invasive carcinoma | 40 (59.9%) | 0.68 (0.87–0.52) | 1 | 0.06 |
| Lobular carcinoma | 12 (17.9%) | 0.72 (0.82–0.55) | 0.98 | 0.27 |
| DCIS | 6 (9%) | 0.78 (0.88–0.52) | 0.89 | 0.63 |
| Metaplastic carcinoma | 7 (10.5%) | 0.68 (0.85–0.50) | 0.95 | 0.22 |
| Tubular carcinoma | 2 (3%) | 0.78 (0.81–0.75) | 0.83 | 0.73 |

**Table 2.** Mean ADC values and standard deviations distribution of defined groups of KI 67

| ADC | Ki67 | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0–5% | 5–10% | 10–20% | 20–40% | 40–50% | 50–80% | > 80% |
| Mean value | 0.7145 | 0.5571 | 0.5839 | 0.584 | 0.604 | 0.732 | 0.728 |
| ST deviation | 0.19811 | 0.34368 | 0.19626 | 0.25628 | 0.14188 | 0.34518 | 0.15503 |

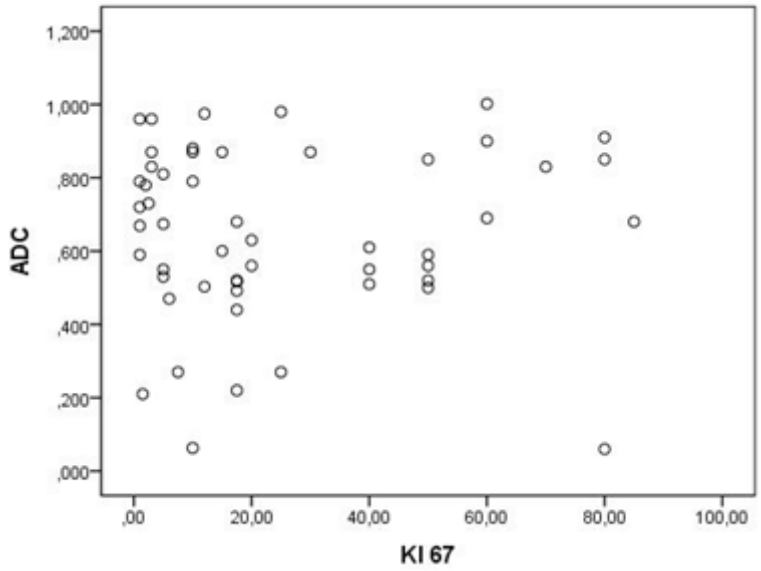


**Figure 1.** Values of ADC for defined categories of Ki67

There was no significant difference in values of ADC and Ki67.

The pooled correlation coefficient between ADC mean and Ki67 for all histological subtypes of breast carcinomas was r = 0.156 (p = 0.243). There was no significant correlation between parameters. Pearson's correlation coefficients and mean ADC for each category of Ki67 are shown in table 3 and figure 2.

ROC curve for malignant lesions is shown in figure 3. The cut off value of ADC for malignant lesions was 0.792 (sensitivity 98.6%, specificity 65.7%).

**Table 3.** Correlation coefficients between ADC mean and defined groups of KI 67 in breast carcinoma

| Ki67 | ADC |
|---|---|
| 0–5% | r = -0.053, p = 0.85, n=15 |
| 5–10% | r = 0.356, p = 0.489, n = 6 |
| 10–20% | r = -0.426, p = 0.168, n = 12 |
| 20–40% | r = -0.225, p = 0.667, n = 6 |
| 40–50% | *n=5 |
| 50–80% | r = -0.404, p = 0.368, n = 7 |
| >80% | r = 0.288, p = 0.420, n = 10 |
| pooled KI 67 | r = 0.156, p = 0.243, n=58 |

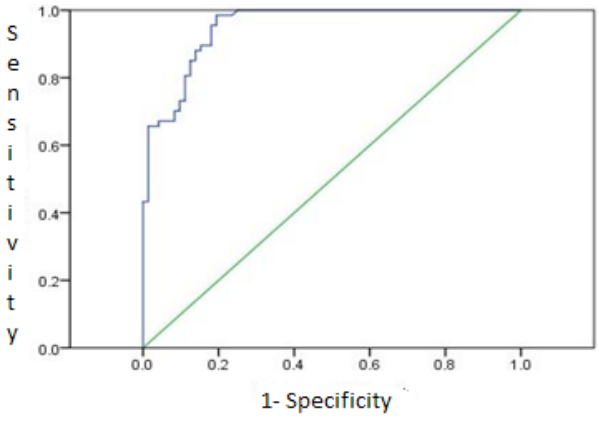


**Figure 2.** ADC values vs. Ki67

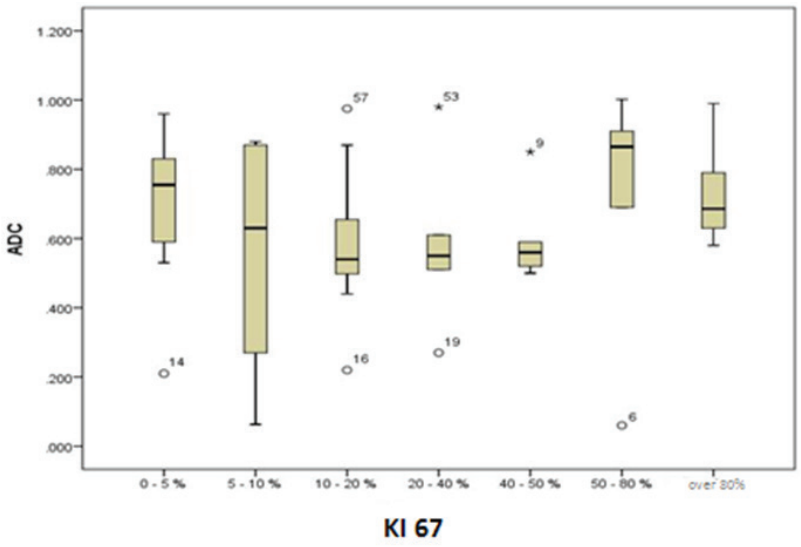


**Figure 3.** ROC curve for malignant breast lesions

## Discussion

Ki67 is a marker of cell proliferation and can predict the prognosis for patients with breast carcinoma [17, 18]. Because of this, it is important to predict expression of Ki67 on imaging parameters. ADC reflects water diffusion in tissue and is in inverse correlation with cell number in tumors [19], and statistically significant correlation with nucleic size/volume [4]. Some previous studies showed the phenomenon that ADC can be associated with Ki67 [4, 15]. It is unknown the exact cause of this association. Ki67 is shown to be responsible for cell proliferation as nuclear cell protein synthesized through the whole mitosis except the G0 phase [20, 21]. Also, it is possible that mitotic phases may an increase of cytoplasmic proteins and cytoplasmic viscosity [22]. This may lead to decrease ADC.

Reported data about associations between ADC and Ki67 in breast cancers are very inconsistent. Some studies identified significant correlations between parameters [23, 24], other did not. It is suggested that that ADC can be used as a biomarker for proliferation in ovarian cancer. But ADC cannot be used as a proliferation biomarker in breast cancer because of weak correlations between ADC and Ki67. Interpretation of results of previous studies is difficult because of different study design and analysis. Different values of Ki67 expression are used to discriminate cancers with low or high proliferative activity [8, 25, 26], and some defined more than two Ki67 categories.

In previous studies, several problems were identified. Firstly, some studies contained relatively small patient samples which were examined with use of different MRI equipment with different technical parameters (field strength, DWI sequences and b-values). Secondly, published correlation coefficients were various due to different subjects included, different ratio of histological subtypes of tumors or different method of analysis (ROI size, location, etc.).

The cut off values of mean ADC was determined for malignant lesions in our study. The cut off ADC value for malignant lesions was 0.792 (sensitivity 98.6%, specificity 65.7%). Therefore, ADC could be used as marker for distinguishing malignant lesions of breast with very good sensitivity, but low specific-

ity. This could be improved with use of dynamic contrast-enhanced magnetic resonance mammography (DCE-MRM).

Our study has some limitations. Firstly, it contained relatively small patient sample. Therefore, it could not identify if there was significant associations between ADC and histological subtypes of breast cancer, or Ki67 and subtypes of breast cancer because of small sample in some histological groups. Secondly, we did not calculate correlation coefficients for each histological subtype included, because the included tumors represent the most frequent subtypes of breast carcinoma and we consider these should be analyzed as a group. Thirdly, we used different MRI equipment and methods of analysis (first of all, b values, size and positioning of ROI).

## Conclusion

In conclusion, weak correlations between ADC and Ki67 in breast cancer were found, thus ADC cannot be used as a reliable imaging marker for proliferative activity in this entity. However, ADC can be used as a marker for distinguishing malignant lesions of breast with high sensitivity, but low specificity that could be improved using dynamic contrast-enhanced magnetic resonance mammography (DCE-MRM).

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** The Ethics Committee of the General hospital "Sveti Vračevi", Bijeljina, Republic of Srpska, Bosnia and Herzegovina, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

**Conflicts of interest.** The authors declare no conflict of interest.

### References:

1. Rahbar H, Patridge SC. Multiparametric MR imaging of breast cancer. Magn Reson Imaging Clin N Am 2016;24(1):223–8.
2. Kuhl CK, Shrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated breast magnetic resonance imaging (MRI): first post-contrast subtracted images and maximum-intensity projection - a novel approach to breast cancer screening with MRI. J Clin Oncol 2014;32(22):2304–10.
3. Fornasa F. Diffusion-weighted Magnetic Resonance Imaging: What Makes Water Run Fast or Slow? J Clin Imaging Sci 2011;1:27.
4. Surov A, Caysa H, Wienke A, Spielmann RP, Fiedler E. Correlation between different ADC fractions, cell count, Ki-67, total nucleic areas and average nucleic areas in meningothelial meningiomas. Anticancer Res 2015;35(12):6841–6.
5. Bostan TB, Koç G, Sezgin G, Altay C, Gelal MF, Oyar O. Value of apparent diffusion coefficient values in differentiating malignant and benign breast lesions. Balkan Med J 2016;33(3):294–300.
6. Marini C, Lacconi C, Giannelli M, Cilotti A, Moretti M, Bartolozzi C. Quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesion. Eur Radiol 2007;17(10):2646–55.
7. Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. J Magn Reson Imaging 2002;16(2):172–8.
8. Choi SY, Chang YW, Park HJ, Kim HJ, Hong SS, Seo DY. Correlation of the apparent diffusion coefficiency values on diffusion-weighted imaging with prognostic factors for breast cancer. Br J Radiol 2012;85(1016):e474–9.

9. Kim SH, Cha ES, Kim HS, Kang BJ, Choi JJ, Jung JH, et al. Diffusion-weighted imaging of breast cancer: correlation of the apparent diffusion coefficient value with prognostic factors. J Magn Reson Imaging 2009;30(3):615–20.
10. Martincich L, Deantoni V, Bertotto I, Redana S, Kubatzki F, Sarotto I, et al. Correlations between diffusion-weighted imaging and breast cancer biomarkers. Eur Radiol 2012;22(7):1519–28.
11. Shin HJ, Kim SH, Lee HJ, Gong G, Baek S, Chae EY, et al. Tumor apparent diffusion coefficient as an imaging biomarker to predict tumor aggressiveness in patients with estrogen-receptor-positive breast cancer. NMR Biomed 2016; 29(8):1070–8.
12. Mori N, Ota H, Mugikura S, Takasawa C, Ishida T, Watanabe G, et al. Luminal-type breast cancer: correlation of apparent diffusion coefficients with the Ki-67 labeling index. Radiology 2015;274(1):66–73.
13. Sun K, Chen X, Chai W, Fei X, Fu C, Yan X, et al. Breast Cancer: Diffusion Kurtosis MR Imaging-Diagnostic Accuracy and Correlation with Clinical-Pathologic Factors. Radiology 2015;277(1):46–55.
14. Surov A, Clauser P, Chang YW, Li L, Martincich L, Partridge SC, et al. Can diffusion-weighted imaging predict tumor grade and expression of Ki-67 in breast cancer? A multicenter analysis. Breast Cancer Res 2018;20(1):58.
15. Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009;11(2):102–25.
16. Sinn HP, Kreipe H. A Brief Overview of the WHO Classification of Breast Tumors, 4th Edition, Focusing on Issues and Updates from the 3rd Edition. Breast Care (Basel) 2013;8(2):149–54.
17. Li L, Han D, Wang X, Wang Q, Tian J, Yao J, et al. Prognostic values of Ki-67 in neoadjuvant setting for breast cancer: a systematic review and meta-analysis. Future Oncol 2017;13(11):1021–34.
18. Tao M, Chen S, Zhang X, Zhou Q. Ki-67 labeling index is a predictive marker for a pathological complete response to neoadjuvant chemotherapy in breast cancer: a meta-analysis. Medicine (Baltimore) 2017;96(51):e9384.
19. Surov A, Meyer HJ, Wienke A. Correlation between apparent diffusion coefficient (ADC) and cellularity is different in several tumors: a meta-analysis. Oncotarget 2017;8(35):59492–9.
20. He X, Chen Z, Fu T, Jin X, Yu T, Liang Y, et al. Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic meta-analysis. BMC Cancer 2014;14:153.
21. Schlüter C, Duchrow M, Wohlenberg C, Becker MH, Key G, Flad HD, et al. The cell proliferation-associated antigen of antibody Ki-67: a very large, ubiquitous nuclear protein with numerous repeated elements, representing a new kind of cell cycle-maintaining proteins. J Cell Biol 1993;123(3):513–22.
22. Valentine MT, Perlman ZE, Mitchison TJ, Weitz DA. Mechanical properties of Xenopus egg cytoplasmic extracts. Biophys J 2005;88(1):680–9.
23. Onishi N, Kanao S, Kataoka M, Iima M, Sakaguchi R, Kawai M, et al. Apparent Diffusion Coefficient as a Potential Surrogate Marker for Ki-67 Index in Mucinous Breast Carcinoma. J Magn Reson Imaging 2015;41(3):610–5.
24. Shen L, Zhou G, Tong T, Tang F, Lin Y, Zhou J, et al. ADC at 3.0 T as a noninvasive biomarker for preoperative prediction of Ki67 expression in invasive ductal carcinoma of breast. Clin Imag 2018;52:16–22.
25. Zhuang Z, Zhang Q, Zhang D, Cheng F, Suo S, Geng X, et al. Utility of apparent diffusion coefficient as an imaging biomarker for assessing the proliferative potential of invasive ductal breast cancer. Clin Radiol 2018;73(5):473–8.
26. Molinari C, Clauser P, Girometti R, Linda A, Cimino E, Puglisi F, et al. MR mammography using diffusion-weighted imaging in evaluating breast cancer: a correlation with proliferation index. Radiol Med 2015;120(10):911–8.

# Da li vidljivi koeficijent difuzije (ADC) može biti imidžing marker za proliferativnu aktivnost kod karcinoma dojke?

Jelena Marić[1], Jasmina Boban[2,3], Tatjana Ivković-Kapicl[2,3], Dragana Đilas[2], Viktorija Vučaj-Ćirilović [2,3], Dragana Bogdanović-Stojanović[4]

[1]JZU bolnica "Sveti Vračevi", Bijeljina, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet u Novom Sadu, Medicinski fakultet, Novi Sad, Srbija

[3]Institut za onkologiju Vojvodine, Centar za imidžing dijagnostiku, Sremska Kamenica, Srbija

[4]Poliklinika "Health Medic", Novi Sad, Srbija

**Uvod.** Multiparametrijska magnetno-rezonantna mamografija (mMRM) ima važnu ulogu u detekciji, evaluaciji i praćenju tumora dojke. Cilj ove studije je da ispita da li imidžing parametar, konkretno Apparent Diffusion Coefficient (ADC), može biti marker za proliferativnu aktivnost kod karcinoma dojke.

**Metode.** Ova kohortna studija uključila je 67 lezija kod 50 pacijentkinja koje su pregledane mMRM na skeneru 3T. Perkutane biopsije i hirurške ekscizije izvođene su posle snimanja u periodu do tri nedelje. Ki67 indeks je procenjen mikroskopski. Sedam Ki67 kategorija je definisano: 0–5%, 10–20%, 20–40%, 40–50%, 50–80% i više od 80%. Korišćene su metode deskriptivne statistike. Korelacije su određene korišćenjem Pirsonovog korelacionog testa. Konstruisana je i analizirana ROC kriva za određivanje "cut-off" vrednosti i dijagnostičkog potencijala. Statistička značajnost je bila postavljena na $p < 0,05$.

**Rezultati.** Različiti podtipovi karcinoma dojke su bili zastupljeni: duktalni karcinom (59,9%), lobularni karcinom (17,9%), metastatski karcinom (10,5%), duktalni karcinom in situ (9%) i tubularni karcinom. "Cut off" vrednost ADC za karcinom dojke bila je 0,792 (senzitivnost 98,6%, specifičnost 65,7%). Nije postojala statistički značajna razlika u vrednostima ADC za različite kategorije Ki67. Nije postojala statistički značajna korelacija između srednje vrednosti ADC i Ki67 na nivou celog uzorka ($r = 0,156$, $p = 0,243$).

**Zaključak.** ADC se ne može koristiti kao pouzdan imidžing marker za proliferativnu aktivnost kod karcinoma dojke.

**Ključne reči:** karcinom dojke, ADC, difuzioni imidžing, Ki67

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):29–39

UDK: 577.161.2:641:613.292(497.6)
DOI: 10.59137/BII202301307B

*Original article*

# Content-related quality of food supplements with vitamin D on the market of Republic of Srpska

**Ljubica Bojanić**[1,2],
**Mirjana Djermanović**[1,2]

[1]Public Health Institute of Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

[2]University of Banja Luka, Faculty of Medicine, Department of Pharmacy, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Primljen – Received: 20/02/2023
Prihvaćen – Accepted: 26/04/2023

**Corresponding author:**
*Ljubica Bojanić, mr ph*
*Jovana Dučića 1, 78000 Banja Luka*
*ljubica.bojanic@gmail.com*



**Summary**

**Introduction**. Vitamin D is a liposoluble vitamin that has many important roles in the human body. Daily requirements for vitamin D are met through intake of food and exposure to sunlight. The high frequency of vitamin D deficiency is a public health problem that can be corrected using food supplements (FS), which is why its consumption is increasing. The quality of FS, including the content of active components, depends on the good manufacturing practice which is not strictly regulated for the production of FS, as well as the formulation, packaging and storage. Because of that, the quality of FS can be variable. The aim of our pilot study was to examine the conformity of the actual determined content of vitamin D and the declared content in 49 FS, in the form of tablets and capsules, present on the market in Republic of Srpska.

**Method**. Determination of vitamin D content was performed by high-performance liquid chromatography (HPLC).

**Results**. The range of the determined content of vitamin D in relation to the declared content, expressed as a percentage, was from 64,4% to 188,8%, whereby the deviation is not statistically significant (mean: 100.50%; CI 95% -0.54 to 0.17; p=0.313 tablets; mean: 98.02%; CI 95% -3.00 to 0.42; p=0.127 capsules). When measurement uncertainty is taken into account, only one sample (2.0%) was outside the legally allowed range (88.8% more than labeled).

**Conclusion**. Therefore, it has been shown that most of the examined products are of satisfactory quality in terms of vitamin D content, but it is necessary to continuously monitor the food supplements that are on the market.

**Keywords**: cholecalciferol, food supplements, safety, label, HPLC

## Introduction

Vitamin D is one of the most important nutrients necessary for the proper development and functioning of our body. According to its chemical structure, vitamin D belongs to the group of steroids. The two most important forms of vitamin D are ergocalciferol (D2) and cholecarciferol (D3). Vitamin D is a fat-soluble vitamin. Due to its metabolism and mechanism of action, it is also considered a hormone [1]. The human body provides vitamin D through synthesis in the skin after exposure to UV-B radiation, as well as through intake of food and food supplements (FS) [1,

2]. The amount of endogenously synthesized vitamin D depends on the intensity of exposure to solar radiation, which is influenced by numerous factors such as geographical area, season, altitude, time spent outside, use of sunscreen, clothing, age, skin color, numerous diseases etc. In the case of reduced endogenous synthesis, due to insufficient exposure to UV-B radiation, it is necessary to compensate vitamin D through food or FS [2, 3]. Foods that are the source of vitamin D include fish (fatty fish is the best), egg yolks, some offal such as liver (especially cod liver), butter and milk (which are fortified in some countries), cocoa and cocoa products, mushrooms, meat to a lesser extent, etc. [4–6].

Today, the consumption of FS, especially vitamins and minerals, is very popular among general population. Also, the awareness about the importance of adequate intake of vitamin D is growing as the lack of vitamin D is becoming a growing public health problem. Accordingly, the intake of vitamin D through FS is increasing, which is why it is extremely important to control the quality of this group of products. The quality control of FS is very complex and includes both, the control of potentially harmful contaminants and the content of active components, as well as the labeling of products, which must comply with the requirements of current legislation. Also, FS are available to general population in pharmacies as well as in various stores and online shops, so very often people buy FS on their own, without adequate advice from health care professionals about its use. This can lead to excessive or inadequate use and numerous interactions with drugs if used together [7]. Some studies have shown possible deviations of the actual content of vitamin D in relation to the labeled value (LV) in FS [8–10]. For example, a research carried out in Slovenia showed that determined vitamin D was 36% to 206% compared to labeled one [8]. Therefore, due to inadequate product formulation, packaging or storage, there may be a change in the content of the active component in the FS compared to the LV, which may mislead the consumer in terms of product dosage. Because of that, it is very important to control the content of active substances in FS.

The aim of our pilot study was to examine FS with vitamin D present on the market in Republic of Srpska, what doses of vitamin D are contained and whether the determined vitamin D content corresponded to the labeled content on the product itself, i.e. to examine the quality in terms of vitamin D content in FS available to the general population.

## Method

Vitamin D has been examined in 49 samples of FS in form of tablets (n=34) and capsules (n=15) present on the market of Republic of Srpska. FS with vitamin D were selected by random sampling from pharmacies and stores and did not include all supplements with vitamin D present on the market. The number of all FS with vitamin D on the market is unknown as there is no comprehensive register for these products. This pilot study was conducted from July 2019 to December 2020.

Determination of vitamin D is based on a reference document that is an extension of the standard method "SRPS EN 12821:2012 - Food products - Determination of vitamin D by high-performance liquid chromatography - Measurement of cholecalciferol (D3) and ergocalciferol (D2)". It was modified in part of the subject of test and validated by the procedure by which it was determined that the test method was reliable for the intended analytical determinations in the given conditions in accordance with the ISO/IEC 17025 standard [11]. The method is based on the determination of vitamin D2 or D3 by high-performance liquid chromatography (HPLC), which includes a technique in which a continuous flow of the mobile phase is applied along a column with a stationary phase, in order to

separate analyzed components of the mixture and their further qualitative and quantitative analyses in the examined sample [12]. Determination of vitamin D content was performed on an HPLC Agilent 1200 Series, DAD detector. Sample preparation involved the release of vitamin D from the samples by alkaline hydrolysis with a mixture of ethanol and aqueous KOH solution in the presence of ascorbic acid as an antioxidant (saponification). After saponification, vitamin D was extracted with n-hexane. Determination of vitamin D2 or D3 in the sample extract solution was performed using a semi-preparative normal phase column (silica gel, 5 μm; 4 x 250 mm), followed by determination on an analytical C18 reverse phase column (5 μm; 4 x 250 mm) by chromatography using DAD detector (UV spectrometry, $\lambda$ = 265 nm) (Figure 1). A mixture of n-hexane and 2-propanol (99:1 V/V) was used as a solvent for the normal phase of semi-preparative HPLC, while a mixture of acetonitrile and methanol (70:30 V/V) was used as a mobile phase for analytical reverse phase HPLC.

Linearity for vitamin D3 was determined in the range from 2.5 μg/mL to 100 μg/mL, and for vitamin D2 in the range from 5 to 100 μg/mL (Figure 2). The measured limits of detection for both vitamins were 1.25 μg/mL, and the limit of determination for vitamin D3 was 2.5 μg/mL, while for D2 it was 5 μg/mL.

Descriptive statistics was used to analyze the results and for statistical analysis the IBM SPSS Statistics software 25 was used. The results of descriptive statistics were presented as determined values (DV) ± measurement uncertainty, rounded to 2 decimal places, and percentage of difference between DV and LV.

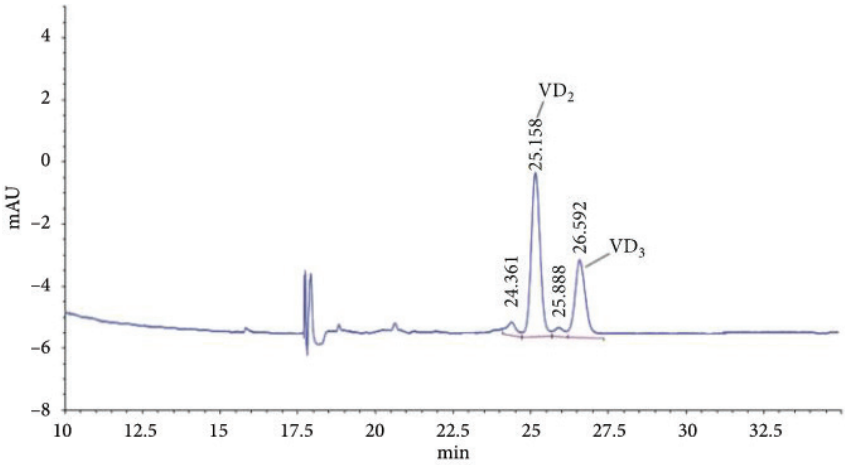


**Figure 1.** Chromatogram of vitamin D determination

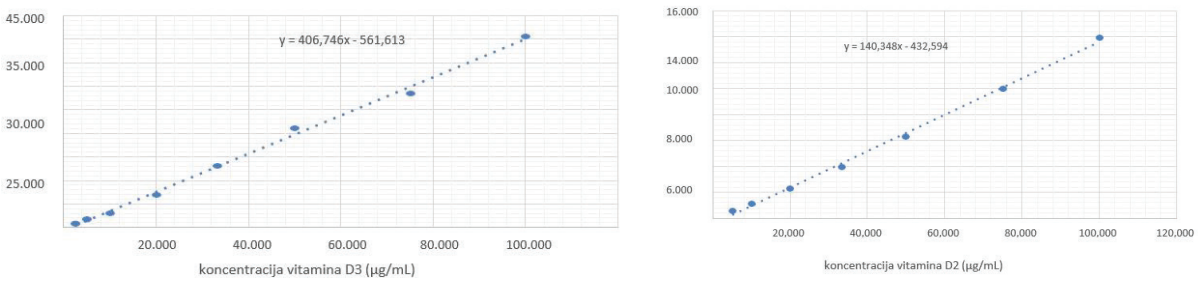


**Figure 2.** Calibration curve for vitamin D3 and vitamin D2

## Results

Vitamin D content was tested in 49 samples of FS present on the market of Republic of Srpska and containing vitamin D2 or D3, alone or in combination with other active substances, in the form of capsules and tablets, including effervescent tablets. Thirty four samples in the form of tablets and 15 samples in the form of capsules were tested.

Tables 1 and 2 show the results obtained from the determination of vitamin D by the

**Table 1.** Vitamin D in FS in the form of tablets

| Number of the sample | DV1 (± measurement uncertainty) | LV2 (-20% +50%) | Unit of measurement | (DV/LV) *100% | Difference of DV in relation to LV (%) |
|---|---|---|---|---|---|
| Sample 1 | 5.43 ± 1.10 | 5 (4.0–7.5) | µg/tablet | 108.6 | ↑8.6 |
| Sample 2 | 5.62 ± 1.12 | 5 (4.0–7.5) | µg/tablet | 112.4 | ↑12.4 |
| Sample 3 | 5.75 ± 1.15 | 5 (4.0–7.5) | µg/tablet | 115 | ↑15 |
| Sample 4 | 5.08 ± 0.98 | 5 (4.0–7.5) | µg/tablet | 101.6 | ↑1.6 |
| Sample 5 | 5.10 ± 0.87 | 5 (4.0–7.5) | µg/tablet | 102 | ↑2 |
| Sample 6 | 4.55 ± 0.91 | 5 (4.0–7.5) | µg/tablet | 91 | ↑9 |
| Sample 7 | 9.40 ± 1.88 | 10 (8.0–15.0) | µg/tablet | 94 | ↑6 |
| Sample 8 | 8.10 ± 1.62 | 10 (8.0–15.0) | µg/tablet | 81 | ↑19 |
| Sample 9 | 4.20 ± 0.84 | 5 (4.0–7.5) | µg/tablet | 84 | ↑16 |
| Sample 10 | 4.20 ± 0.84 | 5 (4.0–7.5) | µg/tablet | 84 | ↑16 |
| Sample 11 | 4.80 ± 0.96 | 5 (4.0–7.5) | µg/tablet | 96 | ↑4 |
| Sample 12 | 8.20 ± 1.64 | 10 (8.0–15.0) | µg/tablet | 82 | ↑18 |
| Sample 13 | 4.20 ± 0.84 | 5 (4.0–7.5) | µg/tablet | 84 | ↑16 |
| Sample 14 | 7.10 ± 1.42 | 7.5 (6–11.25) | µg/tablet | 94.7 | ↑5.3 |
| Sample 15 | 4.72 ± 0.94 | 2.5 (2.0–3.75) | µg/tablet | 188.8 | ↑88.8 |
| Sample 16 | 11.70 ± 2.34 | 10 (8.0–15.0) | µg/tablet | 117 | ↑17 |
| Sample 17 | 9.26 ± 1.85 | 10 (8.0–15.0) | µg/tablet | 92.6 | ↑7.4 |
| Sample 18 | 17.05 ± 3.41 | 20 (16.0–30.0) | µg/tablet | 85.2 | ↑14.8 |
| Sample 19 | 5.71 ± 1.14 | 5 (4.0–7.5) | µg/tablet | 114.2 | ↑14.2 |
| Sample 20 | 5.20 ± 1.04 | 6 (4.8–9.0) | µg/tablet | 86.7 | ↑13.3 |
| Sample 21 | 4.30 ± 0.86 | 5 (4.0–7.5) | µg/tablet | 86 | ↑14 |
| Sample 22 | 5.70 ± 1.14 | 5 (4.0–7.5) | µg/tablet | 114 | ↑14 |
| Sample 23 | 5.43 ±1.09 | 5 (4.0–7.5) | µg/tablet | 108.5 | ↑8.5 |
| Sample 24 | 5.51 ± 1.10 | 5 (4.0–7.5) | µg/tablet | 110.2 | ↑10.2 |
| Sample 25 | 5.00 ± 0.98 | 5 (4.0–7.5) | µg/tablet | 100 | 0 |
| Sample 26 | 4.48 ± 0.90 | 5 (4.0–7.5) | µg/tablet | 89.6 | ↑10.4 |
| Sample 27 | 4.77 ± 0.95 | 5(4.0–7.5) | µg/tablet | 95.4 | ↑4.6 |
| Sample 28 | 7.70 ± 2.00 | 7.5 (6.0–11.25) | µg/tablet | 102.7 | ↑2.7 |
| Sample 29 | 8.60 ± 1.72 | 7.5 (6.0–11.25) | µg/tablet | 114.7 | ↑14.7 |
| Sample 30 | 5.80 ± 1.16 | 5 (4.0–7.5) | µg/ daily dose | 116 | ↑16 |
| Sample 31 | 5.0 ± 0.98 | 5 (4.0–7.5) | µg/2 tablets | 100 | 0 |
| Sample 32 | 2.70 ± 0.54 | 3 (2.4–4.5) | µg/tablet | 90 | ↑10 |
| Sample 33 | 8.40 ± 1.68 | 10 (8.0–15.0) | µg/tablet | 84 | ↑16 |
| Sample 34 | 9.10 ± 1.82 | 10 (8.0–15.0) | µg/tablet | 91 | ↑9 |

1 Determined value of vitamin D
2 Labeled value of vitamin D

HPLC method, their comparison to the labeled amount, as well as the deviations of the stated values.

The results in the tables are shown in the labeled units of measurement, that is, in μg per tablet, capsule or daily dose, g or mg per 100g, or in percentages for deviations. DV of vitamin D in the examined tablets ranged from 2.70 μg to 17.05 μg per tablet, and in capsules from 1.55 μg to 46.54 μg per capsule. Measurement uncertainty included in the interpretation of the results ranged from ± 0.31 μg to ± 9.31 μg, depending on the amount of vitamin D in the samples. LV ranged from 2.5 μg to 50 μg of vitamin D per pharmaceutical dosage form, amounting from 100 IU to 2000 IU, respectively. The tables show the percentage of difference of the determined value of vitamin D in relation to the labeled value (DV/LV*100%). This value ranged from 81% to 188.8% in tablet samples, while in capsule samples this value ranged from 64.4% to 170.0%.

The statistical parameters for all examined samples showed no statistical significance in difference of DV compared to LV (mean: 100.50%; Cl 95% -0.54 to 0.17; p=0.313 for tablets; mean: 98.02%; Cl 95% -3.00 to 0.42; p=0.127 for capsules).

**Table 2.** Vitamin D in FS in the form of capsules

| Number of the sample | DV[1] (± measurement uncertainty) | LV[2] (-20% + 50%) | Unit of measurement | (DV/LV) *100% | Difference of DV in relation to LV (%) |
|---|---|---|---|---|---|
| Sample 1 | 1.55 ± 0.31 | 1.7 (1.36–2.55) | μg/capsule | 91.2 | ↑8.8 |
| Sample 2 | 46.54 ± 9.31 | 50 (40–75) | μg/capsule | 93.1 | ↑6.9 |
| Sample 3 | 4.21 ± 0.84 | 5 (4.0–7.5) | μg/capsule | 84.2 | ↑15.8 |
| Sample 4 | 6.08 ± 1.22 | 5 (4.0–7.5) | μg/capsule | 121.6 | ↑21.6 |
| Sample 5 | 4.20 ± 0.84 | 5 (4.0–7.5) | μg/capsule | 84 | ↑16 |
| Sample 6 | 8.50 ± 1.70 | 5 (4.0–7.5) | μg/capsule | 170 | ↑70 |
| Sample 7 | 16.10 ± 3.92 | 25 (20.0–37.5) | μg/capsule | 64.4 | ↑35.6 |
| Sample 8 | 8.70 ± 1.74 | 10 (8-15) | μg/capsule | 87 | ↑13 |
| Sample 9 | 43.00 ± 8.60 | 50 (40.0–75.0) | μg/capsule | 86 | ↑14 |
| Sample 10 | 2.49 ± 0.50 | 2.22 (1.78–3.33) | mg/100g | 112.2 | ↑12.2 |
| Sample 11 | 4.20 ± 0.84 | 5 (4.0–7.5) | μg/capsule | 84 | ↑16 |
| Sample 12 | 5.0 ± 0.5 | 5(4.0–7.5) | mg/100g | 100 | 0 |
| Sample 13 | 2.30 ± 0.46 | 2.22 (1.78–2.66) | mg/100g | 103.6 | ↑3.6 |
| Sample 14 | 9.84 ± 0.51 | 10 (8.0–15.0) | μg/capsule | 98.4 | ↑1.6 |
| Sample 15 | 9.06 ± 0.47 | 10 (8.0–15.0) | μg/capsule | 90.6 | ↑9.4 |

1 Determined value of vitamin D

2 Labeled value of vitamin D

## Discussion

Vitamin D is one of the most important nutrients playing an important role in growth, development and functioning of the human body. It improves the absorption of calcium and phosphate in the intestines, and by stimulating the function of osteoblasts, it contributes to the mineralization of the bone system [13]. It stimulates the cells of innate and acquired immunity, thereby strengthening the body's defense against infection, including infection caused by the SARS-COV 2 virus [14–16]. The basic anti-infective mechanism is based on the expression of cathelicidin and beta-defensin 2 in phagocytes and epithelial cells, which leads to inhibition of virus replication in the body [14–18]. Most of the effects of vitamin D are achieved by binding to the vitamin D receptor (VDR) and forming a heterodimeric complex, which further binds to the promoter regions of certain DNA genes called vitamin D responsive elements (VDREs). They affect gene expression, and as a result, the synthesis of cathelicidin and defensin β-2 in macrophages is stimulated. This leads to an increased phagocytic ability and chemotaxis of macrophages and monocytes which increases the efficiency of our immune system against infection and reduce the possibility of respiratory tract infections (RTIs) [14, 17, 18].

Age and chronic comorbidities, such as obesity and diabetes, significantly complicate the clinical picture of infection with SARS-COV 2 virus. Adequate supplementation can increase the level of regulatory T lymphocytes and thus reduce the risk of pneumonia and upper RTIs [18]. To reduce the risk of RTIs, some studies suggest that people with vitamin D deficiency could take vitamin D in dose of 10000 IU/day for several weeks before peak season for RTIs, to reach an optimal level of vitamin D in circulation, and then the dose is reduced to 5000 IU/day as long as it needs. With this regimen of oral supplementation, an optimal level of vitamin D in blood of 40 do 60 mg/mL (100 do 150 nmol/L) is achieved and maintained in long-terms with no side effects [18–20]. Furthermore, some guidelines say that in vitamin D deficient individuals, optimal levels of vitamin D can be achieved by taking 50.000 IU/week or 6.000 IU/day for several months, followed by a maintenance dose of 1.500–2.000 IU/day [21]. One study showed that the use of vitamin D in the dose of 100.000–200.000 IU for 8 weeks (1800–3600 IU/day) or 10.000 IU/day for four months did not cause any side effects [19]. Current research shows that acute toxicity of vitamin D is very rare, and the acute toxic dose has not been clearly defined to date, while chronic toxicity can be manifested after taking the dose higher than 50.000 IU/day for more than a month [22]. It is also necessary for the health of the muscular system [23]. It reduces the risk of developing cardiovascular diseases, and in the case of an already present disease, vitamin D supplementation reduces the degree of possible complications and mortality [24]. Vitamin D inhibits many processes such as carcinogenesis and inflammation, which contributes to the improvement of some other conditions such as diabetes mellitus [24, 25].

Specific risk factors and population groups in which vitamin D deficiency can be expected are: people who are rarely exposed to the sun, wear protective clothing and use sun protection products, people with dark skin, obese people, people taking medications that affect metabolism of vitamin D, hospitalized patients, elderly people and pregnant women. Also, low concentrations of vitamin D in the blood can be expected in numerous diseases, especially in osteoporosis, malabsorption of various etiologies, autoimmune diseases, acute and chronic kidney and liver diseases, neurological, endocrine and psychiatric diseases.

Daily requirements for vitamin D change with age and depend on physiological needs and the state of the organism. Concentrations of 25-hydroxycholecalciferol from 75 to 150

nmol/L are desirable in the population, and those lower than 50 nmol/L are insufficient for the health of the musculoskeletal system [26]. Considering all of the above, the European Food Safety Authority (EFSA) has recommended the optimal daily intake of vitamin D in food, namely for infants and newborn children 400 IU/day of vitamin D, for children over two years of age and adolescents 500 IU/day, while for the population aged 19 to 70 a daily dose of 600 IU/day is sufficient to achieve a vitamin D concentration of 50 nmol/L or above. For the population older than 70 years the recommended daily intake is 800 IU/day (20 μg) [2, 27]. Also, EFSA has determined an upper intake limit that is considered safe - 1000 IU/day for all infants up to 1 year of age, 2000 IU/day for children from 1 to 10 years of age and 4000 IU/day for children over 11 years of age and adults [28]. According to other sources, the maximum allowed daily intake of vitamin D for children is 1000 IU/day and for adults 2000 IU/day [29]. The stated limits refer to a healthy population. In disease states, they are much higher, as well as for patients with malabsorption syndrome, and they must be determined individually [30].

Thanks to the raising of awareness about the deficiency of vitamin D due to inadequate intake and its importance, there has been a significant increase in the consumption of FS containing vitamin D, so it is extremely important that such products on the market are of satisfactory quality, including the content of active components. Conditions that must be met by FS in order to be placed on the market are prescribed according to the Law on Food (Official Gazette of Republic of Srpska, No. 19/17) and the Rulebook on Food Supplements (Official Gazette of Republic of Srpska, No. 10/18). When labeling FS, it is necessary to state the declaration of nutritional value, which includes the amount recommended for daily use of vitamins and minerals or other active substances present in the product. According to the Rulebook on providing information to consumers about food (Official Gazette of Republic of Srpska, No. 9/18), the provision of information on food should be done in such a way that does not mislead the end consumer, which particularly refers to the characteristics of food, including the composition and quantities of food ingredients.

Research carried out in Slovenia showed that out of 24 tested FS containing vitamin D, two samples did not correspond to the prescribed permitted deviation of vitamin D from the LV, whereby one sample had a lower value than the labeled (36%), while the other contained a significantly higher amount than labeled (206%) [8]. Other studies showed that among examined samples, the measured value of vitamin D deviated by 8% to 177% from LV or 93% to 172% [9, 10].

The obtained results of our research show that there are certain minor differences in the determined content of vitamin D compared to the declared content, depending on the form of the FS itself. According to the Rulebook on Food and Health Claims (Official Gazette of Republic of Srpska, No. 19/18), the permitted deviation of the LV from the actual DV may be from -20% to +50% for vitamins in FS, i.e. the content must be within the range of 80% to 150% of the LV, including the measurement uncertainty.

During the analysis of FS in the form of tablets (Table 1), the DV of vitamin D was above the LV on the package itself in 14 samples (41.18%). The deviations ranged from +1.6% to +88.8%. In 20 samples (58.82%) the DV was below the declared value and the deviations ranged from -4% to -16%. It should be noted that only one sample (sample 15) was outside the permitted range according to the Regulation on Food and Health Claims, even when the measurement uncertainty was taken into account. This means that out of a total of 34 samples in tablet form 2.9% of the samples did not meet the requirements of the regulation or 2.0% of all examined samples.

During the analysis of products in the form of capsules (Table 2), in four samples (26.67%) the mean DV was above the LV of vitamin D on the packaging itself, with the range of deviations from +3.6% to +70%. In 11 samples (73.33%) the DV was below the declared value. The range of deviations was from -1.6% to -35.6%. One sample (sample 6) had a deviation of 70% higher than the LV and one sample (sample 7) had a deviation of 35.6% lower than the LV when mean values was taken into account. But if the measurement uncertainty for the DV was taken into account, the vitamin D content would met the requirements of the Rulebook on Food and Health Claims. In summary, the deviation of vitamin D content in nutritional supplements in the form of tablets and capsules amounts to -35.6% to +88.8%, i.e. the content is in the range of 64.4% to 188.8% of the declared value, which is close to the results obtained in EU countries [8, 9]. Only one sample does not meet the requirements of the legislation when measurement uncertainty is taken into account. The statistical analysis shows that there is no statistical significance in difference of DV compared to LV in examined samples (mean: 100.50%; Cl 95% -0.54 to 0.17; p=0.313 for tablets; mean: 98.02%; Cl 95% -3.00 to 0.42; p=0.127 for capsules).

## Conclusion

The use of FS has recently been widespread in the general population, especially vitamin D. The content of physiologically active components in FS is a very important segment of product quality, because an insufficient amount does not lead to satisfactory efficiency and misleads the consumer, while an excessive amount can endanger consumers' health due to inadequate dosage, which is why we conducted a pilot study related to vitamin D content in FS. Our pilot research showed that most of the samples were safe and of satisfactory quality in terms of composition. One sample did not have the appropriate content of vitamin D (it was higher than labeled) and it had no statistical significance. Considering that only one sample out of 49 samples (2,0%) did not meet the quality requirements prescribed by legal acts, the quality of the tested FS present on the market of Republic of Srpska could be considered satisfactory.

Given the fact that taking the FS can influence consumers' health, it is necessary to control the qualitative and quantitative composition continuously, especially the active ingredients. In general, the quality and safety of FS should be imperative for producers and subjects in the food business who put them on the market.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** This article does not contain any studies with human participants performed by any of the authors.

**Conflicts of interest.** The authors declare no conflict of interest.

**References:**


1. Kulda V. Metabolizmus vitaminu D [Vitamin D metabolism]. Vnitr Lek 2012;58(5):400–4.
2. EFSA PANEL ON DIETETIC PRODUCTS, NUTRITION AND ALLERGIES (NDA), et al. Dietary reference values for vitamin K. EFSA Journal 2017;15(5): e04780.
3. Holick MF. Sunlight, UV Radiation, Vitamin D, and Skin Cancer: How Much Sunlight Do We Need? Adv Exp Med Biol 2020;1268:19–36.
4. Guo J, Lovegrove JA, Givens DI. 25(OH)D3-enriched or fortified foods are more efficient at tackling inadequate vitamin D status than vitamin D3. Proc Nutr Soc 2018;77(3):282–91.
5. Benedik E. Sources of vitamin D for humans. Int J Vitam Nutr Res. 2022;92(2):118–25.
6. Borel P, Caillaud D, Cano NJ. Vitamin D bioavailability: state of the art. Crit Rev Food Sci Nutr 2015;55(9):1193-205.
7. Poniedziałek B, Niedzielski P, Kozak L, Rzymski P, Wachelka M, Rzymska I, et al. Monitoring of essential and toxic elements in multi-ingredient food supplements produced in European Union. J Consum Prot Food Saf 2018;13:41–8.
8. Žmitek K, Krušič S, Pravst I. An Approach to Investigate Content-Related Quality of Nutraceuticals Used by Slovenian Consumers: A Case Study with Folate and Vitamin D Supplements. Foods 2021;10(4):845.
9. Verkaik-Kloosterman J, Seves SM, Ocké MC. Vitamin D concentrations in fortified foods and dietary supplements intended for infants: Implications for vitamin D intake. Food Chem 2017;221:629–35.
10. Andrews KW, Pehrsson PR, Betz JM. Variability in Vitamin D Content Among Products for Multivitamin and Mineral Supplements. JAMA Intern Med 2013;173(18):1752–3.
11. Projekat SRPS EN 12821:2012 - Prehrambeni proizvodi - Određivanje vitamina D tečnom hromatografijom visoke performanse - Određivanje holekalciferola (D3) i ergokalciferola (D2). Institut za standardizaciju Srbije. Available from: https://iss.rs/sr_Cyrl/project/show/iss:proj:33686
12. Jelić D, Đermanović M. Instrumentalne metode. Banja Luka: Prirodno-matematički fakultet, 2020.
13. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev 2019;40(4):1109–51.
14. Arikoglu T, Akyilmaz E, Yildirim DD, Batmaz SB, Ulger ST, Aslan G, et al. The relation of innate and adaptive immunity with viral-induced acute asthma attacks: Focusing on IP-10 and cathelicidin. Allergol Immunopathol (Madr) 2017;45(2):160–8.
15. Vranešić Bender D, Giljević Z, Kušec V, Laktašić Žerjavić N, Bošnjak Pašić M, Vrdoljak E, et al. Smjernice za prevenciju, prepoznavanje i liječenje nedostatka vitamina D u odraslih. Lijec Vjesn 2016;138(5-6):121–32.
16. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res 2020;32(7):1195–8.
17. Chung C, Silwal P, Kim I, Modlin RL, Jo EK. Vitamin D-Cathelicidin Axis: at the Crossroads between Protective Immunity and Pathological Inflammation during Infection. Immune Netw 2020;20(2):e12.
18. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients 2020;12(4):988.
19. Hadizadeh F. Supplementation with vitamin D in the COVID-19 pandemic? Nutr Rev 2021;79(2):200–8.
20. McCullough PJ, Lehrer DS, Amend J. Daily oral dosing of vitamin D3 using 5000 TO 50,000 international units a day in long-term hospitalized patients: Insights from a seven year experience. J Steroid Biochem Mol Biol 2019;189:228–39.
21. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.
22. Holick MF. Vitamin D Is Not as Toxic as Was Once Thought: A Historical and an Up-to-Date Perspective. Mayo Clin Proc 2015;90(5):561–4.

23. Dzik KP, Kaczor JJ. Mechanisms of vitamin D on skeletal muscle function: oxidative stress, energy metabolism and anabolic state. Eur J Appl Physiol 2019;119(4):825–39.

24. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med 2019;380(1):33–44.

25. Cojic M, Kocic R, Klisic A, Kocic G. The Effects of Vitamin D Supplementation on Metabolic and Oxidative Stress Markers in Patients With Type 2 Diabetes: A 6-Month Follow Up Randomized Controlled Study. Front Endocrinol (Lausanne) 2021;12:610893.

26. Vranešić Bender D, Giljević Z, Kušec V, Laktašić Žerjavić N, Bošnjak Pašić M, Vrdoljak E, et al. Smjernice za prevenciju, prepoznavanje i liječenje nedostatka vitamina D u odraslih. Lijec Vjesn 2016;138:121–32.

27. Martínez Redondo I, García Romero R, Calmarza P, de Arriba Muñoz A, Martínez-Redondo D, Sanz Paris A. Déficit de vitamina D en una población pediátrica sana. La importancia de una adecuada profilaxis [Vitamin D insufficiency in a healthy pediatric population. The importance of early prophylaxis]. Nutr Hosp 2021;38(6):1155–61.

28. Agostoni C, Bresson JL, Tait SF, Flynn A, Golly I, Korhonen H, et al. Scientific Opinion on the Tolerable Upper Intake Level of Vitamin D. EFSA panel on dietetic products, nutrition and allergies (NDA). EFSA Journal 2012;10(7):2813.

29. Fuleihan GH, Bouillon R, Clarke B, Chakhtoura M, Cooper C, McClung M, et al. Serum 25-hydroxyvitamin D levels: variability, knowledge gaps, and the concept of a desirable range. J Bone Miner Res 2015;30(7):1119–33.

30. Fletcher J, Cooper SC, Ghosh S, Hewison M. The Role of Vitamin D in Inflammatory Bowel Disease: Mechanism to Management. Nutrients 2019;11(5):1019.

# Sadržajni kvalitet dodataka ishrani sa vitaminom D na tržištu Republike Srpske

Ljubica Bojanić[1,2], Mirjana Đermanović[1,2]

[1]JZU Institut za javno zdravstvo Republike Srpske, Banja Luka, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet Banja Luka, Medicinski fakultet, Katedra za farmakologiju, Banja Luka, Republika Srpska, Bosna i Hercegovina

**Uvod**. Vitamin D je liposolubilni vitamin koji ima mnogobrojne značajne uloge u ljudskom organizmu. Dnevne potrebe za vitaminom D zadovoljavaju se unosom hrane i izlaganjem sunčevoj svjetlosti. Visoka učestalost nedostatka vitamina D je javnozdravstveni problem koji se može korigovati dodacima ishrani, te danas postoji sve veće nastojanje u potrošnji dodataka. S obzirom da njihov kvalitet, uključujući i sadržaj aktivne komponente, zavisi od dobre proizvođačke prakse, koja nije strogo regulisana za proizvodnju dodataka ishrani, kao i formulacije, pakovanja i načina čuvanja, na tržištu se mogu naći dodaci ishrani različitog kvaliteta. Cilj našeg pilot istraživanja je bio ispitati usklađenost stvarno utvrđenog sadržaja vitamina D i deklarisanog sadržaja u 49 dodataka ishrani u obliku tableta i kapsula prisutnih na tržištu u Republici Srpskoj.

**Metod**. Određivanje sadržaja vitamina D je izvršeno tečnom hromatografijom visokih performansi (HPLC).

**Rezultati**. Opseg utvrđenog sadržaja vitamina D u odnosu na deklarisani sadržaj, izražen u procentima, bio je od 64,4% do 188,8%, pri čemu odstupanje nije statistički značajno (mean: 100,50%; Cl 95% -0,54 do 0,17; p=0,313 tablete; mean: 98,02%; Cl 95% -3,00 do 0,42; p=0,127 kapsule). Kada se uzme u obzir mjerna nesigurnost, samo jedan uzorak u obliku tableta je bio izvan zakonom dozvoljenog opsega (88,8% više od označenog).

**Zaključak**. Dakle, pokazano je da većina ispitanih proizvoda ima zadovoljavajući kvalitet u pogledu sadržaja vitamina D, ali je i dalje neophodno vršiti kontinuiranu kontrolu dodataka ishrani koji se nalaze na tržištu.

**Ključne riječi**: holekalciferol, dodaci ishrani, sigurnost, deklaracija, HPLC

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):40-52

UDK: 616.13-004.6:616.379-008.64
DOI: 10.59137/BII202301308S

*Original article*

# Dyslipidaemias in patients with diabetes mellitus type 2 - a cumulative impact on coronary artery disease occurence

**Kosana Stanetić[1,2], Marijana Radanović Knežević[3], Verica Petrović[1,2], Suzana Savić[1,2], Dijana Tomić Prodanović[4], Brankica Marković[1]**

[1]Primary Health Center Banja Luka, Republic of Srpska, Bosnia and Herzegovina
[2]University of Banja Luka, Faculty of Medicine, Department of Family Medicine, Republic of Srpska, Bosnia and Herzegovina
[3]Primary Health Center Prijedor, Republic of Srpska, Bosnia and Herzegovina
[4]Primary Health Center Teslić, Republic of Srpska, Bosnia and Herzegovina

Primljen – Received: 20/02/2023
Prihvaćen – Accepted: 26/04/2023

**Corresponding author:**
*Kosana Stanetić, Associate Professor*
*Sime Matavulja 4, 78 000 Banja Luka*
*kosana.stanetic@med.unibl.org*



**Summary**

**Introduction**. Cardiovascular complications are one of the leading causes of mortality releted to diabetes mellitus typ 2 (T2DM). Dyslipidemia is one of the associated risk factors for coronary artery disease (CAD) in patients with T2DM. The aims of our study were: to determine the characteristics of lipid disorders in persons with T2DM; to determine the cumulative impact of investigated risk factors (gender, age, genetic predisposition, smoking habits, diabetes mellitus, hypertension, obesity) for the occurence of the coronary artery disease; to determine the influence of lipid profile on coronary artery disease development.

**Methods**. A cross-sectional study was conducted in the Educative Center of the Primary Health Center Banja Luka in the period 01.11.2021–30.04.2022. Adult patients (≥18 years) with T2DM were recruited into the study. The data about socio-demographic characteristics, lifestyle and clinical factors were collected using structural questionnaire as a tool. For all subjects, anthropometric measurements, blood pressure readings, and laboratory findings (fasting blood glucose, HbA1c, lipid profile) were taken.

**Results**. A total of 221 patients with T2DM participated in the study, 52.03% were males. Hypertriglycerdidemia was found in 63.81% subjects, hypercholesterolemia in 56.60%, low HDL-cholesterol in 49.77% subjects and increased level of LDL-cholesterol in 39.37% subjects. Metabolic dyslipidemia (increased triglyceride levels and low HDL levels), representing the major predictor of CAD, was found in 35.29% subjects. Older age, physical inactivity, obesity, hypertension and high levels of fasting glucose in blood were significantly related to dyslipidaemia in patients with T2DM.

**Conclusion**. The representation of dyslipidemia in our subjects with T2DM is high, what increases the risk for coronary artery disease. Therefore, it is necessary not only to implement the therapy for glucoregulation, but also the secondary preventive measures for dyslipidemia, and that is the cardiovascular prevention.

**Key words:** dyslipidemia, diabetes mellitus, risk factors, coronary artery disease

## Introduction

Diabetes mellitus type 2 (T2DM) is a metabolic disorder characterized with chronic hyperglycemia and metabolic disorder of carbohydrates, lipids and proteins, as a consequence of impaired secretion of insulin, impaired insulin effect or both [1]. Cardiovascular complications are one of the leading causes of mortality releted to diabetes [2]. Dyslipidemia is one of the main risk factors for coronary artery disease (CAD) in patients with T2DM that is possible to modify [3].

In these patients, the most common determined pattern of dyslipidemia is hypertriglycerdiemia with low HDL-cholesterol and increased LDL-cholesterol levels [4–6]. Dyslipidemia within T2DM is a consequence of insulin resistence and increased free fetty acids levels due to insulin resistence. The etiology that leads to hypertriglyceridemia in patients with T2DM is directly related to hyperglycemia and insulin resistence, leading to hyperproduction of lipoproteins rich in triglycerids and their decreased clearence, and in some cases impaired postprandial metabolism of lipoproteins [7, 8].

The main risk factors for dyslipidemia are hypertension, high Body Mass Index (BMI), aging, physical inactivity and diabetes mellitus [9]. Therefore, it is importnat to identify the factors that can be related to dyslipidemia, to enable the preventive activities for dyslipidemia and CAD. Early diagnosis and classification of dyslipidemia in patients with T2DM can help clinicians to estimate risk factors for cardiovascular diseases in the future, and to undertake adequate maeasures [10, 11].

Globally, the prevention of dyslipidemia is gradually improving (≥ 80% do 90%) in developing countries such as Ethiopia [12], Kenya [13], Sri Lanka [14], India, Bangladesh [3]. The cardiovascular risk is considerably increased among patients with DM due to an existing dyslipidemia [7]. The studies reveal that approximately 70–80% diabetic patients is goinig to die due tu a cardiovascular disease [3, 15].

The aims of our study were: to determine the characteristics of lipid disorders in persons with T2DM; to determine the cumulative impact of investigated risk factors (gender, age, genetic predisposition, smoking habits, diabetes mellitus, hypertension, obesity) for the occurence of the coronary artery disease; to determine the influence of lipid profile on coronary artery disease development.

## Methods

A cross-sectional study was conducted in the Educative Center of the Primary Health Center Banja Luka (ECPM) in the period 01.11.2021–30.04.2022.

Adult patients (≥18 years) with T2DM treated at ECPM Banja Luka that regularly visit their family physician because of their chronic disease were recruited into the study.

The data about socio-demographic characteristics, lifestyle and clinical factors were collected using structural questionnaire as a tool, interviewing subjects „face to face".

For all subjects, anthropometric measurements (height and weight) were obtained using the Guidelines of the World Health Organization. BMI was calculated as a ratio of person's weight in kilograms and square of height in meters with the following categorisation: underweight (BMI <18.5), normal weight (BMI = 18.5–24.99 kg/m2), overweight (BMI = 25–29.99 kg/m2) and obesity (BMI ≥30 kg/m2).

The blood pressure readings were taken using mercury sphygmomanometer applied to the subjects' right upper arm in the seated position after 5 minutes rest. Hypertension was defined as systolic blood pressure (SBP ≥140 mmHg) or diastolic blood pressure (DBP ≥90 mmHg) in diabetic subjects.

Each subject of the study had a venipuncture for collecting 5 ml of venous blood sample, after overnight fasting.The samples were taken by skilful laboratory attendant according to the routine procedure. Dyslipidemia

was defined as the presence of one or more lipid profil disorders, such as: total cholesterol >5.2 mmol/l, LDL >1.4 mmol/l, triglycerides >1.7 mmol/l or HDL < 1mmol/l for male and <1.2 mmol for female [16].

*Statistical processing*

The data were processed and analyzed using software package SPSS (Statistical Package for the Social Sciences) version 26. For the analysis of tested variables, descriptive statistics and frequency tables were used. For the relation between dyslipidemia and independent variables, the bivariate and multivariate logistic regressions were used. The variables having a significant bivariate analysis at *p* value <0.25 were exported to the multivariate analysis. The multivariate logistic regression was used to identify the related risk factors for dyslipidemia. Statistical significance was defined at *p* value <0.05.

According to given *cut-off* values for each variable, we defined triglycerides-HDL status for the following four categories: (1) triglycerides in reference range, HDL in reference range; (2) increased levels of triglycerides, HDL in reference range; (3) triglycerides in reference range, decreased levels of HDL; and(4) increased levels of triglycerides, decreased levels of HDL. The fourth category, increased levels of triglycerides and decreased levels of HDL represents the category of so called methabolic dyslipidemia. Coxproportional hazards regression model was used to calculate Hazard Ratio (HR) for coronary artery disease in relation to the level of triglycerides and HDL cholesterol (triglycerides-HDL status). Regression models were adjusted for gender, smoking habits and physical activity.

## Results

A total of 221 patients with diabetes mellitus typ 2 (T2DM) were recruited into the study, 52.03% of them were males (n=115) and 47.97% females (n=106). The average age of subjects was 65.36±9.223, ranging from 36 to 90 years. The majority of subjects, 58.4% (n=129) were 50 to 69 years old. Also, the majority of subjects were married (84.6%), had secondary school education (64.3%) and were retired (51.6%). According to body mass index (BMI), the majority of patients 49.3% (n=109) were overweight, while 25.8% of them (n=57) were obese with average BMI 27.96±3.99, i.e. in a range from 20.00 do 38.80. Almost half of the subjects had increased blood pressure readings, 49.80% (n=110). The average fasting blood glucose levels were 9.39±3.17, and the highest level of fasting glucose was 23.94, while the avegarge value of $HgbA_{1c}$ was 7.73±5.02 (Table 1).

The average levels ± standard deviation (SD) for total cholesterol were 5.42±1.22, for triglycerides 2.34±1.38, for LDL cholesterol 3.45±3.93 and for HDL cholesterol 1.45±2.04 (Table 2).

The analysis of isolated components of dyslipidemia showed that hypertriglyceridemia was found in 63.81% subjects (n=141), hypercholesterolemia was found in 56.60% subjects (n=125), decreased HDL levels were found in 49.77% subjects (n=110) and increased LDL-cholesterol levels were found in 39.37% subjects (n=87).

Furthermore, metabolic dyslipidemia (increased triglyceride and decreased HDL levels) was found in 35.29% subjects (n=78), 17.19% males (n=38) and 18.10% females (n=40) (Table 2).

For each form of dyslipidemia, the greatest number of patients was in age group 50–69 years, and compared to other age groups was statisticaly significant for total cholesterol and HDL-cholesterol.

The bivariate analysis identified the variables- the candidates for the multivariate analysis about the correlation of socio-demographic and clinical characteristics of patients with dyslipidemia in a way that the p-value was less than 0.25%, and: male (COR (95%CI) = 0.65 (0.37, 1.12)), the level of education – primary

**Table 1.** Socio-demographic and clinical characteristics of patients

| Variables | Category | Frequences (Percentage) |
|---|---|---|
| **Gender** | Female | 106 (52.00) |
| | Male | 115 (48.00) |
| **Age groups** | 30–49<br>50–69 | 13 (5.90)<br>129 (58.40) |
| | ≥70 | 79 (35.70) |
| **Working status** | Employed<br>Unemployed | 95 (43.00)<br>12 (5.40) |
| | Retired | 114 (51.60) |
| **Marrital status** | Married | 187 (84.60) |
| | Unmarried | 8 (3.60) |
| | Devorved | 8 (3.60) |
| | Widowed person | 18 (8.10) |
| **Education** | Primary school | 40 (18.10) |
| | Secondary school | 142 (64.30) |
| | High school | 27 (12.20) |
| | Faculty | 12 (5.40) |
| **Smoking habits** | Yes | 36 (16.30) |
| | No<br>Former smoker | 174 (77.40)<br>14 (6.30) |
| **Duration of diabetes** | ≤ 4 years<br>5–9 years<br>10–14 years<br>15–20 years<br>≥20 years | 23 (10.40)<br>59 (26.70)<br>103 (46.60)<br>22 (10.00)<br>14 (6.30) |
| **Use of hipolipidemic drugs** | Yes | 118 (53.40) |
| | No | 103 (46.60) |
| **Physical activity** | Physically inactive<br>Moderately physically active<br>Intensively physically active | 60 (27.10)<br>158 (71.50)<br>3 (1.40) |
| **Body mass index (kg/m2)** | < 25.00 | 55 (24.90) |
| | 25.00–29.99 (overweight) | 109 (49.30) |
| | ≥30.00 (obesity) | 57 (25.80) |
| **Hypetension (mmHg)** | Yes | 110 (49.80) |
| | No | 111 (50.20) |
| **Fasting glucose (mmol/l)** | <6.1 mmol/l<br>≥6.1 mmol/l | 22 (10.00)<br>199 (90.00) |

**Table 2.** Lipid profile classification and gender distribution

| Lipidprofile | The average value in total sample±SD | Categories | n (%) | n (%) for male the average value for male ± SD | n (%) for female the average value for female ± SD | p-value*** |
|---|---|---|---|---|---|---|
| TC-total cholesterol (mmol/l) [min – max] | 5.42±1.22 [2.51 – 8.64] | <5.2 | 96 (43.44) | 61 (27.60)<br>54 (24.43)<br>3.74±1.31 | 35 (15.84)<br>71 (32.13)<br>3.92±1.25 | 0.305 |
| | | ≥5.2 | 125 (56.60) | | | |
| TG-triglycerides (mmol/l) [min – max] | 2.33±1.38 [0.58 – 8.80] | <1.7 | 80 (36.19) | 37 (16.74)<br>78 (35.29)<br>3.82±1.24 | 43 (19.46)<br>63 (28.51)<br>3.89±0.18 | 0.261 |
| | | ≥1.7 | 141 (63.81) | | | |
| LDL-cholesterol (mmol/l) [min – max] | 3.45±3.93 [0.12 – 24.40] | <1.4 | 134 (60.63) | 75 (33.94)<br>39 (17.65)<br>1.98±0.85 | 58 (26.24)<br>48 (21.72)<br>2.05±0.71 | **0.048** |
| | | ≥1.4 | 87 (39.37) | | | |
| HDL-cholesterol (mmol/l) [min – max] | 1.44±2.03 [0.63 – 26.00] | ≤1.0 | 110 (49.77) | 28 (12.67)*<br>87 (39.37)*<br>1.21±0.34 | 45 (20.36)**<br>61 (27.60)**<br>1.23±0.27 | 0.084 |
| | | >1.0 | 111 (50.23) | | | |

*Cut-off value for HDL cholesterol for male was set as 1.0 mmol/l

**Cut-off value for HDL cholesterol for female was set as 1.2 mmol/l

***p-value: independent t-test, significance at level p >0.05

school (COR (95% CI) = 0.22 (0.04, 1.14)), physical activity (COR (95% CI) 0.80 (0.44, 1.46)), the duration of diabetes 5–9 years (COR (95%CI) 0.22 (0.07–0.67)). The bivariate analysis of correlation between variables (linear regression), based on the results presented in table 3, shows the following:

The LDL cholesterol levels were moderately to highly related to (Pearson's coefficient, p >0.3) age, family history of dyslipidemia, body mass index, hypertension and fasting blood glucose levels. Also, based on the results obtained from COR (*Crude Odds Ratio*) the conclusion is that family history, body mass index, hypertension, fasting blood glucose, smoking habbits and marrital status were related to increased risk of dyslipidemia, with relatively narrow confidence interval (95% CI), indicating causal connection of above mentioned variables with the risk of dyslipdemia.

To asses the correlations and the adjusted odds ratio (AOR), the variables that had p- coefficient <0.25 were analyzed by multivariate analyzis. The obtained results are presented in table 4.

To identify the independent predictors of dyslipidemia in diabetic subjets, the multivariate regression analysis model was used. After adjusting certain variables, the following results were obtained. Patients with T2DM older than 50 years had 4 times greater risk of dyslipidemia. (AOR: 3.9, 95% CI: 1.6–9.48) compared to younger patients. Patients with diabetes that were physically inactive or moderately physically active had greater risk of dyslipidemia (AOR: 0.80 95% CI (0.48–1.32) compared

**Table 3.** The bivariate analysis of factors related to dyslipidemia

| Variables | Categories | Dyslipidemia | | COR (95% CI) | p-value |
|---|---|---|---|---|---|
| | | No | Yes | | |
| Age | 30–49 | 8 (3.62) | 5 (2.26) | – | – |
| | 50–69 | 79 (35.75) | 50 (22.62) | 0.40 (0.12–1.80) | 0.61 |
| | 70+ | 47 (21.27) | 22 (9.95) | 0.29 (0.09–1.00) | 0.78 |
| Gender | Muški | 76 (34.39) | 39 (13.12) | 0.65 (0.37–1.12) | **0.11** |
| | Ženski | 58 (26.24) | 46 (20.81) | – | |
| Marrital status | Oženjen/Udata | 117 (52.94) | 70 (31.67) | 1.34 (0.50–3.55) | 0.26 |
| | Neoženjen/Neudata | 3 (1.36) | 5 (2.26) | 0.75 (0.14–4.13) | 0.69 |
| | Razveden/a | 4 (1.81) | 4 (1.81) | 1.25 (0.24–6.63) | 0.39 |
| | Udovac/ica | 10 (4.52) | 8 (3.62) | – | |
| Education | Primary school | 21 (9.50) | 19 (8.60) | 0.22 (0.04–1.14) | **0.16** |
| | Secondary school | 85 (38.46) | 57 (25.79) | 0.30 (0.06–1.41) | **0.13** |
| | High school | 18 (8.14) | 9 (4.07) | 0.40 (0.07–2.23) | 0.38 |
| | faculty | 10 (4.52) | 2 (0.90) | – | – |
| Smoking habbits | No | 21 (9.50) | 15 (6.79) | – | – |
| | Yes | 104 (47.06) | 67 (30.32) | 1.11 (0.53– 2.31) | **0.11** |
| | Former smoker | 9 (4.07) | 5 (2.26) | 1.29 (0.36– 4.62) | **0.21** |
| Duration of diabetes | ≤4 years | 18 (8.14) | 5 (2.26) | – | – |
| | 5–9 years | 26 (11.76) | 33 (14.93) | 0.22 (0.07– 0.67) | **0.21** |
| | 10–14 years | 66 (29.86) | 37 (16.74) | 0.50 (0.17– 1.44) | 0.29 |
| | 15–18 years | 16 (7.24) | 6 (2.71) | 1.07 (0.27– 4.17) | 0.28 |
| | ≥20 years | 7 (3.17) | 5 (2.26) | 0.39 (0.09– 1.77) | 0.36 |
| Family history of dyslipdemia | Yes | 108 (48.87) | 73 (33.03) | 1.26 (0.61– 2.56) | 0.55 |
| | No | 26 (11.76) | 14 (6.33) | – | – |
| Physical activity | Yes | 100 (45.25) | 61 (27.60) | – | – |
| | No | 34 (15.38) | 26 (11.76) | 0.80 (0.44–1.46) | **0.21** |
| Body mass index | <25 | 29 (13.12) | 26 (11.76) | – | – |
| | 25–29.99 | 71 (32.13) | 33 (14.93) | 1.68 (0.87–3.24) | 0.90 |
| | ≥30 | 34 (15.38) | 23 (10.41) | 1.33 (0.63–2.88) | 0.46 |
| Hypertension | Da | 67 (30.32) | 43 (19.46) | 1.02 (0.60–1.76) | 0.57 |
| | Ne | 67 (30.32) | 44 (19.91) | – | – |
| Fasting blood glucose | <6.1 mmol/l | 13 (5.88) | 9 (4.07) | – | – |
| | ≥6.1 mmol/l | 121 (54.75) | 78 (35.29) | 1.07 (0.44–2.63) | 0.71 |

**Comments**: the correlation between variables does not exist. The variables-candidates for multivariate analyzis p-value <0.25.

COR, *crude odds ratio*, crude ratio of chances (risk index) (COR >1 - indicates that exposition is related to higher risk; COR <1 - exposition is related to less risk)

95% CI, Confidence Interval (the more narrow the interval is, the more precise COR value is and vice versa)

**Table 4.** The analysis of correlation of lipid profile and predictors for CVD in a group of all subjects

| Predictors | TC-total cholesterol | | TG-Triglycerides | | LDL-cholesterol | | HDL-cholesterol | |
|---|---|---|---|---|---|---|---|---|
| | r | p | r | p | r | p | r | p |
| Age | 0.51 | 0.42 | 0.08 | 0.17 | 0.07 | 0.24 | −0.06 | 0.30 |
| Gender | −0.07 | 0.22 | −0.06 | 0.28 | −0.07 | 0.26 | 0.004 | **0.94** |
| Smoking habbits | 0.008 | **0.89** | 0.005 | **0.93** | −0.07 | **0.91** | 0.30 | 0.64 |
| Hypolipidemic drugs | −0.29 | 0.64 | 0.14 | 0.02 | −0.08 | 0.9 | −0.12 | 0.05 |
| Physical activity | −0.051 | 0.42 | −0.06 | 0.33 | −0.11 | 0.07 | 0.07 | 0.26 |
| BMI | 0.11 | 0.06 | 0.09 | 0.12 | 0.01 | 0.81 | −0.04 | 0.47 |
| Body weight | 0.08 | 0.17 | 0.04 | 0.46 | −0.07 | 0.21 | 0.07 | 0.24 |
| Hypertension | 0.15 | 0.01 | 0.2 | 0.001 | 0.25 | <0.001 | 0.01 | **0.84** |
| Fastin blood glucose | 0.15 | 0.013 | 0.24 | <0.001 | 0.09 | 0.14 | −0.03 | 0.58 |

**Comment**: r - Pearson's correlation coefficient; p - p-value for correlation

**Table 5.** Multivariate analysis of factors releted to dyslipidemia

| Variables | Categories | Dyslipidemia | | AOR (95% CI) | p-value |
|---|---|---|---|---|---|
| | | No | Yes | | |
| Gender | Male | 76 (34.39) | 39 (13.12) | – | – |
| | Female | 58 (26.24) | 46 (20.81) | 1.55 (0.98 – 2.45) | **0.850** |
| Physical activity | Yes | 100 (45.25) | 61 (27.60) | – | – |
| | No | 34 (15.38) | 26 (11.76) | 0.80 (0.48–1.32) | **0.505** |
| Smoking habbits | No | 21 (9.50) | 15 (6.79) | – | – |
| | Yes | 104 (47.06) | 67 (30.32) | 0.9 (0.49–1.66) | 0.097 |
| | Former | 9 (4.07) | 5(2.26) | 0.78 (0.27–2.27) | **- 0.011** |

**Comment**: AOR - Adjusted Odd Ratio; p-value - Pearson's correlation coefficient

to physically active patients. Overweight and obese patients with T2DM were more likely for dyslipidemia onset (AOR: 5.6, 95% CI: 1.3–23.9) compared to patients with normal weight. Patients with hypertension and T2DM had greater risk for dyslipidemia onset compared to patients with normal range of blood pressure (AOR: 2.65, 95% CI: 1.4–4.9). Patients with diabetes and high fasting blood glucose levels had 3 times greater risk for dyslipidemia. (AOR: 3.1, 95% CI: 1.3–7.2) compared to patients with lower fasting blood glucose levels (Table 4).

The results of the correlation between lipid profil and sociodemographic health-related variables are presented in table 4. There is a signifficant correlation between HDL-cholesterol and gender (p >0.70) and hypertension; between LDL-cholesterol and smoking habbits, between total cholesterol and smoking habbits, between total cholesterol and triglyceride levels. The negative correlation was observed for the use of all hypolipidemic drugs and lipid fractions except triglycerides, as well as for physical activity and lipid fractions except HDL-cholesterol.

Table 5 shows that females with T2DM more often develop LDL-dyslipidemia. Also, the degree of correlation between LDL-dyslipidemia and gender (female) is very high (p > 0.7), while the degree of correlation for physical (in)activity is moderate (p > 0.5). Active smokers and dyslipidemia do not have a significant correlation, while that correlation for former smokers is negative, what indicates that negative effects of smoking on lipid profile are reversible.

The characteristics of subjects related to cardiovascular diseases obtained from medical history were analyzed. Approximately 17.19% of subjects had HDL and triglyceride levels in a reference range (n=38), 36.65% had high levels of triglycerides and HDL levels in a reference range (n=81), and 6.3..3% of subjects had triglyceride levels in a reference range and decreased levels of HDL (n=14), while 35.29% of subjects had incrased levels of triglycerides and decreased levels of HDL (metabolicdyslipidemia, n=78). Analysis showed that metabolic dyslipidemia was more often in female, in persons where duration of T2DM was longer than five years, in smokers (active), in persons with increased waist circumference, in persons with poor regulation of blood glucose levels estimated by $HbA_{1c}$.

The stratified analysis based on LDL-cholesterol levels was conducted. A predictive value of triglycerides-HDL-total cholesterol profile for coronary artery disease was tested. The analysis showed that the risk for coronary artery disease was greater in patients with decreased HDL-cholesterol with statistical significance ($p < 0.05$) (Table 6).

**Table 6.** Hazard ratio for coronary artery disease according to triglycerides-HDL-cholesterol ratio

| TG-HDL status | HR (95% CI) | Coronary artery disease P value |
|---|---|---|
| Normal TG-HDL | – | – |
| Increased TG, normal HDL | 1.21 (0.54–2.70) | 0.642 |
| Normal TG, low HDL | **1.98 (1.08–3.62)** | **0.027** |
| Increased TG, low HDL | **2.06 (1.20–3.54)** | **0.008** |

Hazard ratio (HR) was calculated using Cox analyzisadjusted for gender, age, BMI, smoking habits, blood preassure readings, use of antihypertensive drugs, HbA1C, duration of diabetes

**Table 7.** Hazard ratio for macrovascular complications in total sample (n=221)

| | HR (95% CI) | Coronary artery disease P value |
|---|---|---|
| **HDL-C** | | |
| Normal HDL-C | – | – |
| Low HDL-C | 1.25 (1.05–1.47) | **0.010** |
| **TG** | | |
| Normal TG | – | – |
| Increased TG | 1.20 (1.02–1.40) | **0.028** |
| **TG-HDL status** | | |
| Normal TG-HDL | – | – |
| Increased TG, normal HDL | 1.13 (0.85–1.50) | 0.396 |
| Normal TG, low HDL | 1.19 (0.94–1.52) | 0.155 |
| Increased TG, low HDL | 1.37 (1.11–1.69) | **0.004** |

Hazard ratio (HR) was calculated using Cox analyzis adjusted for gender, age, BMI, smoking habbits, blood preassure readings, use of antihypertensive drugs, HbA1C, duration of diabetes

HR results for macrovascular complications in total sample according to HDL-cholesterol and triglycerides ratio are shown in table 7. The obtained results showed that the risk of macrovascular complications, precisely coronary macrovascular complications, was increased in persons with low HDL-cholesterol and increased triglycerides levels, with statistical significance ($p < 0.05$). Also, that risk was increased in persons with so called metabolic dyslipidemia, precisely increased triglycerides levels and low HDL-cholesterol.

## Discussion

Dyslipidemia is one of the leading, but modifying risk factors for coronary artery disease in persons with T2DM, and therefore, it is one of the leading causes of morbidity and mortality in these patients [16]. Furthermore, it is important to identify factors that are potentially related to dyslipidemia, to control this condition and reduce the incidence of coronary artery disease [17].

The prevalence of dyslipidemia in our study was 63.8%. Dyslipidemia was present in the greatest percentage in males, in patients 50 to 69 years old, in persons with secondary school education, moderately physically active patients, and overweight patients. The independent predictors of dyslipidemia in our study were older age, physical inactivity, obesity and increased fasting blood glucose levels.

Socio-demographic factors have a role in dyslipidemia onset in patients with diabetes. In our study, dyslipidemia is significantly related to older age. Such findings are consistent with the results of the studies conducted in Ethiopia [12], China [17] and Thailand [18]. The total prevalence of dyslipidemia in this study can be compared to the results of the studies conducted in Ethiopia (the prevalence of dyslipidemia was 65.5%) [12] and Nigeria (the prevalence of dyslipidemia was 69.3%) [16]. The prevalence of dyslipidemia itself varies from region to region, what arises from differences in diet and genetic predisposition of population. Also, the differences in a pattern of dyslipdemia reported in patients with T2DM could be the consequence of differences in cut-off values of lipid profile in some studies, cultural factors, and lifestyle in population.

Our study showed a statistically significant relation between dyslipidemia and physical (in) activity. Similar findings were reported in the studies conducted in China [17] and Kenya [13].

In this study, dyslipidemia was significantly related to obesity. The overweight and obese subjects were more likely to develop dyslipidemia compared to subjects with BMI <25.00 kg/m2. Similar findings were reported in Ethiopia [12], Kenya [13] and China [17].

Dyslipidemia in this study was also significantly related to hypertension. The patients with hypertension were 2.65 times likely to develop dyslipidemia compared to persons whose blood pressure readings were in normal range. This result is in accordance with the results of the studies conducted in Ethiopia [12] and Nepal [18].

Besides the prevalence of dyslipidemia, this study also showed potential factors that could increase the risk of dyslipidemia in patients with T2DM. The study showed that female patients with diabetes were more likely to develop dyslipidemia than male patients. Similar studies [12, 13, 19, 20] also showed that female gender was significantly more related to dyslipidemia. Older age was in a positive correlation with dyslipidemia, and that was also the finding of other studies [19, 20]. Our subjects with T2DM older than 50 years had 4 times greater risk of dyslipidemia (AOR: 3.9, 95% CI: 1.6–9.48) compared to younger patients. Although there is no evidence that age is directly related to lipid profile, it is an assumption that inheritable genetic characteristics, insulin resistance and degenerative processes can be related to ageing [21]. Other studies reported that older age was related to dyslipidemia in

persons with T2DM due to exhasution of organism and the insufficient physical activity [9]. Our study showed that the obesity was significantly related to dyslipidemia in patients with T2DM. Overweight and obese patients with T2DM were more likely to develop dyslipidemia (AOR: 5.6, 95% CI: 1.3–23.9) when compared to patients with normal weight. Other studies reported similar results, where dyslipidemia was more present among obese patients with T2DM compared to patients with BMI in normal range [10, 15].

This study emphasized that hypertension was significantly related to the prevalence of dyslipidemia in subjects with diabetes, which was similar to the results of other studies [8]. Patients with hypertension and T2DM had higher risk for the development of dyslipidemia, when compared to patients whose blood pressure was in normal range. This study also reported that physical inactivity was significantly related to dyslipidemia among patients with T2DM. Physically inactive or moderately physically active subjects with diabetes had higher risk for dyslipidemia onset (AOR: 0.80 95%CI (0.48–1.32)) when compared to physically active subjects. This finding is in accordance with the findings of other studies conducted in Ethiopia [12], China [17] and Thailand [18].

Several new studies [19, 20] reported that insufficient physical activity and unhealthy diet could potentially lead to increased levels of blood glucose, leading to dyslipidemia onset in persons with T2DM. Our study also showed that patients with diabetes with higher degree of hyperglycemia had 3 times greater risk for dyslipidemia onset (AOR: 3.1, 95% CI: 1.3–7.2) when compared to patients with lower levels of blood glucose. Based on the obtained results, the conclusion is that regular physical activity can help patients with diabetes to have better control of glycemia and lipid profile.

The obtained results showed that present smoking habits were significantly related to the risk of dyslipidemia onset in patients with diabetes. LDL-cholesterol levels had high degree of correlation with smoking habits, total cholesterol and triglyceride levels. This is in accordance with the results of similar studies where the correlation between dyslipidemia and smoking was proven [21–23].

The results of our research showed that the existence of metabolic dyslipidemia (high triglycerides, low HDL-cholesterol) is a significant predictor of coronary heart disease. A study conducted in the United States of America (USA) reached similar results, showing that metabolic dyslipidemia was a high risk for coronary heart disease and an acute coronary event, but not for stroke [24].

In the countries of the Balkan Peninsula and North Macedonia, there is a continuous increase in the number of patients with T2DM. North Macedonia, like most of the countries of the Balkan Peninsula, has a low or middle income, and in all countries it is necessary to work on educating the population about changing the way of eating in order to reduce the risk of contracting T2DM, achieve good glycoregulation, achieve the target values of components from the lipid profile and control of metabolic syndrome. The Mediterranean diet, which has proven to be effective over the last eight decades, is recommended as the best diet to prevent these metabolic disorders [25].

This study shows that the role of a family physician as a "gatekeeper" in health system is not only to awake patients, but also health care professionals that diabetes mellitus typ 2 is a complex metabolic disorder characterized by hyperglycemia and lipid profile disorder. Therefore, it is essential for patients with T2DM not only to carry out the treatment for glucoregulation, but also to carry out the secondary prevention of dyslipidemia, what prevents cardiovascular diseases. The imperative of therapy protocol for T2DM is screening and following up of lipid profile and lipid profile regulation.

## Conclusion

The total prevalence of dyslipidemia among subjects of this study was 63.8%. Dyslipidemia was in the greatest percentage present in male, 50 to 69 years old, with secondary school education, moderately physically active and overweight patients. Hypertriglyceridemia was found in 63.81% subjects, hypercholesterolemia in 56.60%, decreased HDL-cholesterol in 49.77%, and increased LDL-cholesterol in 39.37% subjects. Metabolic dyslipidemia (increased triglyceride and decreased HDL levels) was found in 35.29% subjects. Older age, physical inactivity, obesity, hypertension and increased levels of blood glucose were significantly related to dyslipidemia in patients with T2DM. The results of our study indicate that the risk for macrovascular complications, including coronary artery disease, is increased in persons with metabolic dyslipidemia (decreased HDL-cholesterol and increased triglyceride levels). Family physicians have an important role in regular screening of lipid disorders in patients with T2DM, and pharmacological treatment of these disorders.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** The Ethics Committee of the University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

**Conflicts of interest.** The authors declare no conflict of interest.

### References:

1. World health organization. Global Report on Diabetes. Geneva; 2020. Available from:https://apps.who.int/iris/bitstream/handle/10665/204871/9?sequence=1 [Accessed October 26, 2022]
2. Mash F, Baigent C, Catapano AL,Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111–88.
3. International Diabetes Federation. IDF Diabetes Atlas Ninth Edition 2019. Available from: https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(20)30887-1/fulltext [Accessed October 10, 2022]
4. Daya R, Bayat Z, Raal FJ. Prevalence and pattern of dyslipidemia in type 2 diabetes mellitus patients at a tertiary care hospital. JEMDSA 2017;22(3):31–35.
5. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. Endocr Pract 2017;23(Suppl 2):1-87.
6. Centers for Disease Control and Prevention. National Center for Health Statistics. About Underlying Cause of Death 1999–2019; CDC WONDER Online Database. Available from:http://wonder.cdc.gov/ucd-icd10.html [Accessed Mart 17th, 2023]
7. Hirano T. Pathophysiology of diabetic dyslipidemia. J Atheroscler Thromb 2018;25(9):771–782.

8. Schofield JD, Liu Y, Rao-Balakrishna P, Malik RA, Soran H. Diabetes dyslipidemia. Diabetes Ther 2016;7(2):203–19.
9. Kiplagat SV, Lydia K, Jemimah K, Drusilla M. Prevalence of dyslipidemia and the associated factors among type 2 diabetes patients in Turbo Subcounty, Kenya. J Endocrinol Diabetes 2017;4(5):1–9.
10. 2008-2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases http://www.sefap.it/servizi_lineeguida_200903/Actionplan-PC-NCD-2008.pdf [Accessed November 14, 2022]
11. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2021. Diabetes Care2021;44(Suppl 1):S73–S84.
12. Solomon T, Fessaye A. Cardiovascular disease among diabetic patients in southwest Ethiopia. Ethiop J Health Sci 2010;20(2):122–8.
13. Kiplagat SV, Lydia K, Jemimah K, Drusilla M. Prevalence of dyslipidemia, and the associated factors among type 2 diabetes patients in Turbo Sub-County, Kenya. J Endocrinol Diabetes 2017;4(5):1–9.
14. Salim A, Ghouth B, Bakarman AA, Alaidroos HA, Alajely MH. Prevalence and patterns of dyslipidemia among type 2 diabetes mellitus patients in Mukalla City, Yemen, in 2017. J Community Med Public Health 2019;6(2):100048.
15. Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. Front Cardiovasc Med 2018;5:135.
16. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies. Eur Heart J 2021; 42:3227-37. https://www.eas-society.org/page/dyslipidemia_guide_2019[Accessed October 15, 2021].
17. Qi L, Ding X, Tang W, Li Q, Mao D, Wang Y. Prevalence and risk factors associated with dyslipidemia in China. Int J Environ Res Public Health 2015;60(10):13455–65.
18. Pokharel DR, Khadka D, Sigdel M, YadavNK , Acharya S, Kafle R, et al. Prevalence and pattern of dyslipidemia in Nepalese individuals with type 2 diabetes. BMC Res Notes 2017;10(1):146.
19. 9. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes 2018. Diabetes Care 2018;41(Suppl 1):S86–S104.
20. Bekele S, Yohannes T, Mohammed AE. Dyslipidemia and associated factors among diabetic patients attending general hospital in southern nations, nationalities, and people's region. Diabetes Metab Syndr Obes 2017;10:265–71.
21. Cefalu WT, Bray GA, Home PD, Garvey WT, Klein S, Pi-Sunyer FX, et all. Advancesin the Science, Treatment, and Prevention of the Disease of Obesity: Ref lections Froma Diabetes Care Editors'Expert Forum. Diabetes Care 2015;38(8):1567–82.
22. Bello-Ovosi BO, Ovosi JO, Ogunsina MA, Asuke S, Ibrahim MS. Prevalence and pattern of dyslipidemia in patients with type 2 diabetes mellitus in Zaria, Northwestern Nigeria. Pan Afr Med J 2019;34:123.
23. Narindrarangkura P, Bosl W, Rangsin R, Hatthachote P. Prevalence of dyslipidemia associated with complications in diabetic patients: a nationwide study in Thailand. Lipids Health Dis 2019;18(1):90.
24. Kaze AD, Santhanam P, Musani S, Ahima R, Echouffo-Tcheugui JB. Metabolic Dyslipidemia AND Cardiovascular Outcomes in Type 2 Diabetes Mellitus: Findings From the Look AHEAD Study. J Am Heart Assoc 2021;10(7):e016947.
25. Milenković T, Bozhinovska N, MacutDj, Bjekić-Macut J, Rahelić D, Asimi ZV, et al. Mediterranean Diet and Type 2 Diabetes Mellitus: A Perpetual Inspiration for the Scientific World. A Review. Nutrients 2021;13(4):1307.

# Dislipidemije kod pacijenata sa dijabetes melitusom tipa 2 - kumulativni uticaj na pojavu koronarne arterijske bolesti

Kosana Stanetić[1,2], Marijana Radanović Knežević[3], Verica Petrović[1,2], Suzana Savić[1,2], Dijana Tomić Prodanović[4], Brankica Marković[1]

[1]Dom zdravlja, Banja Luka, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet u Banjoj Luci, Medicinski fakultet, Odjeljenje porodične medicine, Republika Srpska, Bosna i Hercegovina

[3]Dom zdravlja, Prijedor, Republika Srpska, Bosna i Hercegovina

[4]Dom zdravlja, Teslić, Republika Srpska, Bosna i Hercegovina

**Uvod**. Kardiovaskularne komplikacije su jedan od vodećih uzroka smrtnosti vezanih za dijabetes melitus tipa 2 (T2DM). Dislipidemija je jedan od pridruženih faktora rizika za koronarnu bolest srca (KBS) kod pacijenata sa T2DM. Ciljevi našeg istraživanja su: utvrditi karakteristike lipidnih poremećaja kod osoba sa T2DM; utvrditi kumulativni uticaj ispitivanih faktora rizika (pol, dob, genetska predispozicija, pušački status, dijabetes melitus, hipertenzija, gojaznost) za nastanak koronarne bolesti srca; utvrditi uticaj lipidnog statusa na razvoj koronarne bolesti srca.

**Metode**. U Edukativnom centru porodične medicine (ECPM), Doma zdravlja Banja Luka, provedena je studija presjeka u periodu od 1.11.2021. do 30.4.2022. godine. U istraživanje su bili uključeni odrasli pacijenti (≥ 18 godina) oboljeli od T2DM. Podaci o socio-demografskim karakteristikama, životnim navikama i kliničkim faktorima su prikupljani uz pomoć strukturisanog upitnika. Svim pacijentima su izvršena antropometrijska mjerenja, izmjeren krvni pritisak i urađene laboratorijske analize (ŠUK, HbA1c, lipidni profil).

**Rezultati**. U studiji je učestvovao 221 pacijent sa T2DM, 52,03% muškog pola. Hipertrigliceridemija je utvrđena kod 63,81% ispitanika, hiperholesterolemija kod 56,60%, snižen HDL-holesterol kod 49,77% ispitanika i povišen LDL-holesterol kod 39,37% ispitanika. Metabolička dislipidemija (povišeni trigliceridi i snižen HDL) je utvrđena kod 35,29% ispitanika i predstvalja najveći prediktor za KBS. Starija životna dob, fizička neaktivnost, gojaznost, hipertenzija i visok nivo glukoze u krvi su bili značajno povezani sa dislipidemijom među oboljelim od T2DM.

**Zaključak**. Zastupljenost dislipidemije kod naših ispitanika sa T2DM je visoka, što povećava rizik za koronarnu bolest srca. Zbog toga je neophodno provoditi, osim terapije za glikoregulaciju, i sekundarnu prevenciju dislipidemije čime se vrši i prevencija kardiovaskularnih oboljenja.

**Ključne riječi**: dislipidemija, dijabetes melitus, riziko faktori, koronarna bolest srca

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):53–63

UDK: 616.89-008.434.5-053.4
DOI: 10.59137/BII202301301T

*Original article*

# The relationship between risk factors and speech-language disorders in children aged four to six years

**Jelena Tešić[1], Mile Vuković[2], Mirjana Korlaet[3], Sofija Vuković[4]**

[1]Elementary school „Vuk Karadžić" Bijeljina, Republic of Srpska, Bosnia and Herzegovina

[2]University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia

[3]Service Center "Give us a chance - Stars", Banja Luka, Republic of Srpska, Bosnia and Herzegovina

[4]Elementary school „Skender Kulenović" Sarajevo, Bosnia and Herzegovina

Primljen – Received: 11/09/2022
Prihvaćen – Accepted: 07/03/2023

**Corresponding author:**
*Jelena Tešić, Bachelor of Speech and Language Pathology*
*Hajduk Veljkova 8A, 76300 Bijeljina*
*jelena.jovanovic149@yahoo.com*



**Summary**

**Introduction**. In recent years, more and more attention has been paid to the research of factors that can potentially contribute to the development of speech and language impairment. It is believed that the results of these studies can contribute to better planning and implementation of early intervention in the field of speech and language in children. The aim of this research is to determine the influence of risk factors on the appearance of language disorders in children.

**Methods**. A total of 97 children aged four to six who participated in the research were divided into two groups. The first group consisted of 54 respondents with a speech and language impairment, and the second group consisted of 43 respondents with typical language development. In both groups, 70 children with risk factors were found. All children with speech and language impairment had some of the risk factors (diseases of mothers during pregnancy, medication during pregnancy, premature labor, caesarean section, asphyxia, disease of newborns, seizures, third tonsil, shortened frenulum, ear infection), while in the group of children with typical language development, 16 respondents had risk factors. The Global Articulation Test, Vocabulary Test, and Comic Story Test were used to assess speech and language abilities. Data on risk factors were obtained on the basis of a survey for parents, which was constructed for the purposes of this research.

**Results.** The results showed that children with risk factors had significantly worse results on the articulation test and the vocabulary test compared to children without risk factors. The results obtained on the Strip Story test did not show that these two groups differ significantly in terms of the number of words produced, the number of sentences and the grammatical structure of the sentence.

**Conclusion.** In general, the results of this research showed a significant connection between risk factors and speech and language disorder in children.

**Key words:** risk factors, speech-language impairment, articulation, vocabulary, syntax

## Introduction

The development of speech and language is a process in which two basic phases can be distinguished: prelinguistic and linguistic [1]. Crying and screaming represent the first vocalizations of the newborn, which is the beginning of the prelinguistic phase and lasts until the conscious use of the first meaningful word. On average, speaking occurs around the twelfth month of

a child's life, when the first meaningful word appears [1, 2]. With the appearance of the first word, the linguistic phase begins, which lasts until complete mastery of the phonology, grammar and syntax of the native language [1, 3]. Phonological development ends with the acquisition of the ability to automatically and correctly use phonemes in spontaneous speech, around the seventh year of the child's life [4]. The lexical-semantic development of the language begins with the appearance and use of the first word with meaning. The further development of lexical-semantic abilities is reflected in the constant increase in the number of words in speech as well as in the understanding of their meaning. It is estimated that the child aged 18 months speaks on average 50 words, while at the age of five the child should produce between 1800 and 2200 words. Semantic development represents much more than a simple increase in vocabulary. In this process, children have to discover the meaning of words and master the meaning relationships between words. In this way, a mental lexicon is formed in which all the knowledge about the words of the language used by the speaker is stored. The mental lexicon enables the speaker to communicate smoothly, to speak quickly and easily, to understand and remember words, but also to build new words and to integrate linguistic knowledge into the knowledge of the world around him [1, 2].

The development of speech and language is conditioned by biological, psychological and environmental factors. Unfavorable factors of language development can lead to various forms of speech and language pathology. In some disorders of language development, such as developmental language disorder (DLD), for example, there is no clear cause. In other words, children with DLD are delayed in language development and exhibit various pathological patterns, even though they do not have neurological damage, impairment of hearing and vision, or difficulties in intellectual development. In view of this, in recent years, there has been a growing awareness of the importance of research into the influence of various risk factors (prenatal, perinatal and early postnatal) on language development in children.

Disorders in the development of speech and language are characterized by damage to the typical patterns of acquisition of language structure. This disorder belongs to the group of developmental language disorders (ICD-10) and is denoted by the term developmental language disorder. In the past, this disorder was denoted by the term developmental dysphasia, and until recently by the term Specific language disorder (SLD). In children with a developmental language disorder, there is a significant delay in speaking as well as disorders in the development of certain elements of the language structure. The disorder is manifested by deficits in phonology, grammar and semantics [5].

Some empirical data show that premature birth, asphyxia or low body mass can lead to disorders in language development [1, 6]. Other authors did not establish a connection between these factors and the appearance of speech-language disorders [7]. In other studies of this type, it was determined that risk factors (low birth weight, low Apgar score, maternal age, newborn diseases, length of pregnancy) were more often observed in children with language disorders than in children with typical language development [7]. Language development in children was not affected even by frequent middle ear infections, but the occurrence of aphasia in children is often associated with significant illnesses of the mother during pregnancy, exposure to toxic substances, asphyxia of the newborn, epilepsy and brain inflammation or injury [1, 8]. A further review of the literature shows that in the group of children with disorders of speech and language development, there is a significant number of children who were born by caesarean section [9]. Furthermore, unfavorable environmental factors, including a larger number of children in the family, lower edu-

cational status of the mother and growing up with a single parent, were also more frequently recorded in children with speech and language disorders compared to children with typical language development [1, 7].

Given the paucity of information, the relationship between language development and risk factors in children is a topic that has recently attracted increasing attention from researchers. The discovery of risk factors is also important for establishing a database and linking certain risk factors with the characteristics of speech and language disorders. Determining the connection between certain risk factors and the occurrence of speech-language disorders in children would contribute to the initiation of early speech therapy intervention. Early intervention in the area of speech and language in children with risk factors could prevent the occurrence of some disorders in speech and language development or at least alleviate the severity of their manifestation. With the intention of contributing to this topic, the goal of our research was to determine the influence of risk factors on the occurrence of language disorders in children aged four to six years.

## Method

The sample consisted of 97 children (48 boys and 49 girls) aged from four to six years. At the time of the investigation, the children attended the "Čika Jova Zmaj" preschool in Bijeljina. The clinical group consisted of 54 subjects with the disorder in speech-language development, while the control group consisted of 43 subjects with typical language development. A total of 70 parents from both groups of respondents stated that they had some of the risk factors associated with the appearance of speech-language disorders

**Table 1.** Distribution of the total sample according to the occurrence of risk factors

| | | number (%) |
|---|---|---|
| Prenatal risk factors | Medicines | 9 (9.28) |
| | Chronic illness of the mother | 4 (4.12) |
| | Rh incompatibility | 3 (3.09) |
| | Preeclampsia | 2 (2.06) |
| | Without prenatal risk factors | 79 (81.44) |
| Perinatal risk factors | Caesarean section | 22 (22.68) |
| | Vacuum extractor | 3 (3.09) |
| | Asphyxia | 6 (6.18) |
| | Premature birth | 12 (12.37) |
| | Without perinatal risk factors | 54 (55.67) |
| Postnatal risk factors | Epilepsy | 5 (5.15) |
| | Infections | 6 (6.18) |
| | Bilingual family | 1 (1.03) |
| | Third tonsil | 4 (4.12) |
| | Shortened frenulum | 4 (4.12) |
| | Without postnatal risk factors | 77 (79.38) |

(Table 1). Risk factors were more prevalent in the group of children with the disorder in speech and language development (N = 54), while the presence of risk factors was noted in 16 children with typical language development. The most prevalent risk factors were from the group of perinatal risk factors. The parents most often stated that the child was born by caesarean section, and the least common was that a vacuum extractor was used during delivery. In the group of postnatal risk factors, infections immediately after birth were most often cited, and growing up in a bilingual family was the least common. Prenatal risk factors were the least represented, and parents most often stated that the mothers took some medication during pregnancy, while preeclampsia was the least frequently mentioned as a prenatal risk factor.

Firstly, 245 children aged between four to six with preserved intellectual abilities, normal sense of hearing and sense of sight, without severe motor and physical impairments were selected. For further participation in the research, consent was obtained from the parents of 97 children. After obtaining consent for their child to participate in the research, parents were given a survey to collect data on the presence of risk factors. After that, we started testing. The children were tested individually, in a room isolated from noise.

The assessment of speech and language abilities was carried out using three tests: 1. Global articulation test, 2. Comic story test and 3. Vocabulary test for children aged three to seven years.

The global articulation test consists of 30 words and is used for a detailed analysis of voices, both pathological and those that meet the criteria of good pronunciation. A well-pronounced voice by the child is marked with (+), sounds that cannot be classified as either good or bad pronunciation are marked with (+ -), while incorrect pronunciation of sounds is marked with (-). If the child does not articulate the tested voice correctly, the type of deviation is recorded: distortion, substitution or omission of the voice [10].

The vocabulary test is an instrument for assessing the speech and language of children aged three to seven years. It consists of 100 terms that are divided into five tests with 20 words each, according to age. This test examines children's vocabulary and understanding of abstract concepts such as death, life, punishment, pleasure, etc. When assessing the understanding of concepts, the following answers are recorded: (1) does not understand the concept, (2) recognizes the concept, (3) describes the concept and (4) defines the concept. The maximum number of points on this test is 20. A higher number of points on this test indicates a better vocabulary development in children [11].

The comic story test assesses speech and language development with the ability to logically connect images into a meaningful whole. The test consists of four pictures that are interconnected, that is, that represent the sequence of an event. All pictures from the test are adapted to the age of the child and are close to their life experience. Pictures are placed in front of the examinee with the request to look at them carefully and then to tell what is happening in them. The examiner indicates to the child that the pictures shown together illustrate one event. If the respondent is not able to tell the story independently, the examiner helps him by asking questions that prompt the respondent to tell what happened (For example: "And then?", "And what happened next?"). After the data obtained, the children's statements are analyzed by determining: (1) the total number of words in the story, (2) the total number of sentences in the story, (3) the number of ungrammatical sentences and (4) the understanding of the content of the story [10].

Table 2 shows the results of the Kolmogorov-Smirnov test, which shows that the distribution of most of the measures obtained on the sample deviates statistically significantly from the normal distribution model ($p < 0.05$), so we

decided to use non-parametric tests. In the statistical processing of the data, the methods of descriptive statistics and the Mann-Whitney U test were used to check the significance of differences between groups.

## Results

First, the differences in achievements on the Global Articulation Test were assessed between respondents with the risk factors in their history and children without the presence of risk factors. The data presented in table 3 show that respondents who have risk factors on average pronounce a smaller number of correctly articulated sounds (M = 24.1) than respondents who do not have risk factors (Md = 27.04). Voice distortions are more frequent in the group of children with risk factors (M = 2.91), while in children without risk factors, distortions appear on average in one voice. Respondents from the group without risk factors substitute on average of 1.96 voices, while this articulation disorder in the group of children with risk factors occurs in on average of 2.99 voices.

**Table 2.** Assessment of the normality of the distribution of numerical data

| | | K- Z S | p |
|---|---|---|---|
| Global Articulation test | Number of correctly articulated sounds | 0.12 | 0.002 |
| | Number of distortions | 0.20 | 0.000 |
| | Number of substitutions | 0.17 | 0.000 |
| Vocabulary test | Vocabulary test - total score | 0.12 | 0.001 |
| | Total number of sentences | 0.16 | 0.000 |
| Comic Story test | Total word count | 0.08 | 0.16 |
| | Number of ungrammatical sentences | 0.41 | 0.000 |

KZ-S - Kolmogorov-Smirnov Z statistic; p - significance level

**Table 3.** Comparison of achievement on the Global Articulation test between subjects with risk factors and subjects without risk factors

| | Risk factors | N | M | SD | U | z | p |
|---|---|---|---|---|---|---|---|
| Correctly pronounced voices | Without | 27 | 27.04 | 2.21 | 403.5 | -4.38 | 0.00 |
| | With | 70 | 24.10 | 2.91 | | | |
| Distortions | Without | 27 | 1.00 | 1.52 | 499.0 | -3.67 | 0.00 |
| | With | 70 | 2.91 | 2.58 | | | |
| Substitutions | Without | 27 | 1.96 | 1.87 | 704.5 | -1.96 | 0.05 |
| | With | 70 | 2.99 | 2.35 | | | |

N - number of respondents; M - mean; SD - standard deviation; U - Mann-Whitney U score; p - significance level

The Mann-Whitney U test was used to check the significance of the differences between the obtained results. The results showed that children with typical language development had better results on the Global Articulation Test compared to children with speech and language disorders. Table 4 shows that the clinical group had a lower number of correctly articulated voices (M = 23.33) compared to the control group (M = 26.91). Further analysis revealed that subjects from the clinical group had a significantly higher number of voice distortions and substitutions.

Vocabulary assessment in children was performed using the Vocabulary test. The results presented in table 5 show that respondents with risk factors on average score a lower number of points on the Vocabulary test (M = 14.62) compared to respondents without risk factors (M = 16.15). At the same time, it was shown that there were no differences between respondents of different genders in vocabulary development. Children with established speech-language disorders had worse achievements on the Vocabulary test (M = 14.14) compared to children with typical language development (M = 16.19) (Table 6).

**Table 4.** Differences between clinical and control groups in achievements on the Global Articulation test

| | group | N | M | SD | U | z | p |
|---|---|---|---|---|---|---|---|
| Correctly pronounced voices | clinical | 54 | 23.33 | 2.59 | 349.50 | -5.93 | 0.00 |
| | control | 43 | 26.91 | 2.27 | | | |
| Distortions | clinical | 54 | 3.43 | 2.65 | 522.50 | -4.74 | 0.00 |
| | control | 43 | 1.07 | 1.42 | | | |
| Substitutions | clinical | 54 | 3.24 | 2.41 | 819.50 | -2.51 | 0.01 |
| | control | 43 | 2.02 | 1.83 | | | |

N - number of respondents; M - mean; SD - standard deviation; U - Mann- Whitney U score; p - significance level

**Table 5.** Comparison of achievement on the Vocabulary test between subjects with risk factors and subjects without risk factors

| | N | M | SD | U | z | p |
|---|---|---|---|---|---|---|
| Subjects with risk factors | 70 | 14.62 | 3.02 | 659.50 | -2.31 | 0.02 |
| Subjects without risk factors | 27 | 16.15 | 2.07 | | | |

N - number of respondents; M - mean; SD - standard deviation; U - Mann-Whitney U score; p - significance level

**Table 6.** Differences between clinical and control groups in achievements on the Vocabulary test

| Group | N | M | SD | U | z | P |
|---|---|---|---|---|---|---|
| clinical | 54 | 14.14 | 3.15 | 693.50 | -3.41 | 0.001 |
| control | 43 | 16.19 | 1.95 | | | |

N - number of respondents; M - mean; SD - standard deviation; U - Mann-Whitney U score; p - significance level

We did not find a statistically significant influence of risk factors on speech-language development assessed by the Comic Story test, which can be seen from Table 7. On the other hand, this test showed significant differences between boys and girls from our sample (Table 8). On average, boys uttered a slightly higher number of sentences (M = 4.17) than girls (M = 3.53). Also, the number of words pronounced by boys was on average higher (M = 19.92) compared to the number of words pronounced by girls (M = 15.47).

**Table 7.** Comparison of achievement on the Comic Story test between subjects with risk factors and subjects without risk factors

| | Risk factors | N | M | SD | U | z | p |
|---|---|---|---|---|---|---|---|
| The total number of sentences | with | 70 | 3.84 | 1.59 | 916.0 | -.24 | .81 |
| | without | 27 | 3.85 | 1.56 | | | |
| The number of ungrammatical sentences | with | 70 | 0.60 | 1.21 | 869.0 | -.78 | .44 |
| | without | 27 | 0.37 | 0.79 | | | |
| Total number of words | with | 70 | 17.64 | 8.49 | 911.5 | -.27 | .79 |
| | without | 27 | 17.74 | 7.78 | | | |

N - number of respondents; M - mean; SD - standard deviation; U - Mann-Whitney U score; p - significance level

**Table 8.** Comparison of achievement on the Comic Story test in relation to gender

| | Gender | N | M | SD | U | z | p |
|---|---|---|---|---|---|---|---|
| The total number of sentences | Male | 48 | 4.17 | 1.37 | 877.50 | -2.19 | 0.03 |
| | Female | 49 | 3.53 | 1.71 | | | |
| The number of ungrammatical sentences | Male | 48 | 0.56 | 1.28 | 1122.00 | -0.49 | 0.62 |
| | Female | 49 | 0.51 | 0.92 | | | |
| Total number of words | Male | 48 | 19.92 | 7.72 | 753.50 | -3.05 | 0.00 |
| | Female | 49 | 15.47 | 8.35 | | | |

N - number of respondents; M - mean; SD - standard deviation; U - Mann-Whitney U score; p - significance level

## Discussion

Given that a number of children exhibit disorders in the development of speech and language without visible causes, the aim of this research was to determine the relationship between risk factors and the occurrence of speech and language disorders in children aged four to six years. Earlier research shows that heredity and socioeconomic status predict speech and language disorders in children to the greatest extent, and that certain biological factors such as low body weight, low Apgar score, inadequate prenatal care and premature birth have a smaller influence [6, 7]. The results of our research show that the most common risk factors are premature birth, perinatal asphyxia, cesarean delivery, maternal medication during pregnancy, and infection of the newborn. In other studies, the most common risk factors in children were premature birth, difficult birth and childhood diseases [6]. However, the authors of the aforementioned study did not establish a connection between these risk factors and the occurrence of speech-language disorders [6].

Articulation deficits are a common problem in childhood, affecting 5 to 8% of preschool children [12]. The analysis of the data obtained from the examination of articulation in our sample revealed that children with risk factors incorrectly articulate almost twice as many voices as children without the presence of risk factors. Our results coincide with those of other authors who have dealt with this topic. For example, Vuković [1] mentions the more frequent occurrence of articulation disorders in the group of children who have risk factors such as positive family history and low economic status. At the same time, the results of our study showed that children diagnosed with a language development disorder correctly articulated fewer sounds compared to children in the control group, i.e. that children with a speech-language disorder exhibited a greater number of distortion and substitution type errors than children with typical language development. Therefore, the results of our research coincide with the findings of some earlier studies in which it was determined that children with developmental language disorder had a significantly higher number of damaged voices compared to their peers with typical language development [4]. Further analysis of articulatory abilities showed that 44.4% of the children of the examined sample correctly articulated all the sounds of the Serbian language. Comparing this finding with the findings of other authors who determined that 47% of preschool children correctly articulate all 30 sounds of the Serbian language, we can conclude that there is a trend of increasing articulation disorders [13].

Examining the vocabulary revealed that children with risk factors had a poorer vocabulary compared to children without risk factors. The results of our research differ from some previous studies in which no association was found between delays in vocabulary development and risk factors, such as more severe childhood illnesses in early life or the hereditary factor of parental speech and language disorders [6]. On the other hand, it has been shown that environmental factors, such as parents' education and socioeconomic status, have an influence on vocabulary development in children [6]. At the same time, the results of our research showed that children diagnosed with the language development disorder have less developed vocabulary compared to children with typical language development. Our results correspond with the results of other studies that also show that lexical and lexical-semantic deficits form part of the clinical features of the specific disorder of language development [2]. Children who have the developmental language disorder often have difficulties in acquiring the meaning of words and limited vocabulary [6]. Further analysis of the data obtained with the Test dictionary showed that boys and girls do not differ in terms of lexical-semantic abilities. Our findings coincide with the results of other authors who also did not establish a connection

between gender and children's lexical-semantic abilities [14].

Analyzing the results of the Comic Story test, no statistically significant differences were found between children with risk factors and children without risk factors on any of the examined variables. However, it is interesting that significant differences between boys and girls were found on this test. Namely, boys produced larger number of sentences on average compared to girls. Girls also produced smaller number of words in the story compared to boys who produced significantly higher number of words in the comic story. These findings suggest the need for further research on the task of story formation, both in terms of a more precise determination of the relationship between risk factors and the number of words and sentences produced, as well as in terms of grammaticality. It is possible that the inclusion of larger number of respondents with the most common risk factors of children with the diagnosed language disorder and children with typical language development would shed a light on this problem. The need for additional research into the relationship between risk factors and language disorders in children is shown by the results of the authors who state that there is the connection between premature birth and the ability to understand and produce language in children [15].

Our results, as well as the results of some other researches, suggest the possible connection between certain biological risk factors and speech-language disorders, which should be examined in more detail in future research. We assume that a study that would include a larger sample of children and parents, along with an insight into the medical documentation of the respondents, would provide much more data on the connection between certain risk factors and the occurrence of speech and language disorders.

## Conclusion

Based on the analysis and discussion of the obtained results, the connection between risk factors and the occurrence of speech-language disorders in children was determined.

The most common risk factors for children with developmental language disorders were cesarean section, medications taken by mothers during pregnancy, premature birth, asphyxia and infection of the newborn.

Children with risk factors incorrectly articulated almost twice as many voices as children without data on the presence of risk factors.

Children with risk factors had significantly worse lexical-semantic abilities compared to children without risk factors.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** The Ethics Committee of the Ministry of Education and Culture, Republic of Srpska, Bosnia and Herzegovina, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

**Conflicts of interest.** The authors declare no conflict of interest.

## References:


1. Vuković M. Diferencijalne karakteristike jezičkih poremećaja kod dece. II Kongres logopeda Srbije: Govorno-jezički poremećaji razvojnog doba. Beograd, 2015. Zbornik radova. Udruženje logopeda Srbije, Beograd, 2015;11–36.
2. Vuković B, Vuković M, Ćalasan S. Razvoj vokabulara kod djece sa govorno-jezičkim poremećajima i djece tipičnog jezičkog razvoja: preliminarno ispitivanje. Proceedings of Eurlyaid Conference 2017, Early Childhood Intervention: For meeting sustainable development goals of the new millennium. University of Belgrade – Faculty of Special Education and Rehabilitation, Beograd, 2017; 167–174.
3. Jovanović-Simić N, Duranović M, Petrović-Lazić M. Govor I glas. Foča: Medicinski fakultet; 2017.
4. Vuković I, Vuković M. Artikulaciono-fonološki deficit kod dece sa razvojnom disfazijom. Beogradska defektološka škola 2009;2:49–56.
5. Milošević N, Vuković M. Leksičko-semantičke sposobnosti dece sa specifičnim jezičkim poremećajem i nespecifičnim promenama elektroencefalografskih aktivnosti. Specijalna edukacija i rehabilitacija. 2011;10(3):435–43.
6. Korpilahti P, Kaljonen A, Jansson-Verkasalo E. Identification of biological and environmental risk factors for language delay: The Let's Talk STEPS study. Infant Behav Dev 2016;42:27–35.
7. Stanton-Chapman L, Chapman DA, Bainbridge NL, Scott KG. Identification of early risk factors for language impairment. Res Dev Disabil 2002;23(6):390–405.
8. Vuković M. Karakteristike jezičkih poremećaja i oporavak jezičkih sposobnosti kod dece sa traumatskom povredom mozga. Proceedings of Eurlyaid Conference 2017, Early Childhood Intervention: For meeting sustainable development goals of the new millennium. University of Belgrade – Faculty of Special Education and Rehabilitation, Beograd, 2017;109–115.
9. Maksimović S. Učestalost carskog reza kod majki dece sa poremećajima govora, jezika, učenja i ponašanja. Tematski zbornik radova: Specifičnost oštećenja sluha- nove tendencije. 2020;31–48.
10. Kostić Đ, Vladisavljević S, Popović M. Testovi za ispitivanje govora i jezika. Beograd: Zavod za udžbenike i nastavna sredstva; 1983.
11. Vasić S. Veština govorenja: vežbe i testovi za decu i odrasle. Beograd: Pedagoška akademija za obrazovanje učitelja; 1991.
12. Nikolić M, Mijailović G, Katrina-Mitrović V. Identifkacija govorno-jezičkog poremećaja kao simptoma psihomotorne zaostalosti- preduslov za rane intervencije u vrtićima. Proceedings of Eurlyaid Conference 2017, Early Childhood Intervention: For meeting sustainable development goals of the new millennium; University of Belgrade – Faculty of Special Education and Rehabilitation, Beograd, 2017;57–63.
13. Golubović S, Ječmenica N, Jovanović-Simić N, Petrović-Lazić M. Artikulacione i fonološke sposobnosti dece uzrasta od pet do sedam godina. Nastava i vaspitanje 2019;68(2):265–83.
14. Gavriilidou Z. The development of word definitions in Greek Preschoolers. In: Chatzopoulou K, Ioannidou A, Suwon Yoon, editors. Proceedings of the 9th ICGL; 2011. p. 88–96.
15. Chaimay B, Thinkhamrop B, Thinkhamrop J. Risk factors associated with language development problems in childhood-a literature review. J Med Assoc Thai 2006;89(7):1080–6.

# Odnos riziko faktora i govorno-jezičkih poremećaja kod djece uzrasta od četiri do šest godina

Jelena Tešić[1], Mile Vuković[2], Mirjana Korlaet[3], Sofija Vuković[4]

[1]JU OŠ „Vuk Karadžić" Bijeljina, Republika Srpska, Bosna i Hercegovina

[2] Univerzitet u Beogradu, Fakultet za specijalnu edukaciju i rehabilitaciju, Beograd, Srbija

[3]Servis centar „Dajte nam šansu - Zvjezdice", Banja Luka, Republika Srpska, Bosna i Hercegovina

[4]JU OŠ „Skender Kulenović", Sarajevo, Bosna i Hercegovina

**Uvod.** Posljednjih godina se sve više pažnje posvećuje istraživanju faktora koji potencijalno mogu doprinijeti poremećaju razvoja govora i jezika. Smatra se da rezultati ovih istraživanja mogu pomoći boljem planiranju i sprovođenju rane intervencije u oblasti govora i jezika kod djece. Cilj ovog istraživanja je utvrđivanje uticaja riziko faktora na pojavu jezičkih poremećaja kod djece.

**Metode.** U istraživanju je učestvovalo 97 djece uzrasta od četiri do šest godina, koja su podijeljena u dvije grupe. Prvu grupu činilo je 54 ispitanika sa poremećajem u govorno- jezičkom razvoju, a drugu 43 ispitanika tipičnog jezičkog razvoja. U obje grupe pronađeno je 70 djece koja imaju riziko faktore. Sva djeca sa poremećajem u govorno-jezičkom razvoju imala su neki od riziko faktora (oboljenja majki u trudnoći, kao i lijekovi koje su majke pile u toku trudnoće, prematurus, carski rez, asfiksija, bolest novorođenčadi, epileptični napadi, treći krajnik, skraćen frenulum, upala uha), dok je u grupi djece tipičnog jezičkog razvoja 16 ispitanika imalo riziko faktore. Za procjenu govorno-jezičkih sposobnosti korišćeni su Globalni artikulacioni test, Test-rječnik i test Strip priča. Podaci o riziko faktorima dobijeni su na osnovu ankete za roditelje koja je konstruisana za potrebe ovog istraživanja.

**Rezultati.** Rezultati su pokazali da djeca sa riziko faktorima imaju značajno lošije rezultate na testu artikulacije i testu rječnika u poređenju sa djecom bez podataka o riziko faktorima. Rezultati dobijeni na testu Strip priča nisu pokazali da se ove dvije grupe statistički značajno razlikuju u pogledu broja produkovanih riječi, broja rečenica i gramatičkoj strukturi rečenice.

**Zaključak.** Generalno gledano, rezultati ovog istraživanja pokazali su da postoji značajna povezanost između riziko faktora i smetnji u razvoju govorno-jezičkih sposobnosti kod djece.

**Ključne riječi:** riziko faktori, govorno-jezički poremećaji, artikulacija, rječnik, sintaksa

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):64–76

UDK: 616.89-008.43/434-053.4
DOI: 10.59137/BII202301302K

*Original article*

# Pre-skills of reading and writing in children with developmental language disorder and children with typical language development

**Mirjana Korlaet[1], Mile Vuković[2], Jelena Tešić[3]**

[1]Service Center "Give us a chance - Stars", Banja Luka, Republic of Srpska, Bosnia and Herzegovina

[2]University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia

[3]Elementary school "Vuk Karadžić", Bijeljina, Republic of Srpska, Bosnia and Herzegovina

Primljen – Received: 11/09/2022
Prihvaćen – Accepted: 07/03/2023

**Corresponding author:**
*Mirjana Korlaet,*
*Bachelor of Speech and Language Pathology*
*Vojvode Stepe Stepanović 82a,*
*78000 Banja Luka*
*mirjanamilicevic91@yahoo.com*



**Summary**

**Introduction.** In addition to the development of spoken language, typical intellectual abilities, preservation of the senses of hearing and sight, phonological awareness and the ability of graphomotor expression are necessary for mastering the skills of reading and writing. With this in mind, the aim of this research is to determine the level of phonological awareness and the ability of graphomotor expression in children with developmental language disorder (DLD) and children with typical language development (TLD).

**Methods.** The sample consisted of 46 children aged five to seven years, who were divided into two groups based on the status of speech and language abilities. The first group consisted of 23 children with DLD, and the second of 23 children with TLD. The FONT test was used to assess phonological awareness, and the Prediction Test for Dysgraphia was used to assess graphomotor abilities.

**Results.** The results of the research show that children with DLD performed poorly on phonological awareness tasks compared to TLD children. Age proved to be a significant factor in differences in the development of phonological awareness. Achievements on the Prediction Test for Dysgraphia show that children with DLD have almost twice the weaker ability of graphomotor expression compared to TLD children. Furthermore, the research results show that there are significant differences in the level of development of graphomotor skills between children of different ages. Also, no significant difference in achievements on the Prediction Test for Dysgraphia or on the FONT test has been found in relation to gender.

**Conclusion.** Children with developmental language disorder had significantly lower achievements on the phonological awareness test and the Prediction Test for Dysgraphia compared to children with typical language development.

**Key words:** gross motor ability, phonological awareness, developmental language disorder, typical language development, pre-skills of reading and writing

## Introduction

In today's society, most people are exposed to a large amount of written material on a daily basis. From school age onwards, writing and reading accompany almost every human activity. Therefore, it can be said that the life of a modern man is unimaginable without the ability to read and write, and people with a disorder of these skills can be very limited in everyday life [1].

The basic prerequisites for the development of reading and writing are proper speech and language development, the development of phonological awareness, the ability of visual perception and graphomotor expression. Phonological awareness involves the identification and manipulation of sublexical elements within words, such as syllables and phonemes. It makes it possible to divide spoken words into smaller components [2]. More precisely, phonological awareness represents an explicit awareness of the phonological structure of a language, that is, of recognizing the letter-sound connection. Phonological awareness includes a number of functions that contribute to the understanding and precise automated application of the phonetic system of the language. These are auditory perception, auditory discrimination, auditory analysis, auditory synthesis, auditory combining, auditory memory, correct and continuous auditory classification, auditory form or auditory word recognition, rhyme formation, alliteration and intonation or accent [3, 4, 5].

Phonological awareness develops gradually, from simpler to more complex skills. At an early age, children's phonological representations consist of whole words, while during the preschool period they are reorganized into smaller segments, syllables and phonemes. Also, during phonological development, children master words that rhyme. Awareness of syllables is usually present around the third year of a child's life, while recognition of rhyme develops from the fourth to the fifth year [6]. The development of phonological awareness has been shown to be an indicator of later acquisition of reading, which led to the phonemic deficit hypothesis according to which children with poor phonological awareness have weaker reading abilities and vice versa. Research shows that a large number of children with speech-language disorders and phonological deficits during schooling have learning disabilities, especially disabilities in reading and writing [5]. In the sequence of phonological deficits, there is a mismatch between lexical units and the corresponding phonological representations. As a result, children can read word "submarine" either "subarin" or "marin" [2].

In children with difficulties in storing and manipulating phonological representations of lexical units, phonological awareness develops slowly. In order for phonological processing to be successful, three prerequisites are needed: developed phonological awareness of the sound structure of the language, the ability to recall phonological information from long-term memory, and developed phonological coding of information in working memory [2].

The development of graphomotor abilities begins in early childhood with the development of gross motor skills, and later with the development of fine motor skills. Before writing training, the child is involved in the process of artistic expression, which is conditioned by the level of hand motor development and the ability to manipulate a pencil. Graphomotor abilities develop gradually, with each stage of development arising as a result of the development of new internal and external factors [7]. At the age of two, children express themselves by drawing lines on paper - scribbling, while at the age of three they are able to form a circle, and later a square and a triangle. The first drawing of a human figure appears in the form of a tadpole, and before starting school a recognizable drawing appears. Most four- year-old children are able to copy a diagonal line and even a few letters, while most preschoolers know how to write their first and last name [7, 8].

Intensive scribbling, drawing and coloring in pre-school age create a foundation and facilitates children's transition to more precise graphomotor expression - complex psychophysiological mechanism. Graphomotor skills are related to visual perception, orientation in space, fine motor coordination, speech development, etc.

Identifying the abilities that underlie reading and writing, as well as finding the most adequate instruments for assessing a child's readiness to master these skills are the subjects of many modern researches. The increasing occurrence of learning disabilities, especially in the area of reading and writing, has led many experts to focus on researching linguistic abilities related to reading and writing. The results of the research show that many children with a disorder in the development of language during their schooling exhibit learning disabilities, especially in reading and writing [4]. Based on that, the aim of this research is to determine the phonological awareness and ability of graphomotor expression in children with the developmental language disorder compared to children with typical language development.

## Method

A total of 46 subjects, divided into two groups, took part in the research. The first group consisted of 23 children with developmental language disorder (DLD) representing the experimental group, while the control group consisted of 23 children with typical language development (TLD). Table 1 shows the general characteristics of the sample.

Table 1 shows that there were more girls than boys in the sample in both groups. The sample includes children aged five to seven years. The groups differed statistically significantly in relation to age.

Since deficits in learning to read and write are observed in children with the language development disorder, the subject of this paper was the examination of the pre-skills of reading and writing in children with DLD and children with TLD. More precisely, phonological awareness and graphomotor ability (redrawing given graphic shapes) were examined in children aged five to seven years.

The aim of the paper is to determine the level of phonological awareness and the ability of graphomotor expression in children with DLD compared to children with TLD.

**Table 1.** Distribution of respondents according to age and gender

| N | | children with DLD | | children with TLD | |
|---|---|---|---|---|---|
| | | % | N | % | |
| gender | male | 6 | 39.1 | 6 | 26.1 |
| | female | 9 | 60.9 | 17 | 73.9 |
| age | 5 | 5 | 21.7 | 2 | 8.7 |
| | 6 | 11 | 47.8 | 12 | 52.2 |
| | 7 | 7 | 30.4 | 9 | 39.1 |

N - number of respondents

The following were used in the research: Phonological Awareness Test and Prediction Test for Dysgraphia.

1. Phonological Awareness Test - Font [9]

This test was used to assess phonological awareness. A revised version of the test was used for the Serbian-speaking area, which includes eight tests each: 1) joining syllables, 2) syllable segmentation (optional subtest), 3) initial phoneme identification, 4) rhyme recognition, 5) phonemic segmentation, 6) identification of the final phoneme, 7) elimination of the initial phoneme and 8) phonemic substitution (initial phoneme). Each subtest contains six tasks. Test-z tasks were given orally. The examiner notes the accuracy of the answers, according to the true-false principle. The absence of an answer was treated as an incorrect answer. The maximum achievement on each of the subtests can be six points, while the maximum total score on the FONT test is 48 points. This test has good internal consistency and a Cronbach's alpha coefficient of 0.97, which means that the reliability of the used test is very high.

2. Prediction Test for Dysgraphia [10]

The Prediction Test for Dysgraphia primarily examines graphomotor dexterity and visual perception in children. The child is given a

**Table 2.** Achievements of respondents on the FONT test

| | Descriptive statistics | | | | | |
|---|---|---|---|---|---|---|
| | **M** | **SD** | **Md** | **IQR** | **min** | **max** |
| Predictive test for dysgraphia -total score | 10.61 | 3.91 | 12.00 | 4 | 2 | 15 |
| Arrangement of syllables | 5.33 | 1.017 | 6 | 1 | 2 | 6 |
| Syllabic segmentation | 4.89 | 1.30 | 5 | 2 | 1 | 6 |
| Identifying the initial phoneme | 3.72 | 2.15 | 4 | 4 | 0 | 6 |
| Recognizing rhyme | 4.17 | 1.84 | 5 | 3 | 0 | 6 |
| Phonemic segmentation | 3.46 | 2.65 | 4.50 | 6 | 0 | 6 |
| Identifying the final phoneme | 2.35 | 2.07 | 2 | 5 | 0 | 6 |
| Elimination of the initial phoneme | 2.40 | 2.53 | 1.50 | 5 | 0 | 6 |
| Phonemic substitution | 2.46 | 2.45 | 2.50 | 5 | 0 | 6 |
| FONT - total score | 28.76 | 13.55 | 28.50 | 25 | 7 | 48 |
| FONT - medium value | 3.60 | 1.69 | 3.56 | 3.09 | 0.88 | 6 |

M - mean value; SD - standard deviation; Md - median; IQR - interquartile range; min - the smallest value; max - the highest value;

piece of paper with a rectangle drawn on it. On the outside of the contours, in the upper corner, three geometric shapes are drawn: the circle, the cross and the triangle. The child is given the following order: "Your task is to continue drawing these figures around the rectangle in the same order. Try to make them the same size and shape as the ones that were drawn". The explanation procedure can be repeated and this is recorded in the findings. After the child has finished drawing, the examiner evaluates 5 criteria from 0 to 3: the size of the figure (1), the shape of the figure (2), whether the child follows the order of the figures (3), whether the child draws around the rectangle (4) and whether the drawing is finished (5). The maximum number of points that the examinee can achieve on this test is 15, and based on the results of this test, it is determined whether there is a suspicion of dysgraphia.

Data analysis and processing have been performed using a package intended for statistical data processing for the social sciences (Statistical Package for the Social Sciences - SPSS). Descriptive statistics measures (mean value, standard deviation, frequency, median, interquartile range) have been used to describe the data. Considering that most of the measures obtained by the tests used in this research deviate from the normal distribution model, non-parametric techniques have been used in the statistical processing of the data to examine the differences between the groups. Mann-Whitney U test, Kruskal-Wallis test and two-factor analysis of variance (ANOVA) have been applied.

## Results

The FONT test was used to examine phonological awareness in children with DLD and children with TLD. The results are shown in Table 3.

The results show that children with DLD had significantly lower achievements on the FONT test compared to children with TLD (Table 3). Children from both groups achieved the highest average values on the tasks of combining syllables, segmenting syllables and recognizing rhymes. A statistically significant difference was found between children with DLD and TLD children on all subtests of the FONT test ($p < 0.05$). Children with DLD

**Table 3.** The difference between children with DLD and TLD children in the development of phonological awareness

| FONT test | Descriptive statistics | | | | | Mann-Whitney U test | | |
|---|---|---|---|---|---|---|---|---|
| | a group | M | SD | Md | IQR | U | z | p |
| Joining syllables | DLD | 4.74 | 1.42 | 6 | 3 | 150 | -3.17 | 0.02 |
| | TLD | 5.91 | 0.29 | 6 | 0 | | | |
| Syllabic segmentation | DLD | 4.13 | 1.42 | 4 | 3 | 97 | -3.91 | 0.001 |
| | TLD | 5.65 | 0.49 | 6 | 1 | | | |
| Identifying the initial phoneme | DLD | 2.26 | 1.98 | 2 | 3 | 60 | -4.59 | 0.001 |
| | TLD | 5.17 | 1.03 | 6 | 2 | | | |
| Recognizing rhyme | DLD | 3.26 | 2.05 | 3 | 4 | 134 | -2.96 | 0.003 |
| | TLD | 5.09 | 1.00 | 5 | 1 | | | |
| Phonemic segmentation | DLD | 1.17 | 1.70 | 0 | 2 | 1 6 | -5.82 | 0.001 |
| | TLD | 5.74 | 0.75 | 6 | 0 | | | |
| Identifying the final phoneme | DLD | 1.22 | 1.73 | 0 | 3 | 98.5 | -3.74 | 0.01 |
| | TLD | 3.48 | 1.75 | 3 | 3 | | | |
| Elimination of phonemes | DLD | 0.57 | 1.41 | 0 | 0 | 60.5 | -4.74 | 0.001 |
| | TLD | 4.22 | 2.02 | 5 | 3 | | | |
| Phonemic substitution | DLD | 0.61 | 1.50 | 0 | 0 | 49.5 | -4.99 | 0.001 |
| | TLD | 4.30 | 1.74 | 5 | 2 | | | |
| Total score | DLD | 17.96 | 9.28 | 17 | 1 4 | 26 | -5.25 | 0.001 |
| | TLD | 39.57 | 6.75 | 41 | 8 | | | |
| Total score - mean value | DLD | 2.25 | 1.16 | 2.13 | 1.75 | 26 | -5.25 | 0.001 |
| | TLD | 4.95 | 0.84 | 5.13 | 1 | | | |

M - mean value; SD- standard deviation; Md - median; IQR - interquartile range; U - Mann Whitney's U score; z - value Z statistic; p - level of significance

had high average achievements on the subtest of syllable joining, but children with TLD were more successful. High achievements were achieved by children with DLD and on the subtest syllabic segmentation, but here as well, children with TLD had a significantly higher number of correct answers. Identifying the initial phoneme was not a problem for the majority of subjects with TLD, while subjects with DLD had a lower number of correct answers on that subtest. On the rhyme recognition subtest, the TLD children had a very high average score, in contrast to the clinical group. Phonemic segmentation was an even more difficult task for children with DLD, while children with TLD had almost all correct answers on this task. Identifying the final phoneme was problematic for both groups of respondents. However, TLD children were better on this subtest compared to children with DLD. The phoneme elimination task was the most difficult for the subjects with DLD and they had the lowest achievements on that subtest, while the children with TLD most often correctly completed the tasks from that group. On the task of phonemic substitution, children with DLD achieved very low average achievements, while children with TLD also had a large number of correct answers on that task.

We hypothesized that boys and girls would differ in the level of development of phonological awareness and tested this claim using the Mann-Whitney U test. However,

the results of this test showed that there was no statistically significant difference between boys and girls in the level of phonological awareness taking into account the total score (U = 195.5, z = -0.87, p = 0.20). In addition to the above, there was no statistically significant difference in the achievements of boys and girls on the subtests of joining syllables (U = 208, z = -0.74, p = 0.98), syllabic segmentation (U = 223.5, z = -0.22, p = 0.59) and rhyme recognition (U = 216, z = -0.40, p = 0.87). Boys and girls from the studied sample did not differ in their achievements on the subtests of initial phoneme identification (U = 228.5, z = -0.10, p = 0.82), phonemic segmentation (U = 184.5, z = -1.20, p = 0.16), final phoneme identification (U = 228.5, z = -0.10, p = 0.82), phoneme elimination (U = 163, z = -1.72 , p = 0.07) and phonemic substitution (U = 169.0, z = -1.57, p = 0.17).

For the more detailed analysis of the data, we separated the sample and separately observed the achievements of children from the sub-sample with DLD, and then the achievements from the sub-sample of TLD children. No statistically significant differences were found between boys and girls in the group of children with DLD in the level of development of phonological awareness (U = 53, 5, z = -0.60, p = 0.48), achievements on the subtests syllable joining (U = 49, z = -0.96, p = 0.69), syllable segmentation (U = 60 , z = -0.20, p = 0.46), initial phoneme identification (U = 48, z = -0.97, p = 0.63), rhyme recognition (U = 51, z = -0.78 , p = 0.50), phonemic segmentation (U = 54, z = -0.63, p = 0.69), final phoneme identification (U = 59, z = -0.28, p = 0.71) , phoneme elimination (U = 63, z = 0.00, p = 0.40) and phoneme substitution (U = 55, z = -0.76, p = 0.36).

In the group of TLD children, statistically significant differences were found between boys and girls in the level of development of phonological awareness (U = 46.5, z = -0.32, p = 0.76), in achievements on the subtests syllable joining (U = 45, z = -0.86, p = 0.39), syllable segmentation (U = 50, z = -0.09, p = 0.93), initial phoneme identification (U = 47, z = -0.31, p = 0.76), rhyme recognition (U = 35.5, z = -1.17, p = 0.24), phonemic segmentation (U = 48.5, z = -0.30, p = 0.77), final phoneme identification (U = 40, z = -79, p = 0.43), phoneme elimination (U = 29.5, z = -1.55, p = 0.12) and phoneme substitution (U = 40, z = -0.79, p = 0.43).

We assumed that older children had a higher level of phonological awareness than younger children. Given that we had three age groups of children, we used the Kruskal-Wallis test to examine differences in the level of development of phonological awareness in children of different ages. First, we showed age differences in phonological awareness by observing the total sample, and then we examined the interaction of language disorder and age on children's achievements on the FONT test.

Table 4 shows the difference in phonological awareness among children of different ages from the total sample, and there we see that the highest average achievements on the FONT test were achieved by children aged 7, slightly lower by children aged 6, while the youngest children had the lowest achievements on this test and this difference is statistically significant ($\chi 2(2, n = 46) = 7.58$, p = 0.02). Looking at each of the subtests separately, we see that the statistically significant difference between respondents of different ages was found on the subtests identifying the initial phoneme and identifying the final phoneme. The youngest subjects had little success in the task of identifying the initial phoneme. Respondents aged six years had lower average achievements on the task of identifying the initial phoneme compared to the oldest respondents. The youngest respondents managed to identify the final phoneme in a small number of tasks of this subtest, although children aged six had very little success, while the oldest respondents had the most correct answers. The Kruskal-Wallis test did not reveal any statistically significant difference between subjects of different ages in the achievements on the subtests of syllable joining, syllabic segmentation, rhyme recognition, phonemic segmentation, phonemic

**Table 4.** Phonological awareness in children of different ages - total sample (N = 46)

| FONT test | age | Descriptive statistics | | | | | Kraskal-Wallis test | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | M | SD | Md | IQR | χ 2 | df | p |
| Joining syllables | 5 | 7 | 4.43 | 1.62 | 4 | 3 | 5.15 | 2 | 0.08 |
| | 6 | 23 | 5.35 | 1.11 | 6 | 1 | | | |
| | 7 | 16 | 5.69 | 0.87 | 6 | 0 | | | |
| Syllabic segmentation | 5 | 7 | 4 | 1.29 | 4 | 2 | 4.96 | 2 | 0.08 |
| | 6 | 23 | 5.04 | 1.02 | 5 | 2 | | | |
| | 7 | 16 | 5.06 | 1.57 | 6 | 2 | | | |
| Identifying the initial phoneme | 5 | 7 | 1.43 | 2.44 | 0 | 2 | 10.48 | 2 | 0.01* |
| | 6 | 23 | 3.70 | 1.79 | 4 | 2 | | | |
| | 7 | 16 | 4.75 | 1.77 | 6 | 3 | | | |
| Recognizing rhyme | 5 | 7 | 2.71 | 2.14 | 2 | 4 | 5.51 | 2 | 0.06 |
| | 6 | 23 | 4.17 | 1.78 | 5 | 3 | | | |
| | 7 | 16 | 4.81 | 1.33 | 5 | 3 | | | |
| Phonemic segmentation | 5 | 7 | 2 | 2.83 | 0 | 6 | 2.28 | 2 | 0.24 |
| | 6 | 23 | 3.48 | 2.62 | 3 | 6 | | | |
| | 7 | 16 | 4.06 | 2.43 | 6 | 4 | | | |
| Identifying the final phoneme | 5 | 7 | 0.57 | 0.97 | 0 | 2 | 9.21 | 2 | 0.01* |
| | 6 | 23 | 2.13 | 1.52 | 2 | 2 | | | |
| | 7 | 16 | 3.44 | 2.48 | 4 | 6 | | | |
| Elimination of the initial phoneme | 5 | 7 | 1.57 | 2.70 | 0 | 5 | 2.86 | 2 | 0.24 |
| | 6 | 23 | 2.04 | 2.25 | 1 | 4 | | | |
| | 7 | 16 | 3.25 | 2.75 | 4 | 6 | | | |
| Phonemic substitution | 5 | 7 | 1.57 | 2.69 | 0 | 5 | 4.52 | 2 | 0.11 |
| | 6 | 23 | 2.04 | 2.00 | 2 | 4 | | | |
| | 7 | 16 | 3.44 | 2.80 | 5 | 6 | | | |
| Total score | 5 | 7 | 18.29 | 15.66 | 10 | 32 | 7.58 | 2 | 0.02* |
| | 6 | 23 | 27.96 | 11.28 | 27 | 1 5 | | | |
| | 7 | 16 | 34.50 | 13.38 | 41 | 2 6 | | | |
| Total score - arithmetic mean | 5 | 7 | 2.29 | 1.96 | 1.25 | 4 | 7.58 | 2 | 0.02* |
| | 6 | 23 | 3.49 | 1.42 | 3.37 | 1.88 | | | |
| | 7 | 16 | 4.31 | 1.67 | 5.10 | 3.25 | | | |

N - number of respondents; M - mean value; SD - standard deviation; Md - median; IQR - interquartile range; χ2 – Kraskal Wallis chi square statistic; df - number of degrees of freedom; p - level of significance

substitution and initial phoneme elimination ($p > 0.05$).

The results of the two-factor analysis of variance, which examined the influence of the interaction of language abilities and age on the development of phonological awareness found that there was no statistically significant interaction between language abilities and the age of the examinee on the level of phonological awareness tested by the FONT test ($p > 0.05$). The results of the two-factor analysis of variance show that the effects of

the factors age and language disorder are in the statistically significant interaction in their effect on the dependent variable - phonemic substitution ($F = 3.68$, $df1 = 2$, $df2 = 40$, $p = 0.04$). Subsequent comparisons using Tukey's HSD test show that children's achievements on the syllabic segmentation subtest do not differ significantly between groups of children of different ages ($p > 0.05$).

The graphomotor abilities of children were examined with the prediction test for dysgraphia. The achievements of children with DLD and children with TLD were compared. The results of the Mann-Whitney U test are shown in table 5. Subjects with DLD had almost twice lower achievements on the Prediction Test for Dysgraphia than children with TLD. Adequate figure size was more common in children with TLD than in children with DLD. Children with TLD also satisfied the criterion of figure shape when drawing to a much greater extent than children with DLD. The order of the three figures was correctly remembered by almost all children with TLD, while in the group with DLD there were children who made mistakes in the given arrangement of figures when drawing. All TLD children kept the given distance from the edge of the rectangle while drawing figures, while children with DLD were worse in achieving this criterion. Almost all children from DLD completed the drawing to the end, while all children from TLD completed the task to the end.

By comparing the achievements of boys and girls from the examined sample, no statistically significant difference was found on the Prediction Test for Dysgraphia ($U = 213$, $z = -0.46$, $p = 0.65$). Boys and girls did not differ in terms of figure size criteria ($U = 220$, $z = -0.31$, $p = 0.76$), figure shape ($U = 228.5$, $z = -0.11$, $p = 0.92$), following the sequence of figures ($U = 170$, $z = -1.76$, $p = 0.08$), drawing around the rectangle ($U = 229$, $z = -0.10$, $p = 0.92$), finishing drawings ($U = 222$, $z = -0.34$, $p = 0.73$).

Based on the assumption that age influences graphomotor abilities, the achievements of children of different ages on the Prediction Test for Dysgraphia were compared, and the results are shown in table 6. The Kruskal-Wallis test determined a statistically significant difference in the

**Table 5.** Differences between children with DLD and TLD children in the development of graphomotor abilities

| A predictive test for dysgraphia | | Descriptive statistics | | | | Mann-Whitney U test | | |
|---|---|---|---|---|---|---|---|---|
| | a group | M | SD | Md | IQR | U | z | P |
| Size | DLD | 0.52 | 0.85 | 0 | 1 | 115.0 | -3.49 | 0.001 |
| | TLD | 1.74 | 1.21 | 2 | 2 | | | |
| Shape | DLD | 1.43 | 1.08 | 1 | 1 | 97.0 | -4.01 | 0.001 |
| | TLD | 2.70 | 0.70 | 3 | 0 | | | |
| It follows the order of ed | DLD | 1.87 | 1.22 | 2 | 2 | 130.0 | -3.56 | 0.001 |
| | TLD | 2.91 | 0.28 | 3 | 0 | | | |
| Draws around the rectangle | DLD | 1.74 | 1.14 | 1 | 2 | 103.5 | -4.37 | 0.001 |
| | TLD | 3 | 0 | 3 | 0 | | | |
| Finished drawing | DLD | 2.30 | 0.02 | 3 | 1 | 149.5 | -3.51 | 0.001 |
| | TLD | 3 | 0 | 3 | 0 | | | |
| Total score | DLD | 7.87 | 3.65 | 9 | 7 | 32.0 | -5.16 | 0.001 |
| | TLD | 13.35 | 1.50 | 13 | 3 | | | |

M - mean value; SD - standard deviation; Md - median; IQR - interquartile range; U - Mann Whitney's U score; z - value Z statistic; p - level of significance

**Table 6.** Graphomotor skills in children of different ages - total sample (N = 46)

| A predictive test for dysgraphia | age | Descriptive statistics | | | | | Kruskal-Wallis test | | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | M | SD | Md | IQR | χ2 | df | P |
| Size | 5 | 7 | 0.29 | 0.49 | 0 | 1 | 3.78 | 2 | 0.15 |
| | 6 | 23 | 1.26 | 1.21 | 2 | 2 | | | |
| | 7 | 16 | 1.31 | 1.30 | 1 | 3 | | | |
| Shape | 5 | 7 | 1.00 | 1.15 | 1 | 2 | 10.12 | 2 | 0.01* |
| | 6 | 23 | 2.00 | 1.09 | 2 | 2 | | | |
| | 7 | 16 | 2.63 | 0.72 | 3 | 1 | | | |
| Follow the order of the figures | 5 | 7 | 1.43 | 1.27 | 1 | 3 | 7.28 | 2 | 0.03* |
| | 6 | 23 | 2.48 | 0.95 | 3 | 1 | | | |
| | 7 | 16 | 2.69 | 0.79 | 3 | 0 | | | |
| Draws around the rectangle | 5 | 7 | 1.43 | 1.13 | 1 | 2 | 7.10 | 2 | 0.03* |
| | 6 | 23 | 2.48 | 0.95 | 3 | 1 | | | |
| | 7 | 16 | 2.63 | 0.89 | 3 | 0 | | | |
| Finished drawing | 5 | 7 | 1.43 | 1.39 | 2 | 3 | 13.85 | 2 | 0.001 |
| | 6 | 23 | 2.87 | 0.34 | 3 | 0 | | | |
| | 7 | 16 | 2.88 | 0.34 | 3 | 0 | | | |
| Total score | 5 | 7 | 5.57 | 4.47 | 3 | 8 | 8.84 | 2 | 0.01* |
| | 6 | 23 | 11.09 | 3.40 | 12 | 3 | | | |
| | 7 | 16 | 12.13 | 2.50 | 12 | 5 | | | |

N - number of respondents; M - mean value; SD- standard deviation; Md - median; IQR - interquartile range; χ2 - Kraskal Wallis chi square statistic; df - number of degrees of freedom; p - level of significance

level of graphomotor abilities of three different age groups. The youngest age group had lower median score than the other two age groups. To the greatest extent, the oldest subjects drew figures of regular shape, a slightly weaker satisfaction of this criterion was observed in the group of six-year-olds, while the youngest subjects had a lot of difficulty in drawing the given shapes. Five-year-old children did not follow the given sequence of figures when drawing, and errors of this type were also observed in the group of children aged six, while children aged seven made the fewest mistakes when drawing given figures. The youngest respondents had difficulty in maintaining the specified distance from the edge of the rectangle when drawing figures, unlike the older children who had a lot of success in meeting this criterion. The group of 7-year-old children was almost completely successful in satisfying the criterion of a completed drawing, while the youngest respondents stopped the task before completing it. The influence of age on drawing the appropriate figure size has not been determined.

## Discussion

Research in our speaking area has shown that the development of phonological awareness is an indicator of children's later acquisition of reading, as well as that graphomotor abilities influence the development of children's writing skills [7, 8]. Therefore, the aim of this research is to determine phonological awareness and graphomotor abilities, as pre-skills for reading and writing, in children with developmental language disorder (DLD) and children with typical language development (TLD). The results show that children with DLD have significantly lower achievements on the phonological awareness test compared to children with TLD. Our results are in agreement with the results of other studies which also showed that phonological awareness correlated with children's language abilities [11]. According to the results of our research, joining syllables, syllabic segmentation and rhyme recognition were the easiest results of phonological awareness, both in subjects with DLD and subjects with TLD. This is supported by the high achievements on all tasks, with the fact that the children with TLD were still more successful than the children with DLD. Better development of syllabic segmentation, joining of syllables and recognition of rhyme in relation to the development of other elements of phonological awareness were also shown by the research results of other authors [12]. Data from the literature generally show that children with DLD have particularly poor achievements on more complex phonological awareness tasks [13]. In a recently published study, it was shown that children with DLD had better results on tasks of phonological synthesis compared to analysis, with the fact that children with TLD were significantly more successful in all tasks [11]. According to the results of our research, children with DLD had difficulties in identifying initial and final phonemes, phonemic segmentation, substitution and elimination. Eliminating the phoneme and identifying the final phoneme were the most difficult tasks for the children from our sample, while in the research of Golubović et al., the most difficult tasks were the elimination of the initial phoneme and the phoneme substitution task [4]. In other studies conducted on a larger sample of children with DLD and TLD children, it was determined that children with DLD had a significantly lower level of phonemic awareness compared to children with TLD [11], as well as that children with DLD had significantly lower achievements in rhyme recognition and production tasks, which coincides with the results of this research [14].

According to the results of our research, gender had no influence on phonological awareness in preschool children. The difference was not established even when we looked separately at boys and girls from the group with DLD and the group with TLD. In this sense, our results coincide with the results of the research conducted by Golubović et al., which also showed that gender did not represent a significant success factor in phonological awareness tasks [5].

The results of our study showed that children of the youngest age (5 years old) had very low achievements on phonological awareness tasks compared to children aged six and seven years. Other research has also shown that achievements on the phonemic awareness test depend on age [5, 9]. Our data show that older children were more successful than younger children in tasks of identifying the initial and completed phonemes. In contrast to our results, Golubović et al indicate a trend of increasing average scores on the tasks of phonemic segmentation, identification of the final phoneme, elimination of the initial phoneme and phonemic substitution with the age of the subjects [12]. This difference in results may be the result of the fact that the authors of the mentioned study had school-age subjects in their sample, who had

already been included in intensive reading training. Generally speaking, the differences between the results of our research and some earlier researches on phonological awareness can be attributed to the small sample included in this study and the unequal distribution of respondents in age groups.

Regarding the assessment of graphomotor abilities, children with DLD had as twice as poor achievements on the Prediction Test for Dysgraphia compared to children with TLD. This finding indicates the possible presence of deficits in fine motor skills in children with DLD, which were otherwise established in earlier research on the relationship between language and motor skills in children with DLD [15]. Children with DLD more often drew figures of inadequate size and shape, made more mistakes in the given order of figures and showed difficulties in keeping the given distance from the edge of the rectangle while drawing and difficulties in completing the task to the end. According to the high average scores that the children from both groups achieved on this criterion, it can be said that most of the children were persistent and finished the drawing. The results of earlier research on graphomotor skills in preschool children were quite variable. For example, Nikolić et al. stated that the children in their sample were highly motivated and that they all successfully completed the task, while Ćalasan et al. determined that 42.9% of the children included in the sample had difficulty solving the task independently [16, 7].

According to the results of our research, gender did not affect the graphomotor abilities of the children from the examined sample. However, the results of other studies have shown gender differences on the Prediction Test for Dysgraphia. More precisely, boys were found to have a greater presence of elements suspicious of dysgraphia, while girls had difficulty drawing figures of the appropriate size [17].

Our results show that graphomotor skills improve with age. Children of the youngest age had very low achievements on the Prediction Test for Dysgraphia, while graphomotor abilities were significantly better in older children. Similar results were found in earlier researches [18].

## Conclusion

Analyzing the obtained results we can conclude that phonological awareness and graphomotor abilities are more developed in children with TLD compared to children with DLD. It was also determined that success on the test of phonological awareness and graphomotor abilities increased with age in both groups of subjects.

Disturbances in reading and writing can occur in children with the developmental language disorder, but also in children with typical language development. Given that the estimated graphomotor abilities and the level of phonological awareness in children have a predictive role in the development of reading and writing, preschool children should be provided with additional support in developing these abilities. Early recognition of deficits in terms of phonological awareness and the development of graphomotor skills aim to prevent reading and writing disorders. This support is needed by children with language disorders, as well as children with typical language development.

A limitation of this study is the relatively small sample size, so future research should include a larger number of respondents. Another limitation of the study is reflected in the finding of research that used the same tests and a sample of similar characteristics exclusively from the Serbian speaking area, so there is no comparison of the results with research from other speaking areas.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** The Ethics Committee of the Primary school "Desanka Maksimović" Trn, Banja Luka, Republic of Srpska, Bosnia and Herzegovina, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

**Conflicts of interest.** The authors declare no conflict of interest.

## References:


1. Vuković M. Afaziologija. 3. izd. Univerzitet u Beogradu, Fakultet za specijalnu edukaciju i rehabilitaciju, 2011.
2. Ječmenica N, Golubović S. Odnos između socioekonomskog statusa roditelja, fonološke svesnosti i radne memorije kod dece predškolskog uzrasta. Zbornik radova. 11. Međunarodni naučni skup „Specijalna edukacija i rehabilitacija danas", Beograd, Srbija, 29–30.10. 2021;389–97.
3. Golubović S. Fonološki poremećaji. Društvo defektologa Srbije, Beograd; 2017.
4. Golubović S, Ječmenica N, Subotić S, Kobac D. Razvoj fonološke svesnosti kod dece uzrasta od šest do osam godina. Primenjena psihologija 2019;12(2):157–82.
5. Golubović S, Ječmenica N, Jovanović-Simić N, Petrović-Lazić M. Artikulacione i fonološke sposobnosti dece uzrasta od pet do sedam godina. Nastava i vaspitanje 2019;68(2):265–83.
6. Milankov V. Deficit fonološke svesnosti kod dece sa disleksijom i disortografijom. Doktorska disertacija. Univerzitet u Novom Sadu, 2016.
7. Ćalasan S, Vuković M, Pavlović A, Vuković B, Zečević I. Povezanost grafomotornih sposobnosti i lateralizovanosti kod djece predškolskog uzrasta. Beogradska defektološka škola 2015;21(2):25–37.
8. Čolić G, Vuković M. Doprinos fonološke i sintaksičke svesnosti u početnom čitanju. Psihološka istraživanja 2018;21(1):75–90.
9. Subotić S. Konstrukcija testa fonološke svijesti na srpskom jeziku. Primenjena psihologija 2011;4(2):127–49.
10. Kostić Đ, Vladisavljević S, Popović M. Testovi za ispitivanje govora i jezika. Beograd: Zavod za udžbenike i nastavna sredstva, 1983.
11. Milošević NR, Vuković MG, Ristić ID. Phonemic awareness as an indicator of preliteral abilities in Serbian speaking children with and without specific language impairment. Inovacije u nastavi-časopis za savremenu nastavu 2022;35(1):118–31.
12. Golubović S, Radivojević ND, Ječmenica N. Phonological abilities of preschool children. Inovacije u nastavi-časopis za savremenu nastavu 2019;32(3):74–89.
13. Vuković M, Jovanovska M, JerkićRajić L. Phonological awareness in children with developmental language disorder. Arch Public Health 2022;14(1):1–10.
14. Milošević N, Vuković M. Awareness of Rhyme in Preschool Children with Specific Language Impairment and Without Language Difficulties. Croat J Educ 2018;20(2):237–57.
15. Vuković M, Vuković I, Stojanovik, V. Investigation of language and motor skills in Serbian speaking children with specific language impairment and in typically developing children. Res Dev Disabil 2010;31(6):1633–44.
16. Nikolić S, Ilić-Stošović D, Ilić S, Pešić S. Grasp maturity and writing ability among preschool children. Beogradska defektološka škola 2012(3):583–95.
17. Vuković M, Ćalasan S, Jovanović-Simić N, Kulić M. Assessment of dysgraphia in young school children. Biomedicinska istraživanja 2015;6(1):11–7.
18. Lazarević E, Stevanović J, Lalić-Vučetić N. O nekim aspektima pripreme dece predškolskog uzrasta za opismenjavanje: razvoj grafomotorike. Kragujevac, 2016. Zbornik radova. Savremeno predškolsko vaspitanje i obrazovanje: izazovi i dileme, Kragujevac, 2016;87–102.

# Predvještine čitanja i pisanja kod djece sa razvojnim jezičkim poremećajem i djece tipičnog jezičkog razvoja

Mirjana Korlaet[1], Mile Vuković[2], Jelena Tešić[3]

[1]Servis centar "Dajte nam šansu - Zvjezdice", Banja Luka, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet u Beogradu, Fakultet za specijalnu edukaciju i rehabilitaciju, Beograd, Srbija

[3]Osnovna škola "Vuk Karadžić", Bijeljina, Republika Srpska, Bosna i Hercegovina

**Uvod**. Pored razvijenosti govornog jezika, tipičnih intelektualnih sposobnosti, očuvanosti čula sluha i vida, za savladavanje vještina čitanja i pisanja neophodne su fonološka svjesnost i sposobnost grafomotornog izražavanja. S obzirom na to, cilj ovog istraživanja je utvrđivanje nivoa fonološke svijesti i sposobnosti grafomotornog izražavanja kod djece sa razvojnim jezičkim poremećajem (RJP) i djece tipičnog jezičkog razvoja (TJR).

**Metode**. Uzorak je činilo 46 djece uzrasta od 5 do 7 godina, koja su na osnovu statusa govorno-jezičkih sposobnosti podijeljena u dvije grupe. Prvu grupu činilo je 23 djece sa RJP, a drugu 23 djece TJR. Za procjenu fonološke svjesnosti korišćen je FONT test, a za procjenu grafomotornih sposobnosti Predikcioni test za disgrafiju.

**Rezultati**. Rezultati istraživanja su pokazali da su djeca sa RJP bila lošija na zadacima fonološke svjesnosti u poređenju sa djecom TJR. Uzrast se pokazao kao značajan faktor razlika u razvijenosti fonološke svjesnosti. Postignuća na Predikcionom testu za disgrafiju pokazuju da djeca sa RJP imaju skoro dvostruko slabiju sposobnost grafomotornog izražavanja u poređenju sa djecom TJR. Nadalje, rezultati istraživanja su pokazali da postoje značajne razlike u nivou razvijenosti grafomotornih sposobnosti između djece različitog uzrasta. Takođe, nije utvrđena značajna razlika u postignućima na Predikcionom testu za disgrafiju, ni na FONT testu u odnosu na pol.

**Zaključak**. Djeca sa razvojnim jezičkim poremećajem imala su znatno slabija postignuća na testu fonološke svjesnosti i predikcionom testu za disgrafiju u poređenju s djecom tipičnog jezičkog razvoja.

**Ključne riječi**: grafomotorna sposobnost, fonološka svjesnost, razvojni jezički poremećaj, tipični jezički razvoj, predvještine čitanja i pisanja

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):77–86

UDK: 159.923.2:616.28-008.14-053.8
DOI: 10.59137/BII202301303K

*Original article*

# Self-assessment of adults with acquired hearing loss in the context of self-esteem and psychosocial functioning

**Jasmina B. Karić[1], Milena B. Kordić[1], Gorica Vuksanović[2], Jana Mitrić[1]**

[1]University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia

[2]University of East Sarajevo, Faculty of Medicine Foca, Republic of Srpska, Bosnia and Herzegovina

Primljen – Received: 15/03/2023
Prihvaćen – Accepted: 26/04/2023

**Corresponding author:**
*Milena B. Kordić, Assistant*
*Visokog Stevana 2, 11000 Belgrade*
*kordicmilena367@gmail.com*



**Summary**

**Introduction**. The consequences of acquired hearing loss in adults condition their psychosocial functioning and imply changes in the quality of life related to disorders in social and emotional functioning. Hearing loss is considered a risk factor for reduced psychosocial functioning and self-esteem. Psychosocial well-being and preserved self-esteem imply having a positive self-image and realizing that a person is an important part of the social community in which he/she lives. The paper deals with self-esteem and psychosocial functioning of adults with acquired hearing loss. The aim of this research is to determine the level of self-esteem and the degree of expression of consequences in psychosocial functioning, that is, the connection between the level of self-esteem and the degree of expression of consequences in psychosocial functioning in adults with acquired hearing loss.

**Methods**. The research was conducted on a sample of 60 adult subjects with acquired hearing loss and 60 subjects with normal hearing. The average age of the respondents with hearing loss was 54.1 (*SD* = 10.84), and the sample consisted mostly of male respondents (56.7%) with moderate hearing loss (25.4%). The Rosenberg Self-Esteem Scale and the questionnaire for the subjective assessment of the hearing condition - the HHIA questionnaire (Hearing Handicap Inventory for Adults) were used as instruments.

**Results**. The results showed that the respondents expressed moderate or average self-esteem and that there was a connection between self-esteem and psychosocial functioning in adults with acquired hearing loss.

**Conclusion**. Future research could be directed more towards examining self-esteem in more detail in more specific domains of psychosocial functioning of adults with acquired hearing loss.

**Key words**: hearing loss, adults, self-esteem, psychosocial functioning

## Introduction

Hearing loss implies a permanent decrease in auditory sensitivity to sound i.e a reduced ability to perceive sound stimuli and can be congenital or acquired [1, 2]. Acquired hearing loss is one of the most common chronic conditions affecting adults [3, 4]. The consequences of acquired hearing loss in adults condition their psychosocial functioning and imply changes and disorders in social and emotional functioning, i.e. reduced participation in social activities and impaired mental health [5].

Sebastian, Varghese and Gowri [6] conducted research with the aim of determining the relationship between hearing loss and psychosocial functioning, and their results showed that acquired hearing loss in adulthood significantly affected the psychosocial well-being of an individual.

Communication is the first aspect in the psychosocial functioning of adults with acquired hearing loss where the consequences and difficulties are observed [7]. In the context of hearing loss, limitations in communication refer to difficulties in understanding and following direct spoken or telephone communication [8]. Negative communication experiences in individuals with hearing loss firstly lead to the feeling of being left out, resulting in avoiding social interactions and group experiences [9]. Research shows that their participation in social activities significantly decreased after the onset of hearing loss and that hearing loss negatively affected the social aspect of their functioning [10–13].

By further limiting the situations in which they can participate, people with acquired hearing loss are at risk of social isolation [12, 14, 15].

Social isolation, impaired interpersonal interactions reflect on the quality of life of adults with acquired hearing loss, which further often leads to emotional difficulties and changes in psychological functioning [16, 17]. In respondents with hearing loss, the most common mental difficulties that lead to changes in psychological functioning are the increased presence of symptoms of depression, anxiety and phobic anxiety [17, 18–25].

Self-esteem implies the evaluation individuals create or maintain about themselves, which reflects the attitude of acceptance or rejection and refers to the level at which the individuals perceive themselves as capable, successful, significant and valuable [26]. Hearing loss is considered the risk factor for reduced psychosocial functioning and self-esteem. Psychosocial well-being and preserved self-esteem imply having a positive self-image and recognizing that a person is an important part of the social community in which he/she lives [27]. During self-assessment, we are guided by an objective evaluation of our own abilities and skills and an evaluation based on social acceptance. The community sees hearing loss as an obstacle to participation in society, underestimates the abilities of people with hearing impairment and considers them inferior members of society [15, 28, 29]. Individuals with hearing loss tend to question their worth and self-esteem [15].

As communication difficulties become a source of frustration over time, numerous negative emotional reactions develop, such as shame, guilt, discomfort, loneliness, further leading to the loss of self-confidence and self-esteem. Re-experiencing negative emotions leads to the creation of a bad self-image, a feeling of incompetence, and then to complete isolation and depression [30, 31].

Self-esteem is at the core of many problems and changes that arise in the psychosocial functioning of adult individuals. The collapse of the level of self-esteem and the sense of loss of control over oneself, which occurs when the person loses their hearing capacity, are serious triggers of stress, depression and anxiety [32]. Through the previous paragraphs, these symptoms and disorders are described as problems and changes that can occur in the functioning of adults with acquired hearing loss. When self-esteem is included in the overall story, we see that self-esteem and the consequences that occur in psychosocial functioning are closely related and that it is necessary to further investigate this relationship in adult individuals with acquired hearing loss.

*Our objective was* the self-assessment of adults with acquired hearing loss in the context of self-esteem and psychosocial functioning research aiming to determine the level of self-esteem and the degree of expression of consequences in psychosocial functioning, i.e. whether there is a connection between the level of self-esteem and the degree of expression

of consequences in psychosocial functioning in adults with acquired hearing loss damage. The aim of the research was determined through the following tasks:

1. to examine whether there are differences in the level of self-esteem among adults with acquired hearing loss in relation to the degree of expression of consequences in psychosocial functioning;

2. to examine whether there are differences in the level of self-esteem between adults with acquired hearing loss and adults with preserved hearing;

3. to examine whether there are differences in the level of self-esteem among adults with acquired hearing loss in relation to the degree of hearing loss; and

4. to check whether there are differences in the level of self-esteem between respondents of different genders.

## Methods

A total of 120 respondents were included in this research. The sample was divided into group A and group B. The group A consisted of people with acquired hearing loss, while the group B consisted of people with preserved hearing. The groups were equal according to the number of respondents, so there were 60 respondents in each group.

The level of self-esteem was measured using the Rosenberg Self-Esteem Scale [26] consisting of 10 items where five statements of the scale were in the positive direction (e.g. I feel that I have many good qualities) and five in the negative direction (e.g. I feel that there is not much that I can be proud of) with reverse scoring. The respondent should indicate the degree of agreement from 3 - I completely agree to 0 - I do not agree at all.

According to the author of the scale, the results of the general self-esteem scale are divided into three groups: low (score below 15), average/moderate (score from 15 to 25) and high self-esteem (score over 25). At the level of Rosenberg's self-esteem scale, good reliability was registered in this research ($\alpha = 0.85$).

Variables gender and level of hearing loss were obtained using a questionnaire on the sociodemographic characteristics of the respondents, while the degree of expression of consequences in psychosocial functioning variable was obtained through the subjective assessment of hearing condition questionnaire - HHIA questionnaire (Hearing Handicap Inventory for Adults) [33].

The results of the HHIA questionnaire, according to foreign authors, are described by the term hearing handicap, which in this case implies the degree of expression of consequences in psychosocial functioning. The questionnaire contains 25 items, where 13 of those items refer to social issues. Respondents answer these questions with yes, sometimes and no. Scores with less than 16 points on the HHIA questionnaire indicate the absence of a hearing handicap (a low level of expression of consequences in psychosocial functioning), scores from 16 to 42 points indicate a mild to moderate degree of expressiveness of the consequences in psychosocial functioning, while scores with over 42 points indicate the significant hearing handicap (high degree of expressiveness of the consequences in psychosocial functioning). Based on the HHIA questionnaire, in our research, high reliability was registered ($\alpha = 0.94$).

## Results

In the group A the sample consisted mostly of male respondents (56.7%), while in the group B the number of male and female respondents was equal. The age of the subjects ranged from 22 to 65 years, with the average age in the group of subjects with acquired hearing loss being 54.1 (SD = 10.84) and in the group of subjects with preserved hearing 52 (SD =11.49). In the group A, the largest number of subjects had moderate hearing loss (25.4%).

**Table 1.** Sample structure of the group A according to gender and degree of hearing impairment (N=60)

| | Groups of respondents | f | % |
|---|---|---|---|
| **Gender** | Male | 34 | 56.7 |
| | Female | 26 | 43.3 |
| **Degree of hearing loss** | Mild | 14 | 22.2 |
| | Moderate | 16 | 25.4 |
| | Moderately severe | 11 | 17.5 |
| | Severe | 12 | 19.0 |
| | Profound | 7 | 11.1 |

Based on descriptive statistics, it was determined that the largest number of adult respondents with acquired hearing loss, 41 or 68.3%, showed moderate or average self-esteem. The results of the t-test for one sample showed that the **average value of the level of self-esteem** in adults with acquired hearing loss ($N$ = 60, $M$ = 21.42, $SD$ = 4.58) was statistically significantly above the assumed critical value for the low level of self-esteem ($t$ =10.85, $df$ =59, $p$ < 0.001). The obtained average value indicates moderate or average self-esteem in adults with acquired hearing loss, which is in accordance with the data from descriptive statistics.

The average score of the respondents on the HHIA questionnaire ($N$ = 60, $M$ = 35.33, $SD$ = 25.82) fits into the interval from 16 to 42 points, which implies a mild to moderately significant hearing handicap. This result, that is, the level of hearing handicap, actually indicates a mild to moderate degree of expressiveness of the consequences in the psychosocial functioning of adults with acquired hearing loss.

According to the results of the Shapiro-Wilk test, the empirical distribution of measures on the self-esteem level of adults with acquired hearing loss variable ($W$ = 0.98, $p$ = 0.19) does not deviate statistically significantly from the normal distribution model, while in the case of the empirical distribution of measures on the level of hearing handicap variable ($W$ = 0.93, $p$ < 0.01) there is a statistically significant deviation from the normal distribution model. According to the results of the Shapiro-Wilk test, the connection between the level of self-esteem and the level of hearing handicap variables was checked using a non-parametric (Spearman) correlation analysis. The results of Spearman's correlation analysis show that there is the statistically significant relationship between the level of self-esteem and the level of hearing handicap ($r$ = - 0.56, p < 0.001). The values of the correlation coefficient show that there is a negative correlation of moderate intensity between these two variables, where the increase in the level of hearing handicap is associated with the decrease in the level of self-esteem. This result indicates that significant levels of hearing handicap, i.e., greater degree of expression of consequences in psychosocial functioning are associated with lower levels of self-esteem in adults with acquired hearing loss.

**Table 2.** Descriptive data for subjects with acquired hearing loss and subjects with preserved hearing on the self-esteem scale (N=120)

| | Group of respondents | N | M | SD | $SE_M$ |
|---|---|---|---|---|---|
| Level of self-esteem | Adults with acquired hearing loss | 60 | 21.42 | 4.58 | 0.59 |
| | Adults with preserved hearing | 60 | 20.95 | 5.62 | 0.73 |

**M** - average value of the level of self-esteem; **SD** - standard deviation; **SEM** - standard error of the mean

According to the results of the Shapiro-Wilk test, the scores on the self-esteem level variable were normally distributed both in adult subjects with acquired hearing loss ($W$ = 0.98, p = 0.19) and in adult subjects with normal hearing ($W$ = 0.97, p = 0.09). Based on these results, the difference in the level of self-esteem between adult subjects with acquired hearing loss and adult subjects with normal hearing was checked using the t-test for dependent samples. The results of the t-test for dependent samples showed that there was no statistically significant difference between adult subjects with acquired hearing loss and adult subjects with normal hearing regarding the level of self-esteem ($t$ = 0.48, df = 59, $p$ = 0.63, $d$ = 0.06).

According to the results of the Shapiro-Wilk test, the scores on the self-esteem level variable were normally distributed in both male ($W$ = 0.98, $p$ = 0.88) and female ($W$ = 0.93, p = 0.09) adult subjects with acquired hearing loss. The variances in these two groups were approximately equal, as shown by the results of Levene's test ($F$ = 0.01, $df$ = 1, $p$ = 0.94). Based on these results, the difference between male and female respondents in their attitudes towards deafness was checked using the parametric Student's t-test. The results of the Student's t-test showed that the difference between male and female respondents in attitudes towards deafness was not statistically significant ($t$ = - 1.33, $df$ = 58, $p$ = 0.19, $d$ = - 0.34).

According to the results of the Shapiro-Wilk test, the scores on the self-esteem level variable were normally distributed in the subsamples of subjects with mild hearing loss ($W$ = 0.93, $p$ = 0.31), subjects with moderate hearing loss (W = 0.97, $p$ = 0.13) and subjects with moderately severe hearing loss ($W$ = 0.86, $p$ = 0.07), subjects with severe hearing loss ($W$ = 0.91, $p$ = 0.21) and subjects with profound hearing loss ($W$ = 0.83, $p$ = 0.08). The results of Levene's test indicate the approximate equality of variances between all groups of respondents ($F$ = 1.63, $p$ = 0.18). In accordance with the results of the Shapiro-Wilk test, the differences in the level of self-esteem between subjects with different degrees of hearing loss were checked using a parametric test, i.e. using a one-factor analysis of variance. The results of the one-factor analysis of variance showed that there is no statistically significant difference in the level of self-esteem between subjects with different degrees of hearing loss ($F$ = 0.39, $df1$ = 4, $df2$ = 55, p = 0.82, $\eta 2$ = 0.03).

**Table 3.** Descriptive data for male and female respondents on the self-esteem scale (N=60)

| | Gender | N | *average value of the level of self-esteem* | SD | SE M |
|---|---|---|---|---|---|
| Level of self-esteem | Male | 34 | 20.74 | 4.59 | 0.79 |
| | Female | 26 | 22.31 | 4.51 | 0.88 |

**Table 4.** Descriptive data for subjects with different degrees of hearing loss before applying one-factor analysis of variance (N = 60)

| Degree of hearing impairment | N | *average value of the level of self-esteem* | SD |
|---|---|---|---|
| Mild | 14 | 22.21 | 4.14 |
| Moderate | 16 | 20.44 | 5.25 |
| Moderately severe | 11 | 21.82 | 5.21 |
| Severe | 12 | 21.92 | 4.93 |
| Profound | 7 | 20.57 | 2.22 |

## Discussion

The results of the research show that adult respondents with acquired hearing loss express moderate or average self-esteem. In addition, in adult subjects with acquired hearing loss, there is the mild to moderately significant auditory handicap, which actually indicates the mild to moderate degree of expressiveness of the consequences in psychosocial functioning. The results also show that there is a connection (in the form of a negative correlation) between the level of self-esteem and the degree of expression of consequences in psychosocial functioning. More significant levels of hearing handicap, that is, a greater degree of expressiveness of consequences in psychosocial functioning is associated with lower levels of self-esteem in adults with acquired hearing loss. Adult subjects with acquired hearing loss do not differ in their level of self-esteem from subjects from the control group who have normal hearing. Gender and degree of hearing loss did not prove to be a statistically significant factor contributing to changes in the level of self-esteem.

By reviewing of the available literature it was found that communication challenges and the impossibility of quality participation in social interactions, in addition to disrupting daily functioning and causing stress, also led to persons starting to form a negative image of themselves, which can put their self-esteem in question [34]. If the person experiences stress due to hearing loss or changes occur in psychological functioning, this can affect the level of self-esteem [35]. Hearing loss affects the entire psychosocial functioning of the individual, and is mostly associated with reduced participation in social activities, feelings of loneliness, symptoms of anxiety and depression, and impaired self-esteem [36]. Research on the relationship between self-esteem and hearing loss shows that the level of self-esteem in adults with acquired hearing loss is low [19, 32]. Such findings are not consistent with our research.

The respondents in our research show moderate or average self-esteem, which points to the interpretation that they have maintained a certain level of self-esteem and that they manage to deal with the consequences of hearing loss with the mild to moderate degree of expression of the consequences in psychosocial functioning. One explanation could be that in adulthood, self-esteem gradually increases as status, power, and social position increase, peaking in the late 60s. After that, self-esteem declines again due to changes in roles, relationships and psycho-physical functioning, and the strongest decline is caused by facing the transience of life, which begins in the 70s [37]. On the other hand, the problems of adults with acquired hearing loss arise in interaction with other people. Individuals do not know how people from the immediate or distant environment or an unknown person will react to their new situation and whether their attitudes will match established stereotypes [38]. In this context, adult individuals with acquired hearing loss want to preserve their self-image and their social identity and invest more cognitive effort, which can be tiring, frustrating and negative experience [39]. In addition, adults with acquired hearing loss often use defense mechanisms to preserve their previously achieved level of self-esteem. Among the most frequently used mechanisms are rejection and neglect, especially in those persons with mild to moderate hearing loss. As dealing with the acquired loss directly affects self-image, it is easier for individuals to ignore the presence of impairment and refuse interactions and communication [40]. The efforts and mechanisms that adults with acquired hearing loss make to preserve their self-image and self-esteem, in addition to dealing with the consequences of hearing impairment, additionally affect their psychosocial functioning, which creates a vicious circle between hearing loss, psychosocial functioning and self-esteem, with insufficiently clear mechanisms of their mutual influence.

By introducing the group B in our research,

we wanted to check whether there were implications that would make future research to examine the existence of a direct relationship between hearing loss and the level of self-esteem. However, as the results of our research showed that the level of self-esteem of adult respondents with acquired hearing loss did not differ from respondents from the group B who have normal hearing, we believe that hearing loss alone, as a factor, does not directly affect the level of self-esteem in adults with hearing loss. With this type of damage, future research could be directed more towards examining in more detail the level of self-esteem itself, as well as the level of self-esteem in special, more specific domains of psychosocial functioning of adults with acquired hearing loss. A more detailed examination of the level of self-esteem would involve researching the structure of self-esteem from the perspective of factors that affect it , i.e. whether its level is more influenced by the individual's personal experience and experiences or the evaluations and respect expressed by others. With this approach, considering the specifics of the consequences of hearing loss, it should also be checked whether there are changes and differences in the level of self-esteem, especially in relation to the emotional and social components of the functioning of adults encountering this type of impairment.

## Conclusion

Research has shown that there is a connection between self-esteem and psychosocial functioning in adults with acquired hearing loss. The higher degree of expressiveness of consequences in psychosocial functioning leads to the lower level of self-esteem. The moderate or average self-esteem of the respondents in our research indicates that adults with acquired hearing loss managed to maintain a certain level of self-esteem and that they manage to deal with the consequences of hearing loss with the mild to moderate degree of expression of the consequences in psychosocial functioning. Gender and degree of hearing loss did not prove to be statistically significant factors contributing to changes in the level of self-esteem. Adult subjects with acquired hearing loss do not differ in their level of self-esteem from subjects from the group B who have normal hearing.

The obtained results open up a series of new questions that point to the need of examining not only the level, but in general, the entire construct of self-esteem in adults with acquired hearing loss in more detail, with reference to specific domains of psychosocial functioning.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** The Ethics Committee of the University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

**Conflicts of interest.** The authors declare no conflict of interest.

**References:**


1. Babić B. Audiologija i vestibulologija. Beograd: Fakultet za specijalnu edukaciju i reabilitaciju; 2007.
2. Katz J, Steele TC. Introduction to hearing Impairment and hearing disability. In: Hull RH, editor. Introduction to Aural Rehabilitation: Serving Children and Adults with Hearing Loss. 3th ed. San Diego: Plural Publishing; 2019. p. 23–43.
3. Olusanya BO, Neumann KJ, Saunders JE. The global burden of disabling hearing impairment: a call to action. Bull World Health Organ 2014;92(5):367–73.
4. Yang CH, Schrepfer T, Schacht J. Age-related hearing impairment and the triad of acquired hearing loss. Front Cell Neurosci 2015;9:276.
5. Weinstein BE. What hearing impairment measures do not tell us-but self-report measures do. The Hearing Journal 2015;68(11):26–8.
6. Sebastian S, Varghese A, Gowri M. The impact of hearing loss in the life of adults: A comparison between congenital versus late onset hearing loss. Indian J. Otol 2015; 21(1):29.
7. Schow RL, Nerbonne MA, Sanford CA. Overview of Audiologic Rehabilitation. In: Schow RL, Nerbonne MA, editors. 7th ed. Introduction to Audiologic Rehabilitation Pearson Education. Pearsons; 2017. p. 3–31.
8. Tye-Murray N. Foundations of aural rehabilitation: Children, adults, and their family members. 5th ed. San Diego: Plural Publishing; 2020.
9. Laplante-Lévesque A, Hickson L, Worrall L. Rehabilitation of older adults with hearing impairment: a critical review. J Aging Health 2010;22(2):143–53.
10. Monzani D, Galeazzi GM, Genovese E, Marrara A, Martini A. Psychological profile and social behaviour of working adults with mild or moderate hearing loss. Acta Otorhinolaryngol Ital 2008;28(2):61–6.
11. Wänström G, Öberg M, Rydberg E, Lunner T, Laplante-Lévesque A, Andersson G. The psychological process from avoidance to acceptance in adults with acquired hearing impairment. Hear. Balance Commun 2014;12(1):27–35.
12. Hricová M. Coping strategies and social environment of patients with sudden hearing loss. Health Psychol. Rep 2018;6(3):216–21.
13. Shoham N, Lewis G, Favarato G, Cooper C. Prevalence of anxiety disorders and symptoms in people with hearing impairment: a systematic review. Soc Psychiatry Psychiatr Epidemiol 2019;54(6):649–60.
14. Manchaiah VKC, Stephens D. The patient journey of adults with sudden-onset acquired hearing impairment: a pilot study. J Laryngol Otol 2012;126(5):475–81.
15. Lash BN, Helme DW. Managing Hearing Loss Stigma: Experiences of and Responses to Stigmatizing Attitudes & Behaviors. South. Commun. J 2020;85(5):302–15.
16. Blazer DG, Tucci DL. Hearing loss and psychiatric disorders: a review. Psychol Med 2019;49(6):891–7.
17. Scinicariello F, Przybyla J, Carroll Y, Eichwald J, Decker J, Breysse PN. Age and sex differences in hearing loss association with depressive symptoms: analyses of NHANES 2011– 2012. Psychol Med 2019;49(6):962–8.
18. Tambs K. Moderate effects of hearing loss on mental health and subjective wellbeing: results from the Nord-Trøndelag Hearing Loss Study. Psychosom Med 2004;66(5):776–82.
19. Chisolm TH, Johnson CE, Danhauer JL, Portz LJ, Abrams HB, Lesner S, et al. A systematic review of health-related quality of life and hearing aids: final report of the American Academy of Audiology Task Force On the Health-Related Quality of Life Benefits of Amplification in Adults. J Am Acad Audiol 2007;18(2):151–83.
20. Cetin B, Uguz F, Erdem M, Yildirim A. Relationship between Quality of Life, Anxiety and Depression in Unilateral Hearing Loss. Int Adv Otol 2010;6(2):252–7.
21. McMahon CM, Gopinath B, Schneider J, Reath J, Hickson L, Leeder SR, et al. The need for improved detection and management of adult-onset hearing loss in australia. Int J Otolaryngol 2013;2013:308509.
22. Tseng CC, Hu LY, Liu ME, Yang AC, Shen CC, Tsai SJ. Risk of depressive disorders following sudden sensorineural hearing loss: A nationwide population-based retrospective cohort study. J Affect Disord 2016;197:94–9.

23. Leigh-Hunt N, Bagguley D, Bash K, Turner V, Turnbull S, Valtorta N, et al. An overview of systematic reviews on the public health consequences of social isolation and loneliness. Public Health 2017;152:157–71.

24. Arslan F, Aydemir E, Kaya YS, Arslan H, Durmaz A. Anxiety and depression in patients with sudden one-sided hearing loss. Ear Nose Throat J 2018;97(10-11):E7–E10.

25. Sharma RK, Chern A, Golub JS. Age-Related Hearing Loss and the Development of Cognitive Impairment and Late-Life Depression: A Scoping Overview. Semin Hear 2021;42(1): 10–25.

26. Rosenberg M. Society and the adolescent self-image. Princeton: Princeton University Press, 1965.

27. Tye-Murray N. Fundations of Aural Rehabilitation: Children, Adults, and There Family Members. 4th ed. Boston: Delmar Cengage Learning; 2014.

28. Wallhagen MI. The stigma of hearing loss. Gerontologist 2010;50(1):66–75.

29. Manchaiah V, Rönnberg J, Andersson G, Lunner T. Stages of Change Profiles among Adults Experiencing Hearing Difficulties Who Have Not Taken Any Action: A Cross-Sectional Study. PLoS One 2015;10(6):e0129107.

30. Ciorba A, Bianchini C, Pelucchi S, Pastore A. The impact of hearing loss on the quality of life of elderly adults. Clin Interv Aging 2012;7:159–63.

31. Bonetti L, Ratkovski I, Šimunjak B. Suvremena rehabilitacija odraslih osoba sa stečenim oštećenjem sluha. Liječnički vjesnik 2017;139(9-10):0–0.

32. Corna LM, Wade TJ, Streiner DL, Cairney J. Transitions in hearing impairment and psychological distress in older adults. Can J Psychiatry 2009;54(8):518–25.

33. Newman CW, Weinstein BE, Jacobson GP, Hug GA. The Hearing Handicap Inventory for Adults: Psychometric Adequacy and Audiometric Correlates. Ear Hear 1990;11(6):430–3.

34. Hetu R, Riverin L, Lalande N, Getty L, St-Cyr C. Qualitative analysis of the handicap associated with occupational hearing loss. Br J Audiol 1988;22(4):251–64.

35. Espmark AK, Rosenhall U, Erlandsson S, Steen B. The two faces of presbyacusis: hearing impairment and psychosocial consequences. Int J Audiol 2002;41(2):125–35.

36. Nachtegaal J, Kuik DJ, Anema JR, Goverts ST, Festen JM, Kramer SE. Hearing status, need for recovery after work, and psychosocial work characteristics: results from an internet-based national survey on hearing. Int J Audiol 2009;48(10):684–91.

37. Bohorquez G, Bojorque E. Self-esteem, resilience, and sustainable contributions for the productive development of the elderly who undertake in El Oro. Revista Científica y Arbitrada de Ciencias Sociales y Trabajo Social: Tejedora 2021;4(7):29–41.

38. Goffman E. Stigma: Notes on the management of spoiled identity. Englewood Cliffs: Patrice-Hall; 1963.

39. Ruusuvuori JE, Aaltonen T, Koskela I, Ranta J, Lonka E, Salmenlinna I, et al. Studies on stigma regarding hearing impairment and hearing aid use among adults of working age: a scoping review. Disabil Rehabil 2021;43(3):436–46.

40. Hull RH. Counseling Adults with Hearing Loss. Hull RH, editor. In: Introduction to Aural Rehabilitation: Serving Children and Adults with Hearing Loss. 3th ed. San Diego: Plural Publishing; 2019. p. 23–43.

# Samoprocena odraslih osoba sa stečenim oštećenjem sluha u kontekstu samopoštovanja i psihosocijalnog funkcionisanja

Jasmina B. Karić[1], Milena B. Kordić[1], Siniša M. Ristić[2]

[1]Univerzitet u Beogradu, Fakultet za specijalnu edukaciju i rehabilitaciju, Beograd, Srbija

[2]Univerzitet u Istočnom Sarajevu, Medicinski fakultet Foča, Republika Srpska, Bosna i Hercegovina

**Uvod.** Posledice stečenog oštećenja sluha kod odraslih osoba uslovljavaju njihovo psihosocijalno funkcionisanje i podrazumevaju promene u kvalitetu života koje se odnose na poremećaje u društvenom i emocionalnom funkcionisanju. Oštećenje sluha smatra se rizičnim faktorom za sniženo psihosocijalno funkcionisanje i samopoštovanje. Psihosocijalno blagostanje i očuvano samopoštovanje podrazumevaju posedovanje pozitivne slike o sebi i uviđanje da je osoba važan deo društvene zajednice u kojoj živi. Rad se bavi samopoštovanjem i psihosocijalnim funkcionisanjem odraslih osoba sa stečenim oštećenjem sluha. Cilj ovog istraživanja je utvrđivanje nivoa samopoštovanja i stepena izraženosti posledica u psihosocijalnom funkcionisanju, odnosno povezanost nivoa samopoštovanja i stepena izraženosti posledica u psihosocijalnom funkcionisanju kod odraslih osoba sa stečenim oštećenjem sluha.

**Metode.** Istraživanje je sprovedeno na uzorku od 60 odraslih ispitanika sa stečenim oštećenjem sluha i 60 ispitanika urednog sluha. Prosečna starost ispitanika sa oštećenjem sluha iznosi 54,1 (SD = 10,84), a uzorak su u većem broju činili ispitanici muškog pola (56,7%) sa umerenim oštećenjem sluha (25,4%). Kao instrumenti korišćeni su Rouzenbergova skala samopoštovanja (Rosenberg Self-Esteem Scale) i upitnik za subjektivnu procenu slušnog stanja - HHIA upitnika (Hearing Handicap Inventory for Adults).

**Rezultati.** Rezultati su pokazali da ispitanici izražavaju umereno, odnosno prosečno samopoštovanje i da postoji povezanost između samopoštovanja i psihosocijalnog funkcionisanja kod odraslih osoba sa stečenim oštećenjem sluha.

**Zaključak.** Buduća istraživanja mogla bi se više usmeriti ka tome da se detaljnije ispita samopoštovanje u konkretnijim domenima psihosocijalnog funkcionisanja odraslih osoba sa stečenim oštećenjem sluha.

**Ključne reči:** oštećenje sluha, odrasli, samopoštovanje, psihosocijalno funkcionisanje

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):87–100

UDK: 614.253
DOI: 10.59137/BII202301309Ć

*Original article*

# Factors associated with conflict and styles of conflict management among health professionals

**Maja Ćeha[1], Bojan Joksimović[1], Mile Despotović[1,2], Dejan Bokonjić[1], Biljana Mijović[1], Ivana Vukotić[1], Zlatko Maksimović[3], Marija Milić[4]**

[1]University of East Sarajevo, Faculty of Medicine Foca, Republic of Srpska, Bosnia and Herzegovina
[2]College of Applied Health Sciences Cuprija, Republic of Serbia
[3]PHI Hospital "Sveti vračevi" Bijeljina, Republic of Srpska, Bosnia and Herzegovina
[4]University of Priština, Faculty of Medicine, temporarily located in Kosovska Mitrovica, Serbia

Primljen – Received: 21/01/2023
Prihvaćen – Accepted: 02/06/2023

**Corresponding author:**
*Maja Ćeha, MD*
*Cara Lazara 46, 71350 Sokolac*
*majaa502@gmail.com*



**Summary**

**Introduction**. Conflict is a process during which one person consciously and intentionally makes an effort to prevent the other person's efforts, some kind of blockade that will lead to interruption in achieving the goals and interests of the other person. Conflicts in the healthcare team are common and can lead to reduced productivity in the work of healthcare professionals, which can have a negative impact on the care and treatment of patients.

**Methods**. This cross-sectional study involved 100 health professionals, nurses and doctors employed in the primary, secondary and tertiary levels of health care. The research was conducted from March to August 2020. A questionnaire on socio-demographic characteristics of respondents, a questionnaire on conflicts of health professionals, and a standardized scale of depression, anxiety and stress with 21 questions (DASS-21) were used to measure the level of subjective depression, anxiety and stress

**Results**. Seventy-four health workers (74%) had experience of conflict in the workplace, doctors (95%) significantly more often than nurses (58%) (p=0.001). Forty percent of health workers stated that communication problems were the most common cause of conflict. Seventy-nine respondents (79%) chose cooperation and compromise as a style in conflict resolution. Doctors chose cooperation more often (84%) than nurses (74%) and the difference was statistically significant (p=0.048). Subjects who had experience of conflict had significantly higher average values of anxiety (8.01±2.12) (p=0.026) and stress (10.32±2.91) (p=0.008) compared to subjects who had no experience of conflict (6.13±1.91; 6.12±2.03).

**Conclusion**. Doctors were significantly more likely to have conflict situations in the workplace. For conflict resolution doctors were more likely to choose a style of cooperation and compromise than nurses who were more likely to choose a style of conflict avoidance.

**Keywords:** conflict, conflict resolution, health professionals

## Introduction

The notion of conflict depends on the way it is defined. One definition states that conflict is a situation that arises, develops and transforms into a disagreement between at least two people who have opposing views, access to a particular situation, and show interest in the same value [1]. According to author Steven Robbinson, conflict is a process during which one person

consciously and intentionally makes an effort to prevent another person's efforts, some form of blockade that will lead to interruption in achieving the other person's goals and interests [2]. As it can be seen, most definitions of conflict are similar, but what is common to each definition are three characteristics, and these are: the participation of at least two people is necessary for the conflict to arise, participants in the conflict can be individuals or groups, and that there are conflicting views between conflicting persons [3].

The existence of a cause is necessary for the conflict to arise. The root causes of conflict mainly stem from the definition of conflict. Linstead et al. [4] listed a large number of causes of conflict in work organizations, and most often they can be: the nature of work, different work goals, economic resources, roles of external groups, job satisfaction and different needs and desires of employees. Causes of conflict can also be lack of resources, interdependence in work, differences in the values of individuals or groups, personal style, communication problems, change of role in work, overlap in the organization of work and inadequate remuneration [5].

According to the definition of the World Health Organization (WHO), work in a health team should represent the cooperation of several medical experts in achieving a mutual goal, which is the provision of health care to patients and their treatment. Work in a health team must be well-coordinated by the health team leader [6]. In order for the organization in the health team to be of high quality and professional, it is necessary for each member of the health team to take responsibility for the part of the work he/she performs. This is the only way for the health team to achieve good results in patient care through coordinated action, because a larger number of members of the health team, compared to an individual, can achieve greater efficiency and scope of work, and the number of errors in this case is significantly lower [7]. However, if conflicts in healthcare institutions occur among colleagues, in the relationship between nurses and doctors, but also between healthcare professionals and patients and relatives of patients, it can increase the number of errors in treating patients [8, 9].

The occurrence of conflict and its consequences in the health system is a global problem. However, there is not much data in the literature on the difference in frequency, attitudes and factors associated with conflict between nurses and physicians. That is why in our research we paid special attention to determine how frequent the conflicts are, and to determine the differences between nurses and doctors in the frequency of conflict, factors associated with conflict and conflict management among health professionals.

## Methods

### *Study design*

The research was conducted as cross-sectional study in the population of health professionals, medical doctors and nurses employed at the primary, secondary and tertiary level of health care, from March 2020 to August 2020. The sample consisted of health professionals from the "Health Center Sokolac" (primary level of health care), "Psychiatric Hospital Podromanija" (secondary level of health care) and the "Institute for Forensic Psychiatry Sokolac" (tertiary level of health care). The study included 100 subjects (50 nurses and 50 medical doctors) of both sexes, aged 20 to 65 years. Prior to the start of the research, the consents of the competent institutions were obtained, in writing. Participation in the study was voluntary, and the survey was anonymous.

### *Questionnaires*

Data were collected by survey. To obtain the data, a questionnaire was used which was composed of questions for collecting socio-demographic data. The questionnaire on

health workers' conflicts were used to obtain data about the frequency and causes of conflict(s) among health professionals. The Depression Anxiety Stress Scale 21 (DASS-21) for healthcare professionals was used to assess psychological distress symptoms (depression, anxiety and stress) among health professionals. We used a short, translated into Serbian and tested version of DASS-21 questionnaire. The variables in the questionnaire were divided into three subscales: depression, anxiety, and stress. The depression scale is characterized by feelings of hopelessness, loss of self-esteem and motivation. The anxiety scale is based on high levels of physiological arousal, panic and fear. The third scale, the stress scale, is based on tension, anxiety, and inability to relax. The level of depression was examined by statements such as: "I feel that life has no meaning", anxiety: "My mouth is dry", and stress: "It was hard for me to calm down". Each scale was described using seven statements, and higher scores in each subscale denoted higher levels of depression, anxiety, and stress. The respondent's task was to indicate, on the Likert scale from 0 (did not apply to me at all) to 3 (almost entirely or most time applied to me), how much they experienced the above in the past week. The total score on the scales was expressed as the sum of the scores on each particle multiplied by two to be able to estimate the intensity of mental disorders. The larger overall score means that the person has greater psychopathological difficulties and more symptoms of depression, anxiety and stress. Each scale has its critical value and shows the presence of mental disorders if on the depressive subscale they have an overall score greater than 9, on the anxiety subscale the total score greater than 7 and on the stress subscale total score greater than 14. DASS-21 scores are classified as normal, mild, moderate, severe, and extremely severe (34). For the DASS-21 questionnaire no special permission is required for its use and it is publicly available.

*Statistical analysis*

The methods of descriptive and analytical statistics were used in the paper. Among the methods of descriptive statistics, measures of central tendency and measures of variability were used, namely: arithmetic mean with standard deviation and relative numbers for categorical variables. Among the methods of analytical statistics, Student's t test was used for bound samples. Of the nonparametric tests, the chi-square test was used to assess the difference between the groups. The usual value of $p< 0.05$ was taken as the level of statistical significance of differences, while the values of $p< 0.01$ were considered highly statistically significant. Results were statistically analyzed in GraphPad Prism software (GraphPad, La Jolla, CA, USA) and SPSS software package version 21.0 (Statistical Package for Social Sciences SPSS 21.0 Inc, USA).

## Results

One hundred respondents participated in the research, of which 50% were nurses/technicians, while 50% were medical doctors. Of the total number of respondents, 63% were females and 37% were males. Statistical analysis showed that there was a high statistically significant difference between the groups of respondents divided by profession in relation to gender ($p=0.002$), with significantly more women (78%) in the group of nurses/technicians than in the group of doctors of medicine (48%). The average age of the subjects was $43.70 \pm 11.89$ years, the youngest was 20 and the oldest was 65 years old. Respondents were divided into two categories in relation to age, the category in range of 20–40 years (41%) and the category in range of 41–65 years (59%). Table 1 shows that 36% of nurses have completed only secondary education, while 14% of nurses have a university degree from nursing school, 24% of doctors have completed the Faculty of Medicine (medical doctor), while 26% of doctors have completed

**Table 1.** Differences in age, gender, level of health care, years of work experience and level of anxiety, stress and depression between nurses and doctors

| Variables | Nurses (n=50) | | Doctors (n=50) | | Total (n=100) | | P ($\chi^2$) |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| **Age** | | | | | | | |
| 20 to 40 years | 24 | 48 | 17 | 34 | 41 | 41 | 0.155 |
| 41 to 65 years | 26 | 52 | 33 | 66 | 59 | 59 | |
| **Gender** | | | | | | | |
| Male | 11 | 22 | 26 | 52 | 37 | 37 | 0.002 |
| Female | 39 | 78 | 24 | 48 | 63 | 63 | |
| **Education** | | | | | | | |
| Secondary school | 36 | 72 | 0 | 0 | 36 | 36 | 0.056 |
| Faculty of medicine (nursing school) | 14 | 28 | 0 | 0 | 14 | 14 | |
| Faculty of medicine (MD) | 0 | 0 | 24 | 48 | 24 | 24 | |
| Specialty | 0 | 0 | 26 | 52 | 26 | 26 | |
| **Level of health care** | | | | | | | |
| Primary | 17 | 34 | 19 | 38 | 36 | 36 | 0.917 |
| Secondary | 17 | 34 | 16 | 32 | 33 | 33 | |
| Tertiary | 16 | 32 | 15 | 30 | 31 | 31 | |
| **Years of work experience** | | | | | | | |
| 1 to 20 years | 32 | 64 | 37 | 74 | 69 | 69 | 0.280 |
| 21 do 43 years | 18 | 36 | 13 | 26 | 31 | 31 | |
| **Depression (DASS 21)** | | | | | | | |
| Without depression | 49 | 98 | 49 | 98 | 98 | 98 | 1.000 |
| Moderate depresion | 1 | 2 | 1 | 2 | 2 | 2 | |
| **Anxiety (DASS 21)** | | | | | | | |
| Without anxiety | 30 | 60 | 38 | 76 | 68 | 68 | 0.229 |
| Mild anxiety | 4 | 8 | 4 | 8 | 8 | 8 | |
| Moderate anxiety | 11 | 22 | 4 | 8 | 15 | 15 | |
| Severe anxiety | 5 | 10 | 4 | 8 | 9 | 9 | |
| **Stress (DASS 21)** | | | | | | | |
| Without stress | 17 | 34 | 32 | 64 | 49 | 49 | 0.012 |
| Mild stress | 5 | 10 | 4 | 8 | 9 | 9 | |
| Moderate stress | 18 | 36 | 6 | 12 | 24 | 24 | |
| Severe stress | 10 | 20 | 8 | 16 | 18 | 18 | |

DASS 21 = The Depression, Anxiety and Stress Scale - 21 Items; χ2 - Chi-square test

a specialization in a particular field of medicine. Sixty nine percent of respondents have a work experience of 1 to 20 years, while 31% of respondents have a work experience of 21 to 43 years. Thirty-six percent of respondents work in a health center, 33% in a psychiatric hospital, while the remaining 31% of respondents work in the Institute of Forensic Psychiatry. No significant difference between the groups of respondents divided by profession in relation to age, length of service and level of health care was observed. Of the total number of surveyed health professionals, anxiety was observed in 32%, while anxiety was not observed in the remaining 68% of respondents. Mild anxiety was observed in 8% of respondents, moderate in 15%, while severe anxiety was observed in 9% of health care workers surveyed. Measured by the DASS 21 questionnaire, it was found that stress was present in 51% of surveyed health workers, while stress was not present in the remaining 49% of respondents. Mild levels of stress were observed in 9% of respondents, moderate stress in 24%, while severe levels of stress were observed in 18% of surveyed health professionals. Moderate depression was observed in only 2% of respondents, while depression was not observed in the remaining 98% of surveyed health professionals. There was no statistically significant difference between the groups of surveyed health workers divided by profession in relation to the presence and level of anxiety and depression. However, it was observed that nurses and technicians had statistically significantly (p=0.012) more often severe levels of stress (20%), moderate levels of stress (36%) and mild stress (10%) compared to doctors of medicine (8%; 8% and 8%) (Table 1).

Of the total number of surveyed health professionals, the majority (74%) had a conflict at workplace until the moment of the survey, while the remaining 26% stated that so far there had been no conflict situations with a colleague, patient or relative of patients. The high statistically significant difference between nurses and doctors was observed (p=0.001). Doctors significantly more often (95%) stated that they had experienced conflict at workplace when compared to nurses (58%) (Figure 1).

There was no statistically significant difference between the groups of respondents divided by gender, age, level of healthcare, years of experience and factors associated with conflict (Table 2).

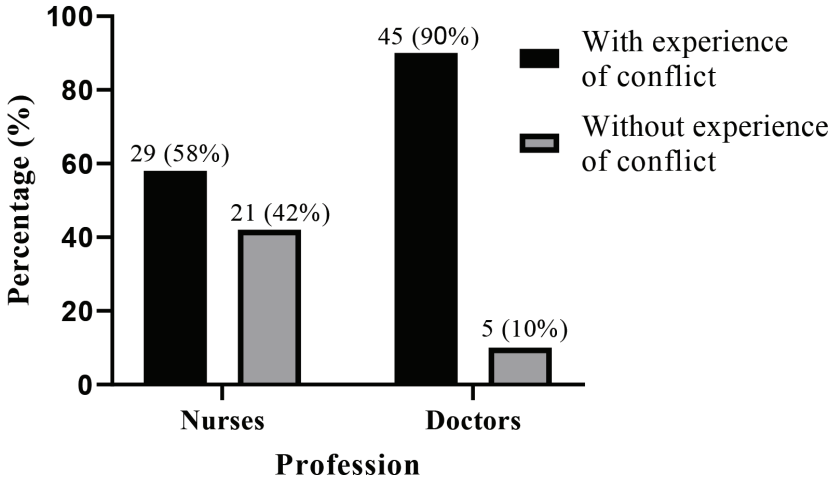


**Figure 1.** The presence of conflict in the workplace among nurses and doctors ($\chi$2=13.306; p=0.001); $\chi$2 - Chi-square test

**Table 2.** Differences in age, gender, level of health care and years of work experience among health professionals divided by presence of conflict

| Variables | Group with conflict (n=74) | | Group without conflict (n=26) | | P ($\chi^2$) |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Age** | | | | | |
| 20 to 40 years | 28 | 37.8 | 13 | 50.0 | 0.278 |
| 41 to 65 years | 46 | 62.2 | 13 | 50.0 | |
| **Gender** | | | | | |
| Male | 31 | 41.9 | 6 | 23.1 | 0.087 |
| Female | 43 | 58.1 | 20 | 76.9 | |
| **Level of health care** | | | | | |
| Primary | 30 | 40.5 | 6 | 23.1 | 0.176 |
| Secondary | 21 | 28.4 | 12 | 46.2 | |
| Tertiary | 23 | 31.1 | 8 | 30.8 | |
| **Years of work experience** | | | | | |
| 1 to 20 years | 52 | 70.3 | 17 | 65.4 | 0.643 |
| 21 do 43 years | 22 | 29.7 | 9 | 34.6 | |
| **Factors that most often lead to conflict** | | | | | |
| Problems in organization | 28 | 37.8 | 6 | 23.1 | 0.187 |
| Personal problems | 16 | 21.6 | 10 | 38.5 | |
| Problems in communication | 30 | 40.5 | 10 | 38.5 | |

DASS 21 = The Depression, Anxiety and Stress Scale - 21 Items; χ2 - Chi-square test

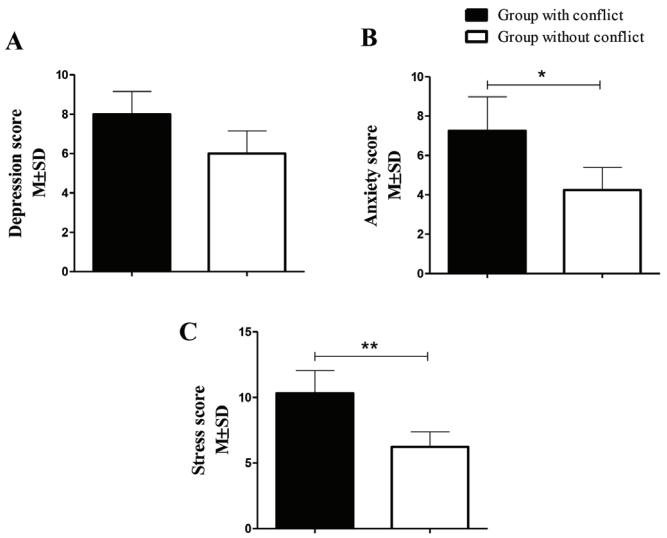


**Figure 2.** Mean values of depression (A), anxiety (B) and stress (C) measured by DASS 21 scale between groups of health professionals divided by presence of conflict until the time of survey. M = mean; SD = standard deviation; DASS 21 = The Depression, Anxiety and Stress Scale - 21 Items; Mann Whitney U test; *p< 0.05; **p< 0.010

Figure 2 shows that there was no significant difference in mean values of depression score among health professionals divided by presence of conflict prior to the time of survey. However, the mean score for anxiety was significantly higher (p=0.026) in a group of health professionals which had a conflict in their carriers (8.01±2.12) when compared to a group of health professionals without a conflict (6.13±1.91). Also, respondents with a presence of conflict had significantly higher (p=0.008) values of stress (10.32±2.91) when compared to a group without conflict in their carriers (6.12±2.03) (Figure 2).

Table 3 shows the frequency of factors leading to conflict in the health team. The largest number of surveyed health workers (40%) stated that it was the problem in communication, 34% of respondents stated that the main factor was the problem in the organization of work, while 26% of respondents stated that the main factor in conflict

**Table 3.** Differences in factors associated with conflict and conflict management between nurses and doctors

| Variables | **Nurses** (n=50) | | **Doctors** (n=50) | | **Total** (n=100) | | P ($\chi^2$) |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Factors that most often lead to conflict | | | | | | | |
| Problems in organization | 16 | 32 | 18 | 36 | 34 | 34 | 0.897 |
| Personal problems | 13 | 26 | 13 | 26 | 26 | 26 | |
| Problems in communication | 21 | 42 | 19 | 38 | 40 | 40 | |
| Ways to resolve conflict | | | | | | | |
| Reconciliation | 2 | 4 | 2 | 4 | 4 | 4 | 0.048 |
| Cooperation and compromise | 37 | 74 | 42 | 84 | 79 | 79 | |
| Conflict avoidance | 11 | 22 | 3 | 6 | 14 | 14 | |
| Bidding | 0 | 0 | 3 | 6 | 3 | 3 | |
| During conflict I keep my opinion to myself | | | | | | | |
| Never | 3 | 6 | 15 | 30 | 18 | 18 | 0.003 |
| Sometimes | 36 | 72 | 31 | 62 | 67 | 67 | |
| Always | 11 | 22 | 4 | 8 | 15 | 15 | |
| During conflict I adapt to the requirements of colleagues | | | | | | | |
| Never | 0 | 0 | 8 | 16 | 8 | 8 | 0.006 |
| Sometimes | 42 | 84 | 39 | 78 | 81 | 81 | |
| Always | 8 | 16 | 3 | 6 | 11 | 11 | |
| During conflict I solve the problem by compromise | | | | | | | |
| Never | 0 | 0 | 0 | 0 | 0 | 0 | 0.043 |
| Sometimes | 18 | 36 | 9 | 18 | 27 | 27 | |
| Always | 32 | 64 | 41 | 82 | 73 | 73 | |
| During conflict I give in to my colleagues | | | | | | | |
| Never | 6 | 12 | 12 | 24 | 18 | 18 | 0.025 |
| Sometimes | 24 | 68 | 36 | 72 | 60 | 60 | |
| Always | 10 | 20 | 2 | 4 | 12 | 12 | |

$\chi^2$ - Chi-square test

in the health team was personal problems with colleagues. No statistically significant difference in the frequency of conflicts in the workplace in relation to age, level of health care, length of service and factors that most often lead to conflicts in health workers was observed. The largest number of respondents (79%) chose cooperation and compromise as a way of resolving conflict, 14% avoided conflict, 4% chose reconciliation as a style of conflict resolution, while 3% of respondents chose bidding as a style of conflict resolution. There was a statistically significant difference (p=0.048) in the ways of resolving conflicts between groups of respondents divided by profession. Doctors of medicine significantly more often (84%) chose cooperation and compromise as a style of conflict resolution compared to nurses and technicians (74%), while nurses and technicians significantly more often (22%) chose conflict avoidance as a style of conflict resolution compared to doctors of medicine (6%). Nurses and technicians (22%) highly statistically significantly (p=0.003) more often kept their opinion to themselves during the conflict compared to doctors of medicine (8%) and highly statistically significantly more often (16%) (p=0.006) adjusted to requirements of colleagues in comparison to doctors of medicine (6%). Doctors of medicine (82%) significantly more often (p=0.043) solved the problem by compromise in relation to nurses and technicians (64%), while nurses and technicians (20%) significantly (p=0.025) more often gave in to their colleagues during conflicts in relation to doctors of medicine (4%) (Table 3).

## Discussion

Conflict in itself is not good or bad, however, the consequences of conflict can be bad or good, depending on the approach to the conflict. From the traditional aspect, the view of the conflict is completely negative, but from the modern contemporary aspect, the conflict is seen as a normal and inevitable situation, so from such opposing views, two consequences of the conflict can be predicted, positive and negative [1]. Conflict in the healthcare team, also, always carries certain consequences that can be positive or negative. The positive aspects of conflict in the healthcare team are that it can improve the quality of decisions made, encourage creativity and innovation, increase interest and curiosity in the team, can become a mean of reducing tension, and enable better adaptation to change. The negative consequences of the conflict are dissatisfaction, weakening of mutual relations, reduced work performance and poor communication among team members. When conflict leads to a struggle among members, which becomes more important than doing the job, there is a danger of work failure and disintegration of the health team [10–12].

Our research was conducted on a sample of 100 health professionals (50% of nurses and 50% of medical doctors) and aimed to identify frequency of the conflicts, and to determine the differences between nurses and doctors in the frequency of the conflicts, factors associated with conflict and the most commonly chosen styles by health workers to overcome conflict. The observed population was mostly female (63%), aged 41 to 65 years (59%) in direct contact with patients in health care facilities of primary (36%), secondary (33%) or tertiary level (31%).

Conflicts are one of the basic social phenomena, which in traditional culture is considered a negative phenomenon and something that should be avoided. The health care system is a very complex system, because the outcome of treatment and care of patients depends on health care workers and their multidisciplinary work. Precisely because of the high level of interdependence in work, health teams are very prone to conflict situations [13]. The most important specifics of the nursing profession are hard, stressful

and highly humane work, which requires a high level of cooperation with the medical profession and patients, and the patient's life often depends on the timely intervention of nurses and technicians. Some of the stressors in the workplace, such as shift and overtime work, jobs that are risky for health, interpersonal conflicts, are constantly present in their workplaces and work environment, which could lead to exhaustion, fatigue, burnout and rise of conflict among health professionals and patients [5, 14]. In a study by Raknes et al. [15] conducted in Norway on a sample of 745 nurses and technicians it was found that 8.4% of nurses had previous conflicts in the workplace, while 3% during the study had a current conflict with the colleague in the workplace. At risk for various forms of conflict in the workplace are especially nurses and emergency technicians, as shown by the results of a study in Pennsylvania, which found that 36% of nurses working in the emergency service in the last 12 months had a conflict in the workplace, unlike 6% of nurses who worked in other wards [16]. In a study by Grieko et al. [17] made in Ireland, the percentage of conflict among health professionals is even higher and amounts to 48%. In a recent cross sectional study made in a General Hospital in Greece by Saridi et al. [18] from 200 of examined health professionals 59.5% reported at least one collision with the colleague, where nurses significantly more often (60%) would quit their job because of frequent conflicts when compared to doctors (7%). In our study, of the total number of surveyed health workers, the majority (74%) had the conflict at work by the time of the survey, while the remaining 26% stated that so far there had not been conflict situations with the colleague, patient or relative. Doctors significantly (p=0.001) more often (95%) stated that they experienced conflicts at workplace when compared to nurses (58%). However, there was no statistically significant difference among the groups of respondents divided by gender, age, level of healthcare, years of experience and factors associated with conflict. The reason of such higher prevalence of conflicts in our group of respondents might be because, majority of our respondents (64%) worked in psychiatric institutions. Numerous studies have documented that psychiatric staff are at high risk for verbal aggression, workplace violence, even physical assault by patients, visitors, coworkers or supervisors [19–21] and recent study by Kelly et al. [21] done in public mental hospital in California demonstrated that from 323 clinical care staff 69.5% had experienced physical assault in the previous 12 months and 73% of employees (nurses and doctors) had the conflict in their workplace. This is similar to prevalence of conflict in our respondents.

In the study by Krajnović et al. [22] conducted in Croatia on a sample of 1354 nurses and technicians it was found that 39% of nurses and technicians during their work experience had conflict situations in the health care team, 38.4% of nurses experienced humiliation by colleagues during their work, 38% experienced insults, while the opinions and attitudes of the surveyed health professionals were ignored in 28.1% of the respondents. The results of this study show that negative behaviors and conflicts in the workplace arise due to stressful working conditions, organizational problems, as well as communication problems [22]. Krajnović et al. [22] stated that 14.5% of respondents had conflict situations with a superior, 12.2% with colleagues, while 7.2% had the conflict with a subordinate due to their inappropriate behavior. In our study of the total number of surveyed health workers, 14% had conflicts with superiors, 31% with associates, 17% with subordinates, 12% with patients or relatives of patients, while 26% of surveyed health workers did not have conflicts at work.

Communication in the field of health care is of great importance because the way of communication of health workers impacts

the course and manner of treatment of patients, their satisfaction, and consequently their health condition. It is very important that health professionals (nurses/technicians and doctors of medicine) have experience in the field of communication and are able to patiently actively listen and observe the patient. Also, in order for the patient's treatment to be effective, it is necessary for the members of the health team to have good and positive communication with each other. Although communication is very important in health care, unfortunately, very little attention is paid to it and it is neglected, and the reasons for that can be heavy workload of health workers, lack of time and fatigue [23]. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) indicates that more than 60% of reported adverse events per patient are due to poor communication in the healthcare team [24]. In our study, the largest number of surveyed health workers (40%) stated that the main cause of conflicts among health workers was the problem in communication. In the cross-sectional study of Azoulay et al., 7 498 intensive care unit staff members were examined and the most common conflict-causing behavior were communication gaps, as well as personal animosity and mistrust [25]. In our study the results are similar where 38% of health workers blame the problems in organization as a source of conflict and 26% of respondents allege that personal problems are to blame for arise of conflict among health workers or between health workers and patients. The direction of the impact of the conflict on the outcome in the organization of the work of the health service depends on the styles and techniques of conflict resolution. The simplest way to resolve the conflict is for the parties in the conflict to have a serious conversation during which both sides will have the opportunity to say what they want and why they want something. Conversations of this kind are crucial and very often the simplest way to resolve conflict. The most important thing for resolving the conflict among health professionals is the existence of empathy, which should be specially developed and expressed by all health professionals (both nurses and doctors) [12]. The dominant style of conflict management of doctors and nurses/technicians in our research is the style of cooperation and compromise. The largest number of respondents (79%) chose cooperation and compromise as the way of resolving conflict, 14% avoided conflict, 4% chose reconciliation as the style of conflict resolution, while 3% of respondents chose bidding as the style of conflict resolution. Doctors of medicine significantly more often (84%) chose cooperation and compromise as the style of conflict resolution compared to nurses and technicians (74%), while nurses and technicians significantly more often (22%) chose conflict avoidance as the style of conflict resolution compared to doctors of medicine (6%) ($p=0.048$). Our results agree with the results of Sportsman et al. [24] in which compromise has been shown to be the most common style of conflict resolution for health professionals. It should be emphasized that we offered the respondents to choose one of these four styles that they most often choose for conflict resolution, but no one has the exclusive style of behavior in conflict situations. The style of behavior in the conflict depends on a number of factors such as the current situation, habits, life experience and previous relationship with that person. Healthcare professionals, in general, show a desire and tend to maintain good interpersonal relationships despite their needs and goals. Both doctors and nurses generally believe that conflict should be avoided in favor of a harmonious collective relationship and that people cannot resolve conflict without compromising interpersonal relationships [26]. However, the style chosen by the largest number of our respondents, which is compromise and cooperation, is considered to be one of the best styles for resolving conflicts in the healthcare team. People who use this style

view conflict as an opportunity to improve relationships and reduce tension. In the science of conflict, conflictology, one of the constant issues is the effectiveness of strategies, so from the aspect of the "ideal model", cooperation and compromise are considered the most effective style of conflict resolution, and one style is called cooperative strategy. Cooperative strategy is the style that contributes to several factors such as the interdependence of conflict participants and their tendency to work together in the future, the tendency of conflict participants not to rely on the use of aggression or force, focusing on solving the problem, not just protecting their own interests and achieving their goals [27]. In a study by Koeling et al. [28] nurses and doctors were examined on behaviors contributing to better communication. The results of this study suggest that doctors believe that nurses need to learn to convey more factual data, while nurses have focused on interpersonal relationships [24]. In situations where this style of cooperative strategy (cooperation and compromise) is rarely used, this indicates that differences in attitudes and opinions are not seen as the opportunity to learn something new [13].

Given the stressful working conditions, especially with the current epidemiological situation (pandemic of COVID-19 infection), we wanted to examine whether some factors such as depression, anxiety or stress affected the occurrence of conflict situations. Although in our study, anxiety was present in 32% of health care workers, stress in 51%, and depression in 2%, we did not observe a significant impact of those factors on the frequency of workplace conflicts. However, we found that nurses and technicians were significantly (p=0.012) more likely to had severe stress levels (20%), moderate stress levels (36%) and mild stress (10%) compared to doctors of medicine (8%; 8%; 8%). Also, our study showed that the mean score for anxiety was significantly higher (p=0.026) in the group of health professionals which had the conflict in their carriers when compared to the group of health professionals without the conflict. Also, respondents with a presence of conflict had significantly higher (p=0.008) values of stress when compared to the group without conflict in their carriers.

The style of adjustment in interpersonal relationships results in a large number of unresolved problems and the cessation of conflicts, which leads to employee dissatisfaction and a decline in the quality of work [26]. In our survey, 8% of respondents stated that they never adapted to the demands of colleagues, the largest number of respondents (81%) stated that they sometimes adapted, while 11% stated that they always adapted to the demands of colleagues when the conflict situation occurred. In our study, we found that nurses and technicians were highly statistically significantly more likely (16%) (p=0.006) to adapt to the requirements of colleagues compared to doctors of medicine (6%). Giving in or withdrawing is the style where a person gives up their goals and intentions and the struggle for interests is left to others. Healthcare professionals who use this style stay away from people who are in conflict as well as conflict situations. They feel helpless and believe it is hopeless to resolve the conflict. They believe it is much easier to withdraw both mentally and physically than to face conflict. Withdrawal style has been cited in the literature as the primary strategy used by nurses, especially in relation to doctors of medicine [26]. This result is confirmed by our results, which show that nurses and technicians significantly ($\chi$2=7,390; p=0.025) more often (20%) give in to their colleagues when conflicts arise compared to doctors of medicine (4%). In our study, nurses and technicians highly statistically significantly ($\chi$2=11,640; p=0.003) more often at the time of conflict retain their opinion for themselves (22%) compared to doctors of medicine (8%). A possible explanation for the more frequent use of styles of holding opinions for oneself,

adapting to the demands of colleagues, and giving in to colleagues among nurses could be their feeling of helplessness in relation to doctors of medicine [29].

Effective conflict resolution in the health care team must be a priority due to its negative impact on the quality of health care provided. Effective conflict management requires professional qualities and skills, as well as changing attitudes towards conflicts. It is therefore essential that health professionals understand the basics of conflict, its causes, and learn ways to resolve them [30]. From the beginning of their education, nurses and doctors should learn, through theoretical lectures and practical exercises, how to negotiate and analyze the different types of strategies used to resolve conflicts [31].

## Conclusion

Our research shows that 74% of health professionals experienced conflict in their workplace, doctors significantly more often than nurses. For 40% of respondents the main cause of the conflict with a patient or colleague is problem in communication. Also, the largest number of respondents (74%) chose cooperation and compromise as the way to resolve the conflict, doctors significantly more often than nurses. Nurses significantly more often chose conflict avoidance as their style of conflict resolution compared to doctors. Nurses and technicians more often kept their opinion to themselves during the conflict and more often adapted to the requirements of colleagues compared to doctors. The level of anxiety and stress is significantly higher in health professionals who experienced conflict at the workplace.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** The Ethics Committee of the Institute for Forensic Psychiatry, Sokolac, Republic of Srpska, Bosnia and Herzegovina, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

**Conflicts of interest.** The authors declare no conflict of interest.

### References:

1. Pondy LR. Organizational conflict: Concepts and models. Adm Sci Q 1967;12(2):296–320.
2. Robbins SP, Judge TA. Organizational behavior: pearson; 2019.
3. McKibben L. Conflict management: importance and implications. Br J Nurs 2017;26(2):100–3.
4. Linstead S, Fulop L, Lilley S, Banerjee B. Management and organization: A critical text: Palgrave Macmillan, Basingstoke; 2004.
5. Pitsillidou M, Farmakas A, Noula M, Roupa Z. Conflict management among health professionals in hospitals of Cyprus. J Nurs Manag 2018;26(8):953–60.
6. Marković J, Marković D, Mesić E, Arsić D, Arsić K, Arsić J, et al. Specifičnosti komunikacijskih veština u medicini. Medicinski časopis PONS 2015;12(1):25–9.
7. Lai AY, Yuan CT, Marsteller JA, Hannum SM, Lasser EC, Heughan J-A, et al. Patient Safety in Primary Care: Conceptual Meanings to the Health Care Team and Patients. J Am Board Fam Med 2020;33(5):754–64.
8. Hart WM, Doerr P, Qian Y, McNaull PM. What Constitutes Effective Team Communication After an Error? AMA J Ethics 2020;22(4):E298–304.

9. Gellis ZD, Kim E, Hadley D, Packel L, Poon C, Forciea MA, et al. Evaluation of interprofessional health care team communication simulation in geriatric palliative care. Gerontol Geriatr Educ 2019;40(1):30–42.
10. Vincek V. Važnost komunikacije u zdravstvenom timu. University North. University centre Varaždin. Department of Nursing, 2018.
11. Streeter AR, Harrington NG. Nurse handoff communication. Semin Oncol Nurs 2017;33(5):536–43.
12. Vujić AS. Resolving conflict at work: what a nurse should know and take/Rešavanje konflikta na poslu: šta medicinska sestra treba da zna i preduzme. Sestrinski žurnal 2014;1(1):50–2.
13. Brestovački B, Milutinović D, Cigić T, Grujić V, Simin D. Conflict styles observed in doctors and nurses in health care organization. Med pregl 2011;64(5-6):262–6.
14. Hämmig O. Explaining burnout and the intention to leave the profession among health professionals–a cross-sectional study in a hospital setting in Switzerland. BMC Health Serv Res 2018;18(1):785.
15. Raknes BI, Einarsen S, Matthiesen S, Hellesøy O. Mobbing på arbeidsplassen–et helseproblem. Norsk Tidsskrift for Arbeidsmedisin 1991;12(3):155–60.
16. Nurses ICN. ''always there for you: United against violence''. International Nurses Day, 2001.
17. Grieco A. Scope and nature of sexual harassment in nursing, 1987.
18. Saridi M, Panagiotidou A, Toska A, Panagiotidou M, Sarafis P. Workplace interpersonal conflicts among healthcare professionals: A survey on conflict solution approach at a General Hospital. International Journal of Healthcare Management 2021;14(2):468–77.
19. Cornaggia CM, Beghi M, Pavone F, Barale F. Aggression in psychiatry wards: a systematic review. Psychiatry res 2011;189(1):10–20.
20. Flannery RB, Wyshak G, Flannery GJ. Characteristics of international staff victims of psychiatric patient assaults: Review of published findings, 2000–2012. Psychiatr Q 2014;85(4):397–404.
21. Kelly EL, Fenwick K, Brekke JS, Novaco RW. Well-being and safety among inpatient psychiatric staff: the impact of conflict, assault, and stress reactivity. Adm Policy Ment Health 2016;43(5):703–16.
22. Krajnović F, Šimić N, Franković S. Identifikacija, opis i analiza uzroka nekih negativnih ponašanja u radnom okružju medicinskih sestara. Med Jad 2007;37(3-4):63–72.
23. Starc J. Učinkovita komunikacija i rješavanje sukoba između medicinske sestre i pacijenta. Journal of Applied Health Sciences= Časopis za primijenjene zdravstvene znanosti 2016;2(2):133–46.
24. Sportsman S, Hamilton P. Conflict management styles in the health professions. J Prof Nurs 2007;23(3):157–66.
25. Azoulay E, Timsit J-F, Sprung CL, Soares M, Rusinova K, Lafabrie A, et al. Prevalence and factors of intensive care unit conflicts: the conflicus study. Am J Respir Crit Care Med 2009;180(9):853–60.
26. Valentine PE. A gender perspective on conflict management strategies of nurses. J Nurs Scholarsh 2001;33(1):69–74.
27. Rahim MA. Managing conflict in organizations. Piscataway; 2010.
28. Coeling HV, Wilcox JR. Steps to collaboration. Nurs Adm Q 1994;18(4):44–55.
29. Almost J. Conflict within nursing work environments: concept analysis. J Adv Nurs 2006;53(4):444–53.
30. Vivar CG. Putting conflict management into practice: a nursing case study. J Nurs Manag 2006;14(3):201–6.
31. Hendel T, Fish M, Galon V. Leadership style and choice of strategy in conflict management among Israeli nurse managers in general hospitals. J Nurs Manag 2005;13(2):137–46.

# Faktori povezani sa nastankom konflikta i stilovi rješavanja konflikta među zdravstvenim radnicima

Maja Ćeha[1], Bojan Joksimović[1], Mile Despotović[1,2], Dejan Bokonjić[1], Biljana Mijović[1], Ivana Vukotić[1], Zlatko Maksimović[3], Marija Milić[4]

[1]Univerzitet u Istočnom Sarajevu, Medicinski fakultet Foča, Republika Srpska, Bosna i Hercegovina

[2]Akademija vaspitačko-medicinskih strukovnih studija, Ćuprija, Srbija

[3]JZU Bolnica "Sveti vračevi" Bijeljina, Republika Srpska, Bosna i Hercegovina

[4]Univerzitet u Prištini sa privremenim sedištem u Kosovskoj Mitrovici, Medicinski fakultet, Srbija

**Uvod**. Konflikt je proces tokom koga jedna osoba svjesno i namjerno čini napor u cilju sprečavanja napora druge osobe, nekim vidom blokade koji će dovesti do prekida u postizanju ciljeva i interesa druge osobe. Pojava konflikta u zdravstvenom timu je česta i može dovesti do pojave smanjene produktivnosti u radu zdravstvenih radnika, što se može negativno odraziti na njegu i liječenje pacijenata.

**Metode**. U ovoj studiji presjeka je učestvovalo 100 zdravstvenih radnika, medicinskih sestara i doktora medicine zaposlenih u primarnom, sekundarnom i tercijarnom nivou zdravstvene zaštite. Istraživanje je sprovedeno od marta do avgusta 2020. godine. Korišćen je upitnik o socio-demografskim karakteristikama ispitanika, upitnik o konfliktima zdravstvenih radnika, a standardizovana skala depresije, anksioznosti i stresa sa 21 pitanjem (DASS-21) je korišćena za mjerenje subjektivnog nivoa depresije, anksioznosti i stresa.

**Rezultati**. Sedamdeset četiri zdravstvena radnika (74%) su imali iskustvo konflikta na radnom mjestu, doktori (95%) značajno češće u odnosu na medicinske sestre (58%) (p=0,001). Četrdeset posto zdravstvenih radnika navodi da je problem u komunikaciji najčešći uzrok konflikta. Sedamdeset devet ispitanika (79%) bira saradnju i kompromis kao stil u rješavanju konflikta. Značajno češće doktori (84%) u odnosu na medicinske sestre (74%) biraju saradnju kao stil u rješavanju konflikta (p=0,048). Ispitanici koji su imali iskustvo konflikta imaju značajno više prosječne vrijednosti anksioznosti (8,01±2,12) (p=0,026) i stresa (10,32±2,91) (p=0,008) u odnosu na ispitanike koji nisu imali iskustvo konflikta (6,13±1,91; 6,12±2,03).

**Zaključak**. Doktori su značajno češće imali konfliktne situacije na radnom mjestu. Doktori za rješavanje konflikta češće biraju stil saradnje i kompromisa u odnosu na medicinske sestre koje češće biraju stil izbjegavanja konflikta.

**Ključne riječi**: konflikt, rješavanje konflikta, zdravstveni radnici

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):101-106

UDK: 616.288:616-022.912
DOI: 10.59137/BII202301310R

*Case report*

# Foreign body in the external auditory canal described as a pseudotumor of the middle ear: a case report

**Nemanja Radivojević[1], Dragoslava Djerić[1,2], Zoran Dudvarski[1,2], Igor Djorić[3], Ivana Živković[4], Siniša Šolaja[5]**

[1]Clinical Center of Serbia, Clinic for Otorhinolaryngology and Maxillofacial Surgery, Belgrade Serbia
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia
[3]Clinical Center of Serbia, Department of Neurosurgery, Belgrade, Serbia
[4]Clinical Center of Serbia, Clinic for Cardiology, Belgrade, Serbia
[5]University Hospital Foca, Department of Otorhinolaryngology and Maxillofacial Surgery, Republic of Srpska, Bosnia and Herzegovina

Primljen – Received: 13/09/2021
Prihvaćen – Accepted: 05/06/2023

**Corresponding author:**
*Siniša Šolaja, MD, Assistant Professor*
*Studentska 5, 73300 Foča*
*solajasinisa@gmail.com*



**Summary**

**Introduction**. The aim of this article was to present a case of a foreign body in the external auditory canal described as a pseudotumor of the middle ear, as well as to point out diagnostic and therapeutic aspects of this problem.

**Case report.** An 8-year-old girl was hospitalized several times in our department due to the surgery of left-sided chronic otitis media. Mastoidectomy and posterior atticotomy were performed during initial hospitalization. Six months later, she was admitted for the second act of the left-sided tympanoplasty. However, two months prior hospitalization, symptoms regarding the right ear appeared: sense of fullness, gradual hearing loss and occasional pain. An otoscopic finding on the right indicated the presence of "tumefaction" in the external auditory canal with a surface that was markedly hyperemic. This pseudotumor was finally interpreted as the foreign body in the external auditory canal.

**Conclusion**. Foreign bodies in the external auditory canal (EAC) are relatively common in pediatric population. The medical history sometimes is not reliable, and the clinical and radiological interpretation of pseudotumor in the external auditory canal or middle ear must include this possibility in the differential diagnosis as well. Surgical exploration and pathohistological diagnosis are necessary to make a definitive diagnosis and to avoid potential complications.

**Key words**: external auditory canal, pseudotumor, foreign bodies, tympanic cavity

## Introduction

Foreign bodies in the external auditory canal (EAC) are encountered mainly in children, who put foreign objects in the ear out of curiosity or it happens by accident. The list of potential foreign bodies is very wide, and the size, nature and consistency of the foreign body are limiting factors for entering the external auditory canal. Different foreign bodies, such as seeds, marbles,

stones, jewelry parts, bobby pins, as well as living foreign bodies, insects and their larvae are described in literature [1].

Finding of the foreign bodies in external auditory canal are relatively common in medicine. In contrast, foreign bodies in the middle ear are very rare [2]. They occur mostly due to the violent perforation of the tympanic membrane and displacement from the external ear canal into the tympanic cavity. This can cause damage of the eardrum and ossicles, leading to the middle ear inflammation. If the eardrum perforation heals spontaneously, conductive hearing loss may persist as the only sign of damage, sometimes even years after the injury [3].

In some cases of „alternative" treatments, „forgotten" or unrecognized foreign bodies of different nature may remain in the external auditory canal. Various pathological changes with or without clinical manifestations may form over time due to the reaction of the surrounding tissue. There have been no comparative studies performed to guide the clinician as to which removal method best suits a particular clinical scenario. A number of foreign bodies found in the EAC are spherical, and cannot be retrieved with forceps as could be done with those irregularly shaped. In those cases, a single failed attempt of foreign body removal may result in complications (laceration, tympanic membrane perforation), but, also more impaction of the body, requiring removal under general anaestesia.

The aim of this article is to present a case of the foreign body in the external auditory canal described as a pseudotumor of the middle ear, as well as to point out diagnostic and therapeutic aspects of this problem.

## Case report

An 8-year-old girl was hospitalized several times in our department due to the surgery of left-sided chronic otitis media. Mastoidectomy and posterior atticotomy were performed during initial hospitalization. Postoperative course went well with satisfactory local findings and improved hearing function. Six months later, she was admitted for the second act of the left-sided tympanoplasty. However, two months prior hospitalization, symptoms regarding the right ear appeared: sense of fullness, gradual hearing loss and occasional pain. Therefore, she was treated in the regional hospital with local antibiotics and short-term oral antibiotics therapy. Last swab of the right ear revealed a fungal infection.

On admission to the clinic, she supposedly had no complaints of the right ear. A local finding on the left ear was satisfactory. She had dry central perforation in the anterior lower quadrant, and a hearing has improved significantly compared to preoperative findings. However, an otoscopic finding on the right indicated the presence of "tumefaction" in the external auditory canal with a surface that was markedly hyperemic.

MSCT of the temporal bone showed the presence of growth, described as a "polypoid mass" located in tympanic cavity, expanding from the promontory towards the lumen of the external auditory canal (Figure 1).

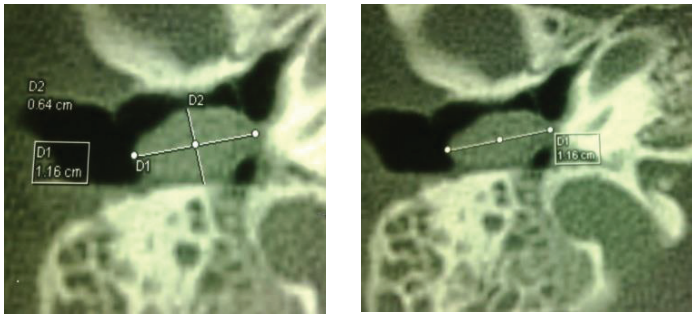


**Figure 1.** MSCT of temporal bone and diameter of foreign body

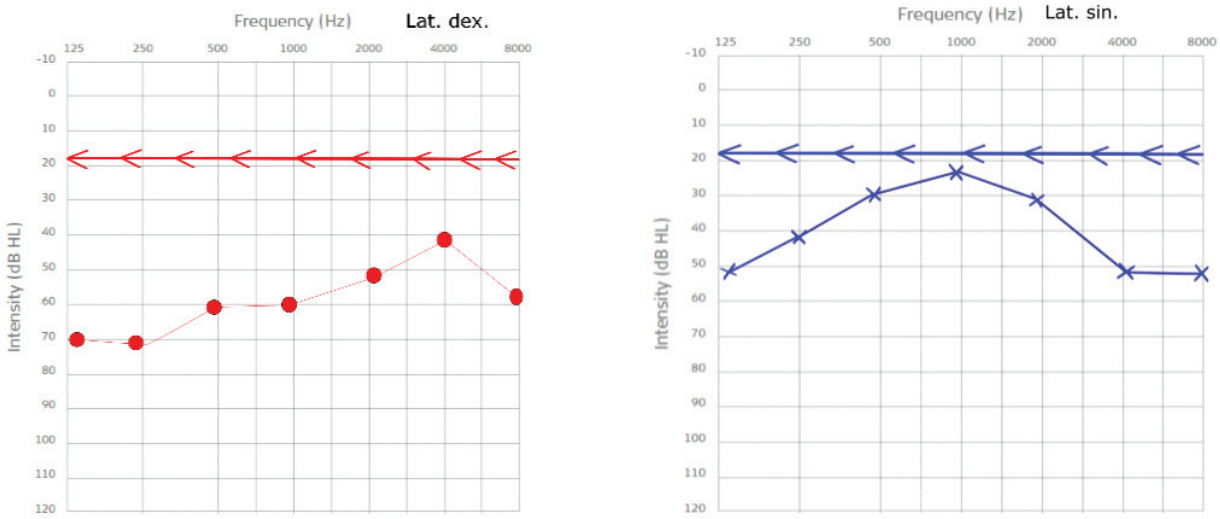


**Figure 2.** Audiometry before surgical treatment

Audiology findings showed right-sided mixed hearing loss (Figure 2).

Consequently, surgery of the right ear was performed, instead of initially planned left ear. The exploration of the right ear discovered a mass, pointed to the foreign body, encapsulated with surrounding proliferative tissue. The mass was removed, and pathohistological findings confirmed the presence of the foreign body (Figure 3).

**Figure 3.** Removed silicone ear protector

Additional medical history indicated the possibility of remained protective cap used for swimming, few months ago. The child was restrained, and the mother denied knowing about it. After removing the mass, a very repressed, retracted, but mobile eardrum was found. Except for slightly thickened mucosa, no pathological changes were found. Postoperative hearing function has been rapidly improved, resulting in recovery of hearing function of the right ear on follow-up examination. Over the next few months, the findings were satisfactory.

## Discussion

The frequency of foreign bodies in the external auditory meatus as well as their characteristics (material, shape and size) have been changing over time. In earlier periods, organic material (grains, seeds) was the most common, while nowadays the range of foreign bodies have been expanded to various structures (batteries, buttons, parts of toys). The occurrence of insects is becoming frequent in some parts in the world [4].

Clinical features, diagnostic and treatment procedures depend on the characteristics of the foreign body. The presence of the foreign body should be considered in patients who develop clinical features and symptoms such as pain, ringing in the ears, severe infections, dizziness and hearing loss. In addition, none of these symptoms may be present.

Chalishazar et al. [5] showed that 25 of 37 children with the foreign body in external auditory meatus had associated middle ear pathology compared to the control group. Schulze et al. [1] also showed that the inflammation of the middle ear was the most common associated pathology in these patients. Otitis externa, hematomas, granulation tissue and perforation of the eardrum are common complications of the foreign body presence in the external auditory canal, but sometimes extra- and intracranial complications can develop.

Goldman et al. [6] describes the case of a patient who developed mastoiditis and brain abscess as a consequence of the presence of the foreign body.

Burke et al. [7] showed a case of a 12 year-old girl with mastoiditis and meningitis due to the presence of cotton fiber in the external auditory meatus. The granuloma around the foreign body is the result of permanent inflammation that is associated with the type of material, in our case the silicone used to make earplugs.

Harris CK et al. [8] presented a case of a 9-year-old child with a polypoid mass in the external auditory canal, and pathohistologically it turned out to be the foreign body with proliferating granulation tissue. He showed that the foreign body reaction had the ability to erode the bone of the external auditory canal. The identification of foreign bodies in the external auditory canal requires, first and foremost, clinical suspicion. Clinical examination, otomicroscopy or otoendoscopy, audiology and CT diagnostics are all part of the diagnostic protocol. This is especially important in ambiguous situations or when some treatment has already been implemented, as in our case.

Described cases of unreported, forgotten or overlooked foreign bodies are important for several reasons. Detailed history is very useful in the diagnostic terms, which was incomplete in our case. Just when the signs of secondary infection appeared, therapy was based on the swab findings. The appearance of granulation tissue around the foreign body contributed to the initial description of CT scans as a pseudotumor of the middle ear.

Differential diagnosis of the foreign body includes several rare, but potentially dangerous conditions, like glomus tumor or other serious pathologic conditions. Knowledge of the differential diagnosis is important in avoiding a delay in establishing the diagnosis and potential morbidity.

Therefore, precise conclusion is only possible with surgical exploration of tympanic cavity, biopsy or complete removal. In our case, the origin of the foreign body has been identified intraoperatively and confirmed by pathohistology after removal.

The quick diagnostic and therapeutic approach prevented the occurrence of possible complications that sometimes could be very serious.

In modern literature, there are very few cases of foreign bodies seen in the middle ear. Sims and Nelson [2] showed four cases of impressions of foreign bodies in the timpanic cavity with subsequent chronic inflammation. Skandour et al. [9] revealed that the presence of the foreign body can remain unnoticed a longer period of time, with the hearing loss and a complete recovery after the extraction. Eleftheriadou et al. [3] described the case of metallic foreign body in the middle ear in a patient who worked as a welder, who got a metal splinter pierced into external auditory meatus, eardrum, and reached the tympanic cavity. Karimnejad K. et al (2017) reported a large review of 1197 pediatric patients with external auditory canal foreign bodies, of which 750 (63%) were presented primarily to the emergency department. Successful

removal was performed in 92.9% and 67.9% of cases in otolaryngology clinic in and the emergency department, respectively. Also, complications were found in 35.7% and 5.0% of patients undergoing removal in the emergency department and in the otolaryngology clinic, respectively [10].

With this work we wanted to point out the possibility of the presence of the foreign body as the cause of recurrent inflammatory and even pseudotumor reactions in the body.

It is often not possible to perform identification and analysis of the foreign body, especially after its delayed removal from the body. We think, however, that it would certainly be of clinical interest to identify and analyze the structure of the foreign body, even speculatively. The composition of the foreign body affects the possibility of its radiological identification, and it also determines the biological reaction to its presence.

## Conclusion

Ear foreign bodies are relatively common in pediatric population. Given that the medical history is sometimes not reliable, the clinical and radiological interpretation of pseudotumor in the external auditory canal or middle ear must include this possibility in the differential diagnosis as well. Surgical exploration is necessary to make the definite diagnosis and to avoid potential complications.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** This article does not contain any studies with human participants performed by any of the authors.

**Conflicts of interest.** The authors declare no conflict of interest.

### References:

1. Schulze SL, Kerschner J, Beste D. Paediatric external auditory canal foreign bodies: A review of 698 cases. Otolaryngol Head Neck Surg 2002;127(1):73–8.
2. Syms 3rd CA, Nelson RA. Impression-material foreign bodies of the middle ear and external auditory canal. Otolaryngology Head and Neck Surgery 1998;119(4):406–7.
3. Eleftheriadou A, Chalastras T, Kyrmizakis D, Sfetsos S, Dagalakis K, Kandiloros D. Metallic foreign body in middle ear: an unusual cause of hearing loss. Head Face Med 2007;3:23.
4. Đerić D, Pavlović B, Folić M, Blažić S, Čvorović Lj. Tick on the tympanic membrane. Med Pregl 2014;67(11-12):404–6.
5. Chalishazar UK, Singh V. Correlation between a foreign body in the external auditory canal and otitis media with effusion. J Laryngol Otol 2007;121(9):850–2.
6. Goldman SA, Ankerstjerne JK, Welker KB, Chen DA. Fatal meningitis and brain abscess resulting from foreign body-induced otomastoiditis. Otolaryngol Head Neck Surg 1998; 118(1):6–8.
7. Burke RT, Gatton B, Melville LD. Mastoiditis and meningitis complicating an aural foreign body. Pediatr Emerg Care 2012;28(10):1070–1.
8. Harris KC, Conley SF, Kerschner JE. Foreign body granuloma of the external auditory canal. Pediatrics 2004;113(4):e371–3.
9. Skandour D, Nouri H, Rochdi Y, Aderdour L, Raji A. [Persistent otorrhea revealing a foreign body of the middle ear]. Arch Pediatr 2014;21(8):873–5.
10. Karimnejad K, Nelson EJ, Rohde RL, Costa DJ. External Auditory Canal Foreign Body Extraction Outcomes. Ann Otol Rhinol Laryngol 2017;126(11):755–61.

# Strano tijelo u spoljašnjem slušnom kanalu opisano kao pseudotumor srednjeg uva: prikaz slučaja

Nemanja Radivojević[1], Dragoslava Đerić[1,2], Zoran Dudvarski[1,2], Igor Đorić[3], Ivana Živković[4], Siniša Šolaja[5]

[1]Klinički centar Srbije, Klinika za otorinolaringologiju i maksilofacijalnu hirurgiju, Beograd Srbija

[2]Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[3]Klinički centar Srbije, Odeljenje za neurohirurgiju, Beograd, Srbija

[4]Klinički centar Srbije, Klinika za kardiologiju, Beograd, Srbija

[5]Univerzitetska bolnica Foča, Odjeljenje za otorinolaringologiju i maksilofacijalnu hirurgiju, Republika Srpska, Bosna i Hercegovina

**Uvod**. Cilj ovog rada bio je da se prikaže slučaj stranog tijela spoljašnjeg slušnog kanala opisanog kao pseudotumor srednjeg uva, kao i da se ukaže na dijagnostičke i terapijske aspekte ovog problema.

**Prikaz slučaja**. Djevojčica od 8 godina je više puta hospitalizovana na našem odjeljenju zbog operacije lijevostrane hronične upale srednjeg uha. Mastoidektomija i zadnja atikotomija su urađene tokom početne hospitalizacije. Šest mjeseci kasnije primljena je na drugi čin lijevostrane timpanoplastike. Međutim, dva mjeseca prije hospitalizacije pojavili su se simptomi desnog uva: osjećaj punoće, postepeni gubitak sluha i povremeni bol. Otoskopski nalaz desno ukazuje na prisustvo "tumefakcije" u spoljašnjem slušnom kanalu sa površinom koja je bila izrazito hiperemična. Ovaj pseudotumor je konačno protumačen kao strano tijelo u vanjskom slušnom kanalu.

**Zaključak.** Strana tijela vanjskog slušnog kanala su relativno česta u pedijatrijskoj populaciji. Anamneza ponekad nije pouzdana, a klinička i radiološka interpretacija pseudotumora u vanjskom slušnom kanalu ili srednjem uvu mora uključiti i ovu mogućnost u diferencijalnoj dijagnozi. Hirurška eksploracija i patohistološka dijagnoza su neophodne za postavljanje konačne dijagnoze i izbjegavanje mogućih komplikacija.

**Ključne riječi:** vanjski slušni kanal, pseudotumor, strana tijela, bubna šupljina

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):107–115

UDK: 576.38:616-036.21
DOI: 10.59137/BII202301298E

*Review*

# Interplay between autophagy and coronavirus: autophagy mechanism

**Nikolina Elez-Burnjaković[1], Ajla Smajlović[2], Milena Dubravac Tanasković[1]**

[1]University of East Sarajevo, Faculty of Medicine Foca, Republic of Srpska, Bosnia and Herzegovina
[2]University of Sarajevo, Institute for Genetic Engineering and Biotechnology, Sarajevo, Bosnia and Herzegovina

Primljen – Received: 22/09/2022
Prihvaćen – Accepted: 26/12/2022

**Corresponding author:**
*Nikolina Elez-Burnjaković, PhD*
*Studentska 5, 73300 Foca*
*nikolinaa85@hotmail.com*



**Summary**

Regardless of the fascinating progress of humanity, biotechnology and medicine, the outbreak of the global pandemic of the SARS-CoV-2 virus has shown us that we are just as vulnerable as in previous eras when communicable diseases decimated the world's population. But the discoveries made so far at the molecular level allow us to connect knowledge interdisciplinary and find solutions and therapeutic strategies where there seems to be no link. It was the previous coronavirus infections that served as a homologous model for finding the connection between the SARS-CoV-2 virus and autophagy. Autophagy, a conserved universal process of all eukaryotic cells responsible for cell survival under stressful circumstances, has been shown to play a significant role in viral invasions. It contributes to both direct and indirect antiviral responses such the elimination of viruses, the presentation of their antigens, and the reduction of inflammatory responses. The autophagy machinery of host cells can, however, be suppressed, evaded, or used by viruses to their benefit. Therefore, autophagy has an ambiguous role in coronavirus-related infections, especially in COVID-19.

**Keywords**: COVID-19, pandemic, autophagy, SARS-CoV-2 virus

## Introduction

Autophagy makes a contribution to to a huge number of diseases, and bacterial and viral infections. Since autophagy is a process used to break down damaged organelles, pathogens, and cells, it aids in cell survival under conditions of deprivation, metabolic stress, and hypoxemia. If improperly activated, autophagy can promote type I cell death (apoptosis) or function as an alternative pathway of cell death, known as autophagic cell death (type II). Autophagy can support in the cancer cell death or operate as a protective mechanism against apoptotic or necrotic death carried on by a wide range of factors [1].

The interaction between autophagy and coronavirus (CoV) infections has received a lot of attention, and numerous hypotheses have been put out to provide light on the underlying molecular mechanisms. According to research, autophagy may play a role in antiviral reactions such the elimination of viruses, the presentation of their antigens, and the inflammatory responses reduction [2]. A type of selective autophagy known as xenophagy involves the capture of viruses, antigens produced from viruses, and viral components by autophagy receptors [3]. Viruses, on the other hand, can block, escape, or use the host cells' autophagy and autophagy-related genes (ATG) proteins to replicate or to manipulate the autophagy to interfere with the cells' antiviral defenses [4, 5]. Therefore, the autophagy is ambiguous in CoV-associated infections, particularly COVID-19 [6].

When autophagy is mentioned, macroautophagy, the best studied process is usually meant, although there are two other autophagy forms, microautophagy and chaperone-mediated autophagy. Chaperone-mediated autophagy is found in higher eukaryotes. Chaperones bind to a specific protein causing its unfolding and enabling it to get through the lysosomal membrane. In microautophagy, the cytoplasmic cargo reaches the lysosome by invagination. Macroautophagy (known as autophagy) is followed by autophagosome formation, a double membrane vesicle (DMV) that encompasses the cytoplasmic cargo, then merging with a lysosome for degradation of cargo.

The process of autophagy includes several phases: initiation, nucleation, membrane closure and maturation, fusion with lysosomes, and degradation of cargo. Each step is regulated by a specific Atg protein [7].

Several classes of Atg proteins are responsible for the formation of autophagosomes: Atg1 kinase and its regulators, phosphatidylinositol 3-kinase complex (PI3K), Atg9, Atg2-Atg18 complex as well as two ubiquitin conjugation systems [7].

Formation of autophagosome begins at the location where phagophores are assembled (PAS) identified in yeast. PAS is a preautophagosomal structure built of Atg protein [8]. Equivalent structure, omegasome is present on the mammalian endoplasmic reticulum (ER) [9].

After initiation, double membrane grows, and in that phase it is called phagophora or isolation membrane. As the membrane grows, it takes on a spherical shape, encompasses the cargo for transport and seal ends to form autophagosome.

Once formed, it can fuse with another autophagosome or with an early or late endosome, forming organelles, amphisomes, before fusion into lysosomes which product is termed autolysosome. In the second case, it can directly merge with lysosome in autolysosome [10].

## Nonselective and selective autophagy

Autophagy can be either selective or non-selective. Non-selective autophagy, which degrades non-specific cytoplasmic content, occurs as a response to a lack of nutrients and energy, with the goal of cell survival. Selective autophagy is involved in cell maintenance and homeostasis. Specific content can be mitochondria, peroxisomes, proteins or microorganisms [11].

Using ubiquitination, cells identify content for selective degradation. The ubiquitin-binding protein sequestosome 1 (SQSTM1/p62) targets viruses and bacteria that are degraded by xenophagy (also known as virophagy) [12]. SQSTM1 functions as an adaptor protein that reacts with phosphatidylethanolamine modified microtubule-associated proteins 1A/1B light chain 3B (LC3-II), resulting in aggrephagy, a type of specific macroautophagy of protein aggregates [13]. Other receptors involved in tagging proteins or pathogens to autophagosomes include NBR1 and optineurin (OPTN) [14].

## Autophagy phases

### *Induction/initiation*

Initiation of autophagosome formation begins with the formation of the ULK-mAtg13-FIP200-Atg101 complex. During nutrient-rich conditions, the ULK-mAtg13-FIP200-Atg101 complex is primarily present in the cytosol. Complex becomes inactivate by mammalian target of rapamycin (mTORC1). During nutrient-rich conditions, the direct interaction of raptor (mTORC1 subunit) and ULK1 leads to the phosphorylation of ULK1 and mAtg13. During starvation, mTORC1 does not interact with the ULK complex, which results in dephosphorylation, and thus activation of the ULK complex [15].

### *Nucleation*

To form an autophagosome, phosphatidylinositol 3-phosphate (PI3P) is necessary. Class III phosphatidylinositol 3 kinase (PI3K; hVps34) generates PI3P. Mammals have two hVps34 complexes that play a role in endosomal transport or fusion of autophagosomes and lysosomes through interaction with UVRAG (UV irradiation resistance-associated gene) and Rubicon (or KIAA0226, Run domain protein as Beclin 1interacting and cysteine rich containing).

Regulation of the PI3K complex occurs through the interaction of beclin 1 (BECN1), which is necessary for autophagy, and other proteins. The antiapoptotic protein Bcl-2 binds beclin 1 preventing its interaction with PIK3C3 inhibiting autophagy [16]. Rubicon inhibits PIK3C3 activity in the UVRAG-PI3K complex [12]. AMBRA1, which binds directly to Beclin 1, and Bif 1, which through UVRAG interacts with Beclin 1 and participates in forming the shape (rounding) of the membrane are two positive regulators of the PI3K complex [17].

Another category of PI3P effectors are WD-repeat proteins that interact with phosphoinositides (WIPI)1-4. WIPI2 is essential for the maturation of omegasomes in autophagosome [18].

### *Elongation*

There are two ubiquitin conjugation systems (UBL), Atg12 and LC3, in the last stages of autophagosome formation, which contribute to the growth and closure of the membrane [19].

Atg12 conjugates with Atg5 protein. On the isolation of the membrane's outer surface, Atg16L attaches to the Atg12-Atg5 complex and breaks from the membrane that was just before or exactly after autophagosome formation [19].

Another UBL system is ubiquitin-like protein LC3, produced as precursor and processed by the cysteine protease Atg4. The Atg4-processed form of LC3 is marked as LC3-I, and it covalently bound to the amino group of phosphatidylethanolamine (PE), and then is marked as LC3-II. LC3-II is membrane-bound, located on the isolation membrane and on the autophagosome, and has a role in membrane binding (joining opposite ends of a growing membrane) [20].

### *Autophagosome maturation and fusion with endosome/lysosome*

The last step of macroautophagy is the maturation of the phagophore, which closes in the finalized autophagosome and fuses with an endosome or lysosome, resulting in the formation of an autolysosome. Microtubules allow autophagosomes to move to lysosomes [21].

## Regulation of autophagy

Regulation of autophagy is controlled by the mTOR (mammalian target of rapamycin) pathway, which negatively regulates this process. Autophagy is controlled by a number of signaling pathways downstream of mTOR, namely

control of autophagy downstream of mTOR by the ULK1-Atg13-FIP200 complex, control of autophagy by amino acid deficiency via Rag/mTOR1, control of autophagy by growth factors via PI3KC1a/Akt/TSC /mTORC1 and the control of autophagy through stress and deprivation of energy via AMPK/TSC/mTORC1 [22].

In addition to classical mTOR autophagy, there have also been described mTOR-independent autophagy control pathways, such as the inositol signaling pathway, Ca2+/calpamin pathway, cAMP/Epac/Ins(1,4,5)P3 pathway, JNK1/Beclin-1/PI3KC3 pathway. Also, there are autophagy control pathways by other mTOR-independent small molecules which mechanism has not yet been described [22].

In CoV infection, mTOR activation of autophagy occurs, although due to the alarming disruption of cellular stability, other autophagy pathways are also linked to viral infection [23].

## Autophagy antiviral mechanisms of SARS-CoV-2 virus infection

In viral infections, AMP-activated protein kinase (AMPK) activates PI3K/protein kinase B while suppressing the mammalian target of rapamycin complex 1 (mTORC1) (Akt1), which as result have autophagy induction and virion encapsulation. After that, the formation of autophagosomes is activated, which then fuse with lysosomes to eliminate its viral content [24]. But, SARS-CoV-2 might have specific mechanisms of avoiding the autophagy-mediated cellular clearance [25]. Therefore, drug-targeting of escape mechanisms can attenuate viral replication. By interfering with various metabolic pathways, such as the regulation of glycolysis by inhibiting AMPK and mTORC1 [26], SARS-CoV-2 may decrease the level of autophagic flow. This may prevent the viral replication of substances like spermidine, which are pro-autophagic. Studies indicated that ACE2 is SARS-CoV-2 the entry receptor, as well as SARS-CoV-1 [27, 28]. Indeed, ACE2 can prevent lung cell autophagy and reduce cell death [28].

## Autophagy proviral mechanisms in SARS-CoV-2 virus infection

Based on the finding that the ATG12 and LC3 proteins were linked to the formation of DMVs during the course of the infection of Vero cells infected with mouse hepatitis virus (MHV), it was suggested that viral replication may involve autophagy [29]. In cells infected with SARS-CoVs, studies have shown that replicase proteins co-localize to complexes in cytoplasma that contain markers for autophagosome membranes, such as LC3 [30]. It has been discovered that NSP6, the viral replicase protein of Avian CoV, can induce the production of autophagosomes with Atg5 and LC3II [31], block further autophagosome expansion, and inhibit the transfer of the virus to the lysosome [32]. The papain-like protease PLP2 (PLP2-TM) of CoVs was identified to interact with LC3 and Beclin-1, increasing autophagosome flux and inhibiting autophagosomes from fusing to lysosomes [33].

## Drugs affecting the autophagic pathway in SARS-CoV-2 virus infection

There are a number of autophagy modulators which are described as a part of communicable and non-comunicable disease therapy. Therapeutic effects of these drugs on the patient during SARS-CoV, MERS-CoV and SARS-CoV2 infection have been also under investigation.

Chloroquine and its derivates, which are used as antimalaric and anti-inflammatory drugs, manifest some pleiotropic characteristics. Chloroquine has potential of lysosome

acidic hydrolases inhibition. Beside these effects, it can lead to autophagosome accumulation with consequential cell death and viral components elimination [34]. From the other hand, in vivo investigation, conducted in mices, showed that chloroquine reduces lung injury during COVID 19 infection, which indicates effects independent from viral replication [35].

Rapamycin and its analogs, as mTORC1 inhibitors, affect many different physiological aspects, such as immune response in mammals [36]. This drug shows similar effect on coronavirus cellular replication as mTORC1 and related kinases. During SARS-CoV and SARS-CoV2 infection autophagic flux seems to be increased because of mTORC1 inhibition, contrary to MERS-CoV infection, when mTORC1 phosphorylation and kinase activity is increased [36].

AMPK activators, also known as autophagy initiators, during SARS-CoV2 infection can be connected with increased level of viral replication. Suprisingly, Bramante and associates demonstrated that metformin (an AMPK activator) treated patients show lower mortality rates but autophagy involment in this case is still not evaluated [37, 38].

Sorafenib is a multikinase inhibitor, which also can initiate autophagy process, by inhibiting mTOR signaling and AMPK phosphorylation promoting [39]. Because of capability of inhibition MERS-CoV and SARS-CoV2 *in vitro* replication, it is considered as promising pharmaceutical for future clinical evaluation [40].

Statins are recently recognized as autophagy inducers. Although the mode of autophagy initiation is not completely studied yet, it is considered that they can inhibit mTORC1 activity [41]. They are traditionally aplied as a part of coronary heart disease therapy, but recent pandemic demonstrated that patients under long term treatment shows a lower risk for severe form of SARS-CoV2 infection. It is believed that this protective effect of statins comes from theirs anti-inflamatory features [41, 42].

Ivermectin represents an antiparasitic pharamceutical, which also posses in vitro antiviral activity. It also can induce autophagy by regulation of mTOR/AMPK pathway [43]. Among other effects, this drug can influence some physiologic activities, as well as some viral enzymes, such as RNA-dependent RNA polymerase and 3-chymotrypsin like protease [44].

Modulators that target lysosomal biogenesis promise some positive effects regarding MERS-CoV and SARS-CoV2 replication [38, 45]. As known, merging between autophagosome and lysosome can put pro-inflammatory pathway under the control and decrease potential damage. Curcumin, digoxin, niclosamide, quercetin, resveratrol and valinomycin are some of modulators which are belonging to this group and that can be used as a potential part of coronavirus therapy [46, 47, 48, 49].

There are some cellular stressors described, which can initiate autophagy after exposure to ROS stress. Pharmaceuticals such as plumbagin and tunicamycin theoretically can be applied in the coronavirus treatment, but theiz clinical evaluation is difficult because they posses important toxity [50].

## Conclusion

The review highlights how autophagy has been directly associated to SARS-CoV-2 infection. Control of autophagy is a crucial regulatory step, as we are aware, in various different communicable and non-communicable diseases. Unfortunately there have not been much data reported on autophagy regulation in COVID-19. Therefore, it is essential to understand mechanisms of autophagy, and to provide newer opportunities for treatment in COVID-19 therapy with autophagy modulators in COVID-19 patients.

**Funding source.** This research was funded by the University of East Sarajevo, Faculty of Medicine Foca, Republic of Srpska, Bosnia and Herzegovina.

**Ethical approval.** This article does not contain any studies with human participants performed by any of the authors.

**Conflicts of interes.** The authors declare no conflict of interest.

*Acknowledgments. The authors are grateful to Faculty of Medicine Foca for support in realization of project "The connection between individual genetic susceptibility and the severity of the clinical picture of SARS-CoV-2 infection".

## References:

1. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell 2008;132(1):27–42.
2. Carmona-Gutierrez D, Bauer MA, Zimmermann A, Kainz K, Hofer SJ, Kroemer G, et al. Digesting the crisis: autophagy and coronaviruses. Microb Cell 2020;7(5):119–28.
3. Orvedahl A, Sumpter R Jr, Xiao G, Ng A, Zou Z, Tang Y, et al. Image-based genome-wide siRNA screen identifies selective autophagy factors. Nature 2011;480(7375):113–7.
4. Mao J, Lin E, He L, Yu J, Tan P, Zhou Y. Autophagy and Viral Infection. Adv Exp Med Biol 2019;1209:55–78.
5. Gorshkov K, Chen CZ, Bostwick R, Rasmussen L, Tran BN, Cheng YS, et al. The SARS-CoV-2 Cytopathic Effect Is Blocked by Lysosome Alkalizing Small Molecules. ACS Infect Dis 2021;7(6):1389–408.
6. Behrouj H, Vakili O, Sadeghdoust A, Aligoli-ghasemabadi N, Khalili P, Zamani M, et al. Epigenetic regulation of autophagy in coronavirus disease 2019 (COVID-19). Biochem Biophys Rep 2022;30:101264.
7. Mizushima N, Yoshimori T, Ohsumi Y. The role of Atg proteins in autophagosome formation. Annu Rev Cell Dev Biol 2011;27:107–32.
8. Suzuki K, Kirisako T, Kamada Y, Mizushima N, Noda T, Ohsumi Y. The pre-autophagosomal structure organized by concerted functions of APG genes is essential for autophagosome formation. EMBO J 2001;20(21):5971–81.
9. Itakura E, Mizushima N. Characterization of autophagosome formation site by a hierarchical analysis of mammalian Atg proteins. Autophagy 2010;6(6):764–76.
10. Yang Z, Klionsky DJ. An overview of the molecular mechanism of autophagy. Curr Top Microbiol Immunol 2009;335:1–32.
11. Weidberg H, Shvets E, Elazar Z. Biogenesis and cargo selectivity of autophagosomes. Annu Rev Biochem 2011;80:125–56.
12. Zhong Y, Wang QJ, Li X, Yan Y, Backer JM, Chait BT, et al. Distinct regulation of autophagic activity by Atg14L and Rubicon associated with Beclin 1-phosphatidylinositol-3-kinase complex. Nat Cell Biol 2009;11(4):468–76.
13. Bjorkoy G, Lamark T, Brech A, Outzen H, Perander M, Overvatn A, et al. p62/SQSTM1 forms protein aggregates degraded by autophagy and has a protective effect on huntingtin-induced cell death. J Cell Biol 2005;171(4):603–14.
14. Wild P, Farhan H, McEwan DG, Wagner S, Rogov VV, Brady NR, et al. Phosphorylation of the autophagy receptor optineurin restricts Salmonella growth. Science 2011; 333(6039):228–33.
15. Ganley IG, Lam du H, Wang J, Ding X, Chen S, Jiang X. ULK1.ATG13.FIP200 complex mediates mTOR signaling and is essential for autophagy. J Biol Chem 2009;284(18):12297–305.
16. Furuya N, Yu J, Byfield M, Pattingre S, Levine B. The evolutionarily conserved domain of Beclin 1 is required for Vps34 binding, autophagy and tumor suppressor function. Autophagy 2005;1(1):46–52.

17. Takahashi Y, Coppola D, Matsushita N, Cualing HD, Sun M, Sato Y, et al. Bif-1 interacts with Beclin 1 through UVRAG and regulates autophagy and tumorigenesis. Nat Cell Biol 2007;9(10):1142–51.

18. Polson HE, de Lartigue J, Rigden DJ, Reedijk M, Urbe S, Clague MJ, et al. Mammalian Atg18 (WIPI2) localizes to omegasome-anchored phagophores and positively regulates LC3 lipidation. Autophagy 2010;6(4):506–22.

19. Mizushima N, Yamamoto A, Hatano M, Kobayashi Y, Kabeya Y, Suzuki K, et al. Dissection of autophagosome formation using Apg5-deficient mouse embryonic stem cells. J Cell Biol 2001;152(4):657–68.

20. Nair U, Yen WL, Mari M, Cao Y, Xie Z, Baba M, et al. A role for Atg8-PE deconjugation in autophagosome biogenesis. Autophagy 2012;8(5):780–93.

21. Monastyrska I, Rieter E, Klionsky DJ, Reggiori F. Multiple roles of the cytoskeleton in autophagy. Biol Rev Camb Philos Soc 2009;84(3):431–48.

22. Sarkar S. Regulation of autophagy by mTOR-dependent and mTOR-independent pathways: autophagy dysfunction in neurodegenerative diseases and therapeutic application of autophagy enhancers. Biochem Soc Trans 2013;41(5):1103–30.

23. Sargazi S, Sheervalilou R, Rokni M, Shirvaliloo M, Shahraki O, Rezaei N. The role of autophagy in controlling SARS-CoV-2 infection: An overview on virophagy-mediated molecular drug targets. Cell Biol Int 2021;45(8):1599–612.

24. Tang SW, Ducroux A, Jeang KT, Neuveut C. Impact of cellular autophagy on viruses: Insights from hepatitis B virus and human retroviruses. J Biomed Sci 2012;19(1):92.

25. Brest P, Benzaquen J, Klionsky DJ, Hofman P, Mograbi B. Open questions for harnessing autophagy-modulating drugs in the SARS-CoV-2 war: hope or hype? Autophagy 2020;16(12):2267–70.

26. Gassen NC, Papies J, Bajaj T, Emanuel J, Dethloff F, Chua RL, et al. SARS-CoV-2-mediated dysregulation of metabolism and autophagy uncovers host-targeting antivirals. Nat Commun 2021;12(1):3818.

27. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181(2):271–80.e8.

28. Li Y, Cao Y, Zeng Z, Liang M, Xue Y, Xi C, et al. Angiotensin-converting enzyme 2/angiotensin-(1-7)/Mas axis prevents lipopolysaccharide-induced apoptosis of pulmonary microvascular endothelial cells by inhibiting JNK/NF-κB pathways. Sci Rep 2015;5:8209.

29. Prentice E, Jerome WG, Yoshimori T, Mizushima N, Denison MR. Coronavirus replication complex formation utilizes components of cellular autophagy. J Biol Chem 2004;279(11):10136–41.

30. Prentice E, McAuliffe J, Lu X, Subbarao K, Denison MR. Identification and characterization of severe acute respiratory syndrome coronavirus replicase proteins. J Virol 2004;78(18):9977–86.

31. Cottam EM, Maier HJ, Manifava M, Vaux LC, Chandra-Schoenfelder P, Gerner W, et al. Coronavirus nsp6 proteins generate autophagosomes from the endoplasmic reticulum via an omegasome intermediate. Autophagy 2011;7(11):1335–47.

32. Cottam EM, Whelband MC, Wileman T. Coronavirus NSP6 restricts autophagosome expansion. Autophagy 2014;10(8):1426–41.

33. Chen X, Wang K, Xing Y, Tu J, Yang X, Zhao Q, et al. Coronavirus membrane-associated papain-like proteases induce autophagy through interacting with Beclin1 to negatively regulate antiviral innate immunity. Protein Cell 2014;5(12):912–27.

34. Shojaei S, Suresh M, Klionsky DJ, Labouta HI, Ghavami S. Autophagy and SARS-CoV-2 Infection: Apossible Smart Targeting of the Autophagy Pathway. Virulence 2020;11(1):805–10.

35. Weston S, Coleman CM, Haupt R, Logue J, Matthews K, Li Y, et al. Broad Anti-Coronavirus Activity of Food and Drug Administration-Approved Drugs Against SARS-CoV-2 In Vitro and SARS-CoV In Vivo. J Virol 2020;94(21):e01218–20.

36. Janes MR, Fruman DA. Immune Regulation by Rapamycin: Moving Beyond T Cells. Sci Signal 2009;2(67):pe25.

37. Gassen NC, Papies J, Bajaj T, Emanuel J, Dethloff F, Chua RL, et al. SARS-CoV-2-Mediated Dysregulation of Metabolism and Autophagy Uncovers Host-Targeting Antivirals. Nat Commun 2021;12(1):3818.

38. Bramante CT, Ingraham NE, Murray TA, Marmor S, Hovertsen S, Gronski J, et al. Metformin and Risk of Mortality in Patients Hospitalised With COVID-19: A Retrospective Cohort Analysis. Lancet Healthy Longev 2021;2(1):e34–e41.

39. Prieto-Domínguez N, Ordóñez R, Fernández A, García-Palomo A, Muntané J, González-Gallego J, et al. Modulation of Autophagy by Sorafenib: Effects on Treatment Response. Front Pharmacol 2016;7:151.

40. Klann K, Bojkova D, Tascher G, Ciesek S, Münch C, Cinatl J. Growth Factor Receptor Signaling Inhibition Prevents SARS-CoV-2 Replication. Mol Cell 2020;80(1):164–74.e4.

41. Zhang XJ, Qin JJ, Cheng X, Shen L, Zhao YC, Yuan Y, et al. In-Hospital Use of Statins Is Associated With a Reduced Risk of Mortality Among Individuals With COVID-19. Cell Metab 2020;32(2):176–87.e4.

42. Peng S, Xu LW, Che XY, Xiao QQ, Pu J, Shao Q, et al. Atorvastatin Inhibits Inflammatory Response, Attenuates Lipid Deposition, and Improves the Stability of Vulnerable Atherosclerotic Plaques by Modulating Autophagy. Front Pharmacol 2018;9:438.

43. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-Approved Drug Ivermectin Inhibits the Replication of SARS-CoV-2 in vitro. Antiviral Res 2020;178:104787.

44. Mody V, Ho J, Wills S, Mawri A, Lawson L, Ebert MCCJC, et al. Identification of 3-Chymotrypsin Like Protease (3clpro) Inhibitors as Potential Anti-SARS-CoV-2 Agents. Commun Biol 2021;4(1):93.

45. Lin SC, Ho CT, Chuo WH, Li S, Wang TT, Lin CC. Effective Inhibition of MERS-CoV Infection by Resveratrol. BMC Infect Dis 2017;17(1):144.

46. Marinella MA. Indomethacin and Resveratrol as Potential Treatment Adjuncts for SARS-CoV-2/COVID-19. Int J Clin Pract 2020;74(9):e13535.

47. Pindiprolu SKSS, Pindiprolu SH. Plausible Mechanisms of Niclosamide as an Antiviral Agent Against COVID-19. Med Hypotheses 2020;140:109765.

48. Ter Ellen BM, Dinesh Kumar N, Bouma EM, Troost B, Van De Pol DPI, van der Ende-Metselaar HH, et al. Resveratrol and Pterostilbene Inhibit SARS-Cov-2 Replication in Air-Liquid Interface Cultured Human Primary Bronchial Epithelial Cells. Viruses 2021;13(7): 1335.

49. Thimmulappa RK, Mudnakudu-Nagaraju KK, Shivamallu C, Subramaniam KJT, Radhakrishnan A, Bhojraj S, et al. Antiviral and Immunomodulatory Activity of Curcumin: A Case for Prophylactic Therapy for COVID-19. Heliyon 2021;7(2):e06350.

50. Dawood AA, Alnori HAM. Tunicamycin Anticancer Drug may Reliable to Treat Coronavirus Disease-19. Open Access Maced J Med Sci 2020;8(T1):129–33.

# Međuigra autofagije i koronavirusa: mehanizam autofagije

Nikolina Elez-Burnjaković[1], Ajla Smajlović[2], Milena Dubravac Tanasković[1]

[1]Univerzitet Istočno Sarajevo, Medicinski fakultet Foča,
Katedra za biologiju ćelije i humanu genetiku, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet Sarajevo, Institut za genetičko inženjerstvo i biotehnologiju, Sarajevo,
Bosna i Hercegovina

Bez obzira na fascinantan napredak čovječanstva, biotehnologije i medicine, izbijanje globalne pandemije SARS-CoV-2 virusa nam je pokazalo da smo jednako ranjivi kao i u prethodnim epohama kada su zarazne bolesti desetkovale svjetsku populaciju. Ali, dosadašnja otkrića na molekularnom nivou nam omogućavaju interdisciplinarna povezivanja znanja i pronalazak rješenja i terapeutskih strategija gdje naizgled nema spone. Upravo su dosadašnje infekcije koronavirusa poslužile kao homologi model za pronalazak veze između SARS-CoV-2 virusa i autofagije. Autofagija, konzerviran univerzalni proces svih ćelija eukariota zaslužan za preživljavanje ćelije u stresnim okolnostima, je pokazala da ima značajnu ulogu u invazijama virusa. Uključena je u direktne i indirektne antivirusne odgovore kao što su uklanjanje virusa, prezentacija njihovih antigena, smanjenje inflamatornih odgovora. Međutim, virusi mogu da potisnu, pobjegnu ili iskoriste mašineriju autofagije ćelija domaćina da bi se replicirali ili modifikovali autofagiju u svoju korist. Stoga, autofagija ima dvosmislenu ulogu kod infekcija povezanih sa koronavirusom, posebno kod COVID-19.

**Ključne riječi:** COVID-19, pandemija, autofagija, SARS-CoV-2 virus

BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):116-124

UDK: 159.913:614.254:[616.98COVID-19]
DOI: 10.59137/BII202301300S

*Review*

# Mental health of healthcare workers during the COVID-19 pandemic

**Maja Skočo[1], Jelena Pavlović[2]**

[1]PHI Hospital Trebinje,
Republic of Srpska,
Bosnia and Herzegovina
[2]University of East Sarajevo,
Faculty of Medicine Foca,
Republic of Srpska,
Bosnia and Herzegovina

Primljen – Received: 04/09/2022
Prihvaćen – Accepted: 13/03/2023

**Corresponding author:**
*Maja Skočo, Bachelor of Nursing*
*Cerska 10, 89101 Trebinje*
*maja.milic87@gmail.com*



**Summary**

Health workers, doctors and nurses and other health staff, due to their occupation and daily exposure to stressful situations, are the most exposed to professional burnout and the dangers of numerous mental disorders. The aim of this review was to point out, based on data from recent literature, the importance and level of mental health of doctors and nurses during the COVID-19 pandemic. Mental health is influenced by various factors, from social changes and circumstances to personal experiences in society. Extended working hours, night work, shift work, responsibility when making decisions, contact with the sick, contact and care for patients in the terminal phase of the disease, care for their families, and also the professional burnout of health workers have increased the morbidity of numerous psychological disorders and psychosomatic diseases in health workers, especially during viral epidemics and pandemics.

The World Health Organization advocates the thesis that the feeling of pressure in the current situation associated with the COVID-19 pandemic is normal, and that taking care of mental health is just as important as taking care of physical health.

**Keywords**: healthcare workers, mental health level, COVID-19 pandemic

## Introduction

The World Health Organization defined mental health as "a state of well-being in which each individual realizes his own potential, can cope with normal life stresses, can work productively and can contribute to his community" [1]. Positive mental health implies the ability to adapt to stressful situations, the ability to create positive feelings about oneself, i.e. maintaining a sense of personal worth and self-esteem, as well as engaging in productive activities that help people develop, create and maintain friendships and good interpersonal relationships. Mental health is influenced by various factors, from social changes and circumstances to personal experiences in society. Working people spend most of the day at their workplaces, so it is understandable that the workplace with all its characteristics can affect the mental health of every employed person,

especially healthcare workers. A high-quality working environment helps to a large extent to preserve the mental health and working ability of employees, while, on the other hand, poor environment and difficult working conditions of employees contribute to the development of mental disorders [1].

Health workers, doctors and nurses and other health staff, due to their occupation and daily exposure to stressful situations, are most exposed to professional burnout and the dangers of numerous mental disorders. At the end of 2019, a new virus from the coronavirus family appeared in Wuhan, China, which was first called the novel SARS-CoV virus, and then the SARS-CoV-2 virus [2]. It is a highly contagious disease that first caused an epidemic of acute respiratory syndrome (COVID-19), and in the period between January and April 2020, the epidemic turned into a global pandemic, and very quickly spread to other countries all over the world. The COVID-19 pandemic has been a great challenge for countries around the world since its inception, especially for healthcare workers facing with the challenge of providing care to a large number of patients [3].

For healthcare workers around the world, the word "exhaustion" has taken on a new meaning. The pandemic has brought many problems and new challenges, as well as the presence of fear and uncertainty, but also the appearance of problems with the functioning of health workers who were involved in the treatment of patients suffering from the COVID-19 infection, as well as all other patients. Taking care of their own mental health and well-being is equally important, as is physical protection at work. Health workers during the pandemic had an important task, i.e. to implement numerous interventions in their work processes, to provide quality health care to the sick and infirm.

A meta-analysis from 2018 spoke about the high rates of burnout syndrome, but also about the impaired mental health of healthcare workers before the COVID-19 pandemic [4]. The prevalence of burnout syndrome among physicians was 67.0% for total burnout, 72.0% for emotional exhaustion, 68.1% for depersonalization, and 63.2% for poor personal achievement [5]. Health workers, nurses and doctors, belong to the professions that are most exposed to the burnout syndrome, which was further increased by the crisis caused by the COVID-19 pandemic [5]. The stressful situations in which healthcare workers find themselves are often linked to mental and physical health. Health workers carry out numerous diagnostic procedures and provide care to patients. Extended working hours, night work, shift work, responsibility for contributing to decisions, contact with the sick, contact and care for patients in the terminal phase of the disease, care for their families, but also the professional burnout of healthcare workers increase the morbidity of numerous mental disorders and psychosomatic diseases in healthcare workers, especially during viral epidemics and pandemics [6, 7, 8]. Research has shown that depression in the workplace is most often manifested in the form of fatigue, decreased concentration, and physical symptoms in the form of various pains. Such persons become passive, withdrawn and unproductive at the workplace, and depression can also affect their ability to judge or make decisions. People with this disorder quit their jobs or change jobs more often [8].

The prevalence of mental disorders at workplaces (stress, anxiety, depression) has been increasing since 2015, and expectations that impaired mental health will surpass all other work-related illnesses are justified. According to the research conducted by the European Agency for Safety and Health at Work on the prevalence of occupational stress, it is evident that stress at the workplace is present in every third employed person in Europe, that is, there is a visible increase in occupational stress in the period from 1995 to 2005 with a prevalence of 28% to 31%. The problem

of professional stress annually causes the loss of a million working days, which makes costs of 20 billion euros and 5 million registered accidents and various injuries at work [9].

The aim of this review was to point out, based on data from recent literature, the importance and the level of mental health of doctors and nurses during the COVID-19 pandemic.

## Burnout syndrome among healthcare workers

Professional burnout syndrome occurs in people who are continuously exposed to stress at the workplace, when an individual encounters events or situations that he/she cannot cope with, or if they exceed his/her abilities. This syndrome is manifested by a feeling of exhaustion, chronic fatigue, loss of energy, idealism and motivation, which can be accompanied by various symptoms of a psychological and physical nature such as insomnia, diseases of the heart and blood vessels, then anxiety, depression and many others. The most vulnerable demographic category is young people, who are twice as likely to suffer from depression as average-aged workers. Burnout syndrome at work, which is related to professional stress according to the International Classification of Diseases ICD-11 (International Classification of Diseases - ICD -11) issued by the WHO, has been declared a legitimate medical diagnosis [10].

A large number of organizational factors such as the type of work, conflicting professional services, working conditions, scope of work tasks, length of working hours, contribute to a large extent to the stressogenicity of a certain profession. In recent years, interest in the phenomenon of professional burnout has been very widespread in various scientific fields, but it is also the subject of a large number of extensive scientific researches related to stress in general. However, still there is neither generally accepted definition of this term nor a generally accepted theoretical model that would offer a universal explanation of how stress leaves a negative impact on people's psychophysical health. Scientists view stress as a complex bio-psycho-social phenomenon that occurs as a systemic response of the organism (psycho-neuro-endocrine-immunological reaction) to the action of various stressors that disturb the psycho-physiological and psycho-social balance of the organism [11].

Timely recognition of symptoms can give an advantage in better stress control. So far, the results have indicated the fact that healthcare workers are exposed to a much higher level of stress at the workplace compared to the general population under normal circumstances, and are also exposed to a higher risk of psychosomatic diseases. Healthcare workers showed the highest risk of adverse psychological reactions during the COVID-19 pandemic, while contact with the coronavirus infection is associated with a significant increase in stress among healthcare workers [12]. However, feeling stigmatized is not associated with infection risks and is most prevalent among nurses and nursing assistants [13].

The 2020 meta-analysis by Batra et al, related to the COVID-19 pandemic, which included 65 studies and a total sample of 79,437 respondents, showed a prevalence of anxiety of 34.4%, depression 31.8%, stress 40.3%, post-traumatic stress syndrome 11, 4%, insomnia 27.8%, psychological stress 46.1% and burnout 37.4%. The analysis showed a higher prevalence of anxiety and depression among women, nurses and people on the front line of the fight against the pandemic, in contrast to lower prevalence among men, doctors and health workers on the second line [13]. The level of stress when dealing with a biological threat such as COVID-19 in healthcare workers can potentially cause post-traumatic stress syndrome, as well as increase the rate of psychosomatic diseases [14, 15].

In addition to psychological symptoms, frontline health workers are at higher risk of

viral infections, sudden death and work-related disorders, including cardiovascular disease [16]. Relevant research from the available literature supports the fact that the pandemic threatens the psychological well-being of the youngest and highly qualified professionals [12, 14]. A relevant study from 2021 on the burnout syndrome and the suicide rate of healthcare workers during the COVID-19 pandemic showed the presence of professional burnout in 42% of respondents, of which 79% stated that they were in burnout even before the COVID-19 pandemic [17]. Work-related stress is a characteristic reaction of employees because there are some work tasks that must be performed, and sometimes these demands exceed the knowledge and abilities of healthcare workers and they are often unable to cope with them [18]. Also, it is very important to recommend providing training to managers of institutions to acquire the necessary knowledge about the threat of mental health in the workplace so that they are able to recognize warning signs, take appropriate measures and possibly refer the employee to the procedure of providing professional assistance, if it is estimated that he/she needs help [19].

## Mental health of healthcare workers during the COVID-19 pandemic

The World Health Organization advocates the thesis that the feeling of pressure in the current situation associated with the COVID-19 pandemic is normal, and that taking care of mental health is just as important as taking care of physical health [20]. The COVID-19 pandemic has put healthcare workers in a situation where they have to make impossible decisions and work under extreme pressure. These decisions may include ways to allocate inadequate patient resources equally, how to balance one's own needs with the patient's physical and mental health needs, how to balance duties and wishes to patients, family, and friends, how to provide care to all seriously ill patients when resources are limited and inadequate. All this can damage the mental health of healthcare workers [21]. These problems can affect the working ability of healthcare workers and the quality of services provided. It is known that a negative work environment can lead to mental health problems. Although the World Health Organization emphasized the importance of mental health during the pandemic, most countries still do not focus on this problem [22, 23, 24].

Direct exposure to infection during the treatment of infected patients, working with suspected patients and also the potential possibility of infection, number of newly infected and hospitalized, high workload, wear of personal protective equipment, fear of inadequate use of protective equipment, care for loved ones, the lack of certain medications and feeling insufficient support, unsafe discharges of patients from the hospital, loss of health professionals and citizens due to death, lack of staff, emotional and ethical involvement in making difficult decisions, uncertainty about the duration of the pandemic, these are all extremely stressful situations to which health workers are exposed, which ultimately leads to damage to physical health, affecting the thinking process, the emotional well-being and behavior of the individual. A special emotional and psychological burden is also imposed during the healthcare of patients in isolation and quarantine. Very often orders to work in quarantine occur during working hours, which puts workers in a situation where it is impossible to go home to their loved ones. In particular, nurses involved in the care and treatment of coronavirus patients are very sensitive to unfavorable psychological conditions that cause reported difficulties in functioning at the business and private level [25]. The research, which involved 12,596 nurses working in different departments, indicated that 34.8% of them had sleep problems or poor sleep quality, 33.9% of

them believed that a similar disaster would happen again in the future, 28.1% became especially nervous or scared during unexpected events, 27.6% showed symptoms of irritation or got angry easily, 24.6% had negative thoughts or memories related to their experiences with the pandemic, while 13.3% had symptoms of trauma [26]. However, even before the onset of the pandemic, nurses were a vulnerable group for burnout in the workplace due to their emotional work with patients in various health and emotional states mostly unpleasant, which required managing not only their own emotions, but also the emotions of patients, i.e. a kind of regulation their suffering and pain [26]. Health care workers of a younger age, especially women and mothers of minor children, experience a greater dose of stress, because the female gender and interaction with COVID-19 patients is associated with anxiety and depression because it causes fear of infecting themselves or family members. One of the possible reasons for this can be also that older healthcare workers show fewer symptoms and difficulties with mental health because they have experienced a lot in their work practice and for this reason they have developed better coping skills. Stressors that impair their health are frustration over the impact of prescribed measures for the performance of work, lack of practical support such as a lack of adequate protective equipment, inadequate and insufficient staff training, lack of fairness in the organization, lack of support and understanding from superiors, conflicts related to professional roles, and interpersonal conflicts. This type of stress increases psychological pressure in the workplace. Also, stress can be caused by work organized in shifts, night work, standby at work and extraordinary calls to work in the employee's free time. Such situations shorten rest, sleep and recovery of workers, resulting in bad mood, irritability, drop in concentration, decrease in communication skills, and decrease in the ability to deal with emotional difficulties in the workplace [26].

The results of the research published in JAMA (Journal of the American Medical Association) and conducted during the peak of the number of coronavirus patients in Wuhan on 1257 health workers, i.e. 39.2% of doctors and 60.8% of nurses from 34 hospitals, show that 42% of the total number of respondents constantly took care of COVID-19 patients, where high rates of depression (50.4%), anxiety (44.6%), insomnia (34%) and stress (71.5%) were found among them [27].

The way the organism responds to stress depends on the psychological constitution of the person himself/herself, on his/her emotional state, and especially on previous life experiences. However, if exposure to stress lasts continuously, it leads to harmful consequences for the health of the person. The modern processes of globalization, the development of information and communication technologies and the demographic change of the workforce are radically changing the context of work, the working environment and the structure of work organizations, which results in the fact that work in many areas has already become, or will become even more intense and complex in the future and more responsible, requiring increased "mental-emotional stress", with more complex work patterns and more complex interpersonal relationships [28].

The encouraging fact is that the World Health Organization and many institutions have proposed guidelines for providing psychological support to healthcare workers during the pandemic, which is why it is important to use all evidence-based strategies to maximize already excessive resources [29]. According to the World Health Organization, healthcare workers need to be provided with adequate education, workplace support, and promotion of positive coping strategies to reduce their psychological distress [30].

The COVID-19 pandemic poses a significant challenge to the mental health of healthcare workers due to frequent exposure to stressful situations and increased risk of various mental

disorders such as anxiety, depression, PTSD, burnout syndrome and others. Therefore, it is important to implement specific strategies to prevent these disorders. Support from colleagues is of great importance. Healthcare workers often work in teams, so it is important that they support and help each other. Regular work meetings and discussions about stressful situations can help reduce the risk of burnout. Long working hours can be harmful to mental health, so it is important to establish a balance between work and personal life to avoid burnout and stress. Providing education on stress management methods can also help healthcare workers cope with stress and reduce the risk of mental disorders. Providing a safe and healthy working environment reduces stress and the risk of mental disorders. Healthcare institution management can help healthcare workers by providing adequate support, including financial support, appropriate working conditions, flexible working hours, regular breaks, as well as mental health programs and access to psychologists or counselors. There are many strategies the can be applied to reduce the risk of mental disorders and maintain good mental health in healthcare workers. It is important that these strategies are implemented at the individual and organizational level to ensure a healthy and safe working environment for all healthcare workers [30].

## Conclusion

The COVID-19 pandemic has led to many changes on the personal, family and social level of each individual, but also to many changes in the functioning of the health system. Previous research and extensive clinical practice indicate the existence of frequent and intense problems related to mental health, which are the consequence of the COVID-19 pandemic. It is of great importance to timely develop strategies for the prevention, treatment and rehabilitation of health workers with burnout syndrome, which would maintain the mental health of health workers, but also quality health care and assistance provided to patients within the health system.

**Funding source.** The authors received no specific funding for this work.

**Ethical approval.** This article does not contain any studies with human participants performed by any of the authors.

**Conflicts of interest.** The authors declare no conflict of interest.

### References:

1. World Health Organization. Promoting mental health: concepts, emerging evidence, practice: Summary Report. World Health Organization, 2004.
2. Kisely S, Warren N, McMahon L, Dalais C, Henry I, Siskind D. Occurrence prevention, and management of the psychological effects of emerging virusoutbreaks on healthcare workers: rapid review and meta- analysis. BMJ 2020;369:m1642.
3. Su JC, Shen LJ, Chen HC. Maintaining mental health among medical staff during the COVID-19 pandemic: Taiwan's experience. J Formos Med Assoc 2021;120(3):923–5.
4. Drmić S, Murn L. Sindrom sagorijevanja među zdravstvenim radnicima u pandemiji bolesti COVID-19. Hrvat čas zdr znan 2021;1(1):25–9.
5. Rotenstein LS, Torre M, Ramos MA, Rosales RC, Guille C, Sen S, et al. Prevalence of burnout among physicians a systematic review. JAMA 2018;320(11):1131–50.
6. Eschleman KJ, Mathieu M, Cooper J. Creating a recovery filled weekend: Themoderating effect

of occupation type on the relationship between non-work creative activity and state of feeling recovered at work. Creat Res J 2017;29(2):97–107.

7. Hobfoll SE, Halbesleben J, Neveu JP, Westman M. Conservation of resources in theorganizational context: The reality of resources and their consequences. Annu Rev Organ Psychol Organ Behav 2018;5:103–28.
8. Karatepe OM, Yavas U, Babakus E, Deitz GD. The effects of organizational andpersonal resources on stress, engagement, and job outcomes. Int J Hosp Manag 2018;74:147–61.
9. Milczarek M, González ER, Schneider E. OSH in figures: Stress at work-facts and figures. Office for Official Publ. of the Europ. Communities; 2009.
10. World Health Organization (WHO). Burn-out an "occupational phenomenon": International Classification of Diseases, 2019. Retrieved https://www.who.int/mental_health/evidence/burn–out/en/
11. Gold JA. Covid-19: adverse mental health outcomes for healthcare workers. BMJ 2020;369:m1815.
12. Sorokin MY, Kasyanov ED, Rukavishnikov GV, Makarevich OV, Neznanov NG, Morozov PV, et al.Stress and stigmatization in health-care workers during the COVID-19 pandemic. Indian J Psychiatry 2020;62(Suppl 3):S445–S453.
13. Batra K, Singh TP, Sharma M, Batra R, Schvaneveldt N. Investigating the psychological impact ofCOVID-19 among healthcare workers: A meta-analysis. Int J Environ Res Public Health 2020;17(23):9096.
14. Asaoka H, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Post-traumatic stress symptoms among medical rescue workers exposed to COVID-19 in Japan. Psychiatry Clin Neurosci 2020;74(9):503–5.
15. Yi J, Kang L, Li J, Gu J. A Key Factor for Psychosomatic Burden of Frontline Medi-cal Staff: Occupational Pressure During the COVID-19 Pandemic in China. Front Psychiatry 2021;11:590101.
16. Zhang F, Wang H, Chen R, Hu W, Zhong Y, Wang X. Remote monitoring contributes to preventingoverwork-related events in health workers on the COVID-19 frontlines. Precis Clin Med 2020;3(2):97–9.
17. Holmes EA, O'Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry 2020;7(6):547–60.
18. Leka S, Jain A, Iavicoli S, Di Tecco C. An Evaluation of the Policy Context on Psychosocial Risks and Mental Health in the Workplace in the European Union: Achievements, Challenges, and the Future. Biomed Res Int 2015;2015:213089.
19. Hennekam S, Richard S, Grima F. Coping with mental health conditions at work and its impact on self-perceived job performance. Employee Relations: The International Journal 2020;42(3):626–45.
20. World Health Organization. COVID 19 Public Health Emergency of International Concern (PHEIC) Global Research and Innovation Forum: Towards a Research Roadmap. R&D Blueprint: World Health Organization. 2020;1–7.
21. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence ofdepression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: Asystematic review and meta-analysis. Brain Behav Immun 2020;88:901–7.
22. Preti E, Di Mattei V, Perego G, Ferrari F, Mazzetti M, Taranto P, et al. The Psychological Impact of Epidemic and Pandemic Outbreaks on Healthcare Workers: Rapid Review of the Evidence. Curr Psychiatry Rep 2020;10:22(8):43.
23. Dutheil F, Aubert C, Pereira B, Dambrun M, Moustafa F, Mermillod M, et al. Suicide among physicians and health-care workers: A systematic review and meta-analysis. PLoS One 2019;14(12):e0226361.
24. Chen Q, Liang M, Li Y, Guo J, Fei D, Wang L, et al. Mental health care for medical staff in China during the COVID-19 outbreak. Lancet Psychiatry 2020;7(4):e15–e16.
25. Lu W, Wang H, Yuxing L, Li L. Psychological status of medicalworkforce during the COVID-19 pandemic: A cross-sectional study. Psychiatry Res 2020;288:112936.
26. Chen R, Sun C, Chen JJ, Jen HJ, Kang XL, Kao CC, et al. A Large-Scale Survey on Trauma, Burnout, and Posttraumatic Growth among Nurses during the COVID-19 Pandemic. Int J Ment Health Nurs 2020;30(1):102–16.

27. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors Associated With Mental Health Outcomes Among Healt Care Workers Exposed to Coronavirus Disease 2019. JAMA Netw Open 2020;3(3):e203976.

28. Čabarkapa M, Đurišić BM. Psihosocijalni izvori stresa u globalno promenjenom radnom okruženju i zahtevi za promenama u sistemu obrazovanja. U: Dimitrijević B, urednik. Savremene paradigme u nauci i naučnoj fantastici. Niš: Filozofski fakultet; 2014. p. 48–63.

29. Yang L, Yin J, Wang D, Rahman A, Li X. Urgent need to develop evidence-based self-help interventions for mental health of healthcare workers in COVID-19 pandemic. Psychol Med 2021;51(10):1775–76.

30. Chen H, Wang B, Cheng Y, Muhammad B, Li S, Miao Z, et al. Prevalence of posttraumatic stress symptoms in health care workers after exposure to patients with COVID-19. Neurobiol Stress 2020;13:100261.

# Mentalno zdravlje zdravstvenih radnika tokom pandemije COVID-19

Maja Skočo[1], Jelena Pavlović[2]

[1]JZU Bolnica Trebinje, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet u Istočnom Sarajevu, Medicinski fakultet Foča, Republika Srpska, Bosna i Hercegovina

Zdravstveni radnici, ljekari i medicinske sestre i drugo zdravstveno osoblje, zbog vrste svog zanimanja i svakodnevnog izlaganja stresnim situacijama, najviše su izloženi profesionalnom sagorijevanju i opasnostima od brojnih mentalnih poremećaja. Cilj ovog preglednog rada bio je da se, na osnovu podataka iz novije literature, ukaže na značajnost i nivo mentalnog zdravlja ljekara i medicinskih sestara tokom pandemije COVID-19. Na mentalno zdravlje utiču različiti faktori, od društvenih promjena i okolnosti, do ličnih iskustava u društvu. Produženo radno vrijeme, noćni rad, rad u smjenama, odgovornost pri donošenju odluka, kontakt sa oboljelima, kontakt i briga o pacijentima u terminalnoj fazi bolesti, briga o njihovim porodicama, ali i profesionalno sagorijevanje zdravstvenih radnika povećavaju morbiditet brojnih psihičkih smetnji i psihosomatskih bolesti kod zdravstvenih radnika, posebno tokom virusnih epidemija i pandemija.

Svjetska zdravstvena organizacija zastupa tezu da je osjećaj pritiska u trenutnoj situaciji povezan s pandemijom COVID-19 normalan, te da je briga za mentalno zdravlje jednako bitna kao i briga za fizičko zdravlje.

**Ključne riječi:** zdravstveni radnici, nivo mentalnog zdravlja, pandemija COVID-19

## UPUTSTVO AUTORIMA ZA PISANJE ČLANKA ZA ČASOPIS „BIOMEDICINSKA ISTRAŽIVANJA“

**„Biomedicinska istraživanja“** je časopis Medicinskog fakulteta Foča, Univerziteta u Istočnom Sarajevu, sa otvorenim pristupom i slijepom recenzijom, koji izlazi dva puta godišnje, u junu i decembru.

U časopisu „Biomedicinska istraživanja“ objavljuju se originalni naučni radovi, prethodna ili kratka saopštenja, pregledni i stručni radovi, radovi za praksu, edukativni članci, komentari na objavljene članke, prikazi bolesnika, pregledi iz literature, radovi iz istorije medicine, prikazi knjiga, izvještaji sa naučnih i stručnih skupova, novosti i pisma iz svih oblasti medicine, stomatologije, defektologije i zdravstvene njege.

**Otvoreni pristup** časopisu *Biomedicinska istraživanja* omogućava slobodan, besplatan i neograničen onlajn pristup svim člancima poslije njihovog onlajn objavljivanja. Korisnici mogu besplatno da preuzmu, čitaju, kopiraju i štampaju kompletne tekstove svih radova ili da ih koriste za svaku drugu zakonom dozvoljenu svrhu, bez prethodnog odobrenja izdavača ili autora.

Ne postoji naknada za podnošenje članka, za obradu članka, za recenziju, ni naknada za pristup objavljenim člancima.

**Uslovi.** Časopis *Biomedicinska istraživanja* objavljuje samo radove koji nisu ranije objavljeni u cjelosti ili djelimično, osim u obliku sažetka, i koji nisu istovremeno podnijeti za objavljivanje nekom drugom časopisu.

**Opšta pravila**

Tekst članka pisati jasno i jezgrovito sa izbjegavanjem nepotrebnih opširnosti na srpskom jeziku, latinicom ili engleskom jeziku sa kratkim sadržajem, obavezno i na srpskom i na engleskom jeziku. Zbog bolje dostupnosti i veće citiranosti, autorima se preporučuje da radove svih oblika predaju na engleskom jeziku. Originalni radovi, prethodna ili kratka saopštenja, prikazi bolesnika ili slučajeva, pregledni radovi i aktuelne teme, publikuju se isključivo na engleskom jeziku, a ostale vrste radove se mogu publikovati i na srpskom jeziku samo po odluci Uredništva. Skraćenice koristiti izuzetno i to samo za veoma duge nazive hemijskih supstancija ili za nazive koji su poznati kao skraćenice (npr. AIDS, DNK, itd). Ne mogu se skraćivati nazivi simptoma i znakova, kao i imena bolesti, anatomske ili histološke osobenosti. Koristiti mjere metričkog sistema u skladu sa Internacionalnim sistemom jedinica, a za lijekove generička imena, dok se uređaji označavaju trgovačkim nazivima, pri čemu je ime i mjesto proizvođača u zagradi.

Tekst rada kucati u programu za obradu teksta *Word*, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12. Sve margine podesiti na 25 mm, veličinu stranice na A4, a tekst kucati sa lijevim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez dijeljenja riječi.

Stranice numerisati redom u okviru donje margine počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu se označavaju arapskim brojevima u uglastim zagradama - npr. [3, 4] i to onim redoslijedom kojim se pojavljuju u tekstu.

Za izradu grafičkih priloga koristiti standardne grafičke programe za Windows, iz programskog paketa Microsoft Office (Excel). Kod kompjuterske izrade grafika treba izbjegavati upotrebu boja i sjenčenje pozadine.

Uz rukopis članka potrebno je priložiti izjavu sa potpisima svih autora da članak nije ranije objavljivan, niti se trenutno razmatra njegovo objavljivanje u drugom časopisu - publikaciji. Svi prispjeli radovi upućuju se na anonimnu recenziju kod dva recenzenta, stručnjaka iz odgovarajuće oblasti. Radovi se ne honorišu, niti se vraćaju.

**Zahvalnica**

Navesti sve one koji su doprinijeli stvaranju rada, a ne ispunjavaju mjerila za autorstvo, kao što su osobe koje obezbjeđuju tehničku pomoć. Finansijska i materijalna pomoć u obliku sponzorstva, stipendija, poklona, opreme, lijekova i drugog, treba, takođe, da bude navedena. Ne stavljaju se plaćene usluge, npr. stručni prevodi na engleski jezik.

**Propratno pismo** mora sadržati datum slanja, naslov rukopisa i informacije o prethodnoj publikaciji ili prethodnom odbijanju od strane drugog časopisa. Ako je rukopis prethodno odbio drugi časopis, autori treba da opišu kako se poboljšao od trenutka odbijanja. Takođe je potrebno dostaviti kopije svih dozvola za: reprodukovanje prethodno objavljenog materijala, upotrebu ilustracija i objavljivanje informacija o poznatim ljudima ili imenovanje ljudi koji su doprinijeli izradi rada.

**Plagijarizam**

Od 25. septembra 2018. godine svi rukopisi se podvrgavaju provjeri na plagijarizam/autoplagijarizam preko *iThenticate*, a od 2021. godine i preko *SCIndeks Assistant – Cross Check (iThenticate).* Posebna pažnja se posvećuje rukopisima za koje se sumnja da su plagirani u skladu sa dijagramima toka COPE (http://publicationethics.org/resources/flovcharts) i smjernicama ICMJE. Radovi kod kojih se dokaže plagijarizam/autoplagijarizam biće odbijeni.

**Obim rukopisa**

Obim rukopisa (*ne računajući kratak sadržaj i spisak literature*) za pregledni rad može iznositi najviše dvanaest strana, za originalni rad deset strana, za stručni rad i rad iz istorije medicine osam strana, za prethodna saopštenja četiri strane, a za izvještaj, prikaz knjige i pismo dvije strane, a za prikaz slučajeva (bolesnika) do šest strana.

**Dijelovi rada**: naslovna strana, kratak sadržaj sa ključnim riječima, tekst rada, literatura, prilozi (*tabele, grafikoni, slike*).

**Originalni i stručni radovi** treba da imaju sljedeće podnaslove: Uvod (Cilj rada navesti kao posljednji pasus Uvoda), Metod rada, Rezultati, Diskusija, Zaključak, Literatura.

**Pregledni rad čine**: Uvod, Odgovarajući podnaslovi, Zaključak, Literatura. Pregledni rad mora da sadrži najmanje 5 radova autora članka iz uže oblasti iz koje je rad.

**Prikazi bolesnika ili slučaja** čine: Uvod (Cilj rada navesti kao posljednji pasus Uvoda), Prikaz bolesnika, Diskusija, Literatura. Za ostale vrste radova sažetak nema posebnu strukturu.

**Priprema rada**

Radove pripremati u skladu sa Vankuverskim dogovorom (V izdanje, revizija iz 1997. godine) postignutim na inicijativu Međunarodnog komiteta urednika medicinskih časopisa *(International Committee of Medical Journals Editors*) ***Uniform Requirements for Manuscripts Submitted to Biomedical Journals:*** www.icmje.org - http://www.icmje.org/urm_full.pdf.

**Naslovna strana**

Na posebnoj stranici, prvoj stranici rukopisa, treba navesti sljedeće:

- naslov rada bez skraćenica;
- puna imena i prezimena autora bez titula indeksirana brojevima;
- zvanični naziv ustanova u kojima autori rade i mjesto, i to redoslijedom koji odgovara indeksiranim brojevima autora;
- na dnu stranice navesti ime i prezime autora sa kojim će se obavljati korespondencija, njegovu adresu, kontakt telefon i *e-mail* adresu;
- na ovoj stranici, po želji autora navesti izvore finansiranja, kao i izjave zahvalnosti.

**Kratak sadržaj (apstrakt) i ključne riječi.** Uz originalni naučni rad, saopštenje, pregledni stručni i rad iz istorije medicine treba priložiti na posebnoj stranici kratak sadržaj do 250 riječi. U njemu se navode ciljevi i metod rada, glavni rezultati (*ako je moguće navesti brojčane podatke i njihovu statističku značajnost*) i osnovni zaključci rada. Na kraju nabrojati ključne riječi ili kraće fraze (3 do 5) bitne za brzu identifikaciju i klasifikaciju članka. Ukoliko postoji mogućnost, za izbor ključnih riječi treba koristiti *Medical Subject Headings –MeSH* (*http://www.nlm.nih.gov/mesh*). Preporučuje se da riječi iz naslova ne budu korišćenje za ključne riječi.

**Naslov rada, puna imena i prezimena autora, nazive ustanova, kratak sadržaj (apstrakt) i ključne riječi na engleskom jeziku**

Na posebnoj stranici otkucati naslov rada, puna imena i prezimena autora, nazive ustanova, apstrakt i ključne riječi na engleskom jeziku, ukoliko je rad napisan na srpskom jeziku. (Za radove napisane na engleskom jeziku osim kratkog sadržaja na engleskom jeziku potreban je i kratak sadržaj na srpskom jeziku).

**Prilozi** su tabele, slike (fotografije), crteži (sheme, grafikoni), kojih može biti ukupno šest. Svaki prilog se dostavlja kao poseban dokument, obilježen na isti način kao u tekstu. Ako su tabele, grafikoni, sheme ili slike već objavljeni, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

**Tabele.** Svaka tabela se kuca na posebnoj stranici. Tabele se označavaju arapskim brojevima prema redoslijedu navođenja u tekstu. Naslov tabele prikazuje njen sadržaj i kuca se iznad tabele. Korišćene skraćenice u tabeli obavezno objasniti u legendi tabele. Tabele raditi isključivo u programu Word, kroz meni Table-Insert-Table uz Uputstvo autorima definisanje tačnog broja kolona i redova koji će činiti mrežu tabele.

**Slike (fotografije).** Priložiti samo kvalitetno uređene fotografije u crno-bijeloj tehnici i to u originalu. Na poleđini svake slike zalijepiti naljepnicu sa njenim rednim brojem, imenom autora i označenim vrhom slike. Naslov slike otkucati na posebnom listu.

**Crteži (sheme, grafikoni).** Grafikoni treba da budu urađeni i dostavljeni u programu Excel, a zatim linkovani u Word-ov dokument gdje se grafikoni označavaju arapskim brojevima po redoslijedu navođenja u tekstu. Naslove grafikona i legendu za svaki crtež napisati na posebnom listu.

**Literatura.** Kuca se na posebnoj stranici, s dvostrukim proredom, sa arapskim brojevima prema redoslijedu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u preglednom radu u kome je dozvoljeno da ih bude do 50. Oko 80% citata treba da budu originalni radovi, a ostalo mogu da budu knjige, poglavlja u knjigama ili pregledni radovi. Većina citiranih naučnih članaka ne treba da bude starija od pet godina, a citiranje sažetaka treba izbjegavati. Reference se citiraju prema tzv. Vankuverskim pravilima (Vankuverski stil). Koristiti skraćene nazive časopisa po ugledu na „Index Medicus".

**Primjeri citiranja:**

*Članak u časopisu:*

Jasselon J, Kuser BY, Wier MR. Hepatitis B surface antigenemia in a chronic hemodialysis program. Am J Kidney Dis 1987;9(6):456-61.

Navode se imena najviše šest autora, a ako ih je više, iza šestog se dodaje „ i saradnici", odnosno „et al." ukoliko je referenca napisana na engleskom jeziku.

*Poglavlje u knjizi:*

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: Mc-Graw-Hill; 2002. p. 93-113.

*Knjiga:*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

*Članak s kongresa ili sastanka:*

Vuković B, Šeguljev Z, Virusni hepatitisi – aktuelan epidemiološki problem 32. Dani preventivne medicine. Niš, 1998. Zbornik rezimea. Institut za zaštitu zdravlja, Niš, 1998; 51-64.

*Disertacija:*

Radosavljević V. Faktori rizika za nastanak malignih tumora mokraćne bešike. Doktorska disertacija. Univerzitet u Beogradu, 1999.

*Članak za časopis u elektronskom formatu:*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

*web stranica na internetu:*

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: *http://www.cancer-pain.org/.*

**Slanje rukopisa**. Rukopis rada i svi prilozi uz rad dostavljaju se isključivo elektronski preko sistema za prijavljivanje na internet stranici *https://aseestant.ceon.rs/index.php/bioistr*

**Napomena.** Rad koji ne ispunjava uslove ovog uputstva ne može biti upućen na recenziju i biće vraćen autorima da ga dopune i isprave. Pridržavanjem uputstva za pripremu rada znatno će se skratiti vrijeme cjelokupnog procesa do objavljivanja rada u časopisu, što će pozitivno uticati na kvalitet članaka i redovnost izlaženja časopisa.

Za sve dodatne informacije, molimo da se obratite na adresu i broj telefona:
Univerzitet u Istočnom Sarajevu
Medicinski fakultet, Foča
Ul. Studentska 5, 73300 Foča
e-mail: *biomedicinskaistrazivanja@yahoo.com*
tel: 058/210-420; fax: 058/210-007
Uređivačkom odboru časopisa „Biomedicinska istraživanja"

## INSTRUCTIONS FOR AUTHORS

''Biomedicinska istraživanja" is a journal of the Faculty of Medicine Foca, University of East Sarajevo, with an open access and blind peer review, which is published twice a year, in June and December.

The journal ''Biomedicinska istraživanja" publishes original scientific papers, previous or short announcements, review and professional papers, papers for practice, educational articles, comments on published articles, case reports, literature reviews, papers on the history of medicine, book reviews, reports from scientific and professional gatherings, news and letters from all fields of medicine, dentistry, special education and rehabilitation and nursing.

**Open access** to the journal ''Biomedicinska istraživanja'' allows free and unlimited online access to all articles after their online publication. Users may download, read, copy and print the complete texts of all papers free of charge or use them for any other purpose permitted by law, without the prior approval of the publisher or author.

There is no fee for submitting an article, for processing an article, for reviewing, or a fee for accessing published articles.

**Conditions.** The journal ''Biomedicinska istraživanja'' publishes only papers that have not been previously published in whole or partially, except in abstract form, and which have not been submitted for publication to another journal at the same time.

**General guidelines**

The text of the article should be written clearly and concisely, avoiding unnecessary extensiveness in Serbian Latin or English with a short content, obligatory in both Serbian and English. Due to better availability and greater citation, authors are recommended to submit papers of all forms in English. Original papers, previous or short announcements, patient or case reports, review papers and current topics are published exclusively in English, and other types of papers can be published in Serbian only by the decision of the Editorial Board. Abbreviations should be used exceptionally, and only for very long names of chemical substances or for names that are known as abbreviations (i.e. AIDS, DNA, etc.). The names of symptoms and signs, as well as the names of diseases, anatomical or histological features, cannot be shortened. Use metric units in accordance with the International System of Units, and generic names for medicines, while devices should be marked by their trade names, with the name and location of the manufacturer in brackets.

Type the text of the paper in *Word*, with double spacing, exclusively *Times New Roman* font and font size 12. Set all margins to 25 mm, page size to A4, and type the text with left alignment and indentation of each paragraph by 10 mm, without division of words.

Number the pages in order within the bottom margin starting from the title page. Data on the used literature in the text are indicated by Arabic numerals in square brackets - e.g. [3, 4] in the order in which they appear in the text.

Use standard graphic programmes for Windows, Microsoft Office (Excel) to design graphic attachments. Avoid colouring and shading of the background in computer design of graphs.

Along with the manuscript of the article, it is necessary to enclose a statement with the signatures of all authors that the article has not been published before, nor is it currently being considered for publication in another journal - publication. All submitted papers are sent for anonymous review by two reviewers, experts in the relevant field. The papers are not honored or returned.

**Acknowledgment**

List all those who contributed to the creation of the paper and did not meet the authorship criteria, such as the individuals providing technical assistance. Financial and material assistance in the form of sponsorships, scholarships, gifts, equipment, medicines and other should also be mentioned. Paid services are not provided, e.g. professional translations into English.

**Cover letter** must contain the date of submission, the title of the manuscript, and information about the previous publication or previous rejection by another journal. If the manuscript was previously rejected by another journal, the authors should describe how it has been improved since the moment of rejection. It is also necessary to provide copies of all permits for: reproducing previously published material, using illustrations and publishing information about famous people, or naming people who contributed to the paper.

**Plagiarism**

From 25 September 2018, all manuscripts will be subject to plagiarism/autoplagiarism via iThenticate, and from 2021 via SCIndeks Assistant - Cross Check (iThenticate). Special attention is paid to manuscripts suspected of being plagiarized in accordance with COPE flowcharts (http://publicationethics.org/resources/flowcharts) and ICMJE recommendations. Papers proving plagiarism/autoplagiarism will be rejected.

**The length of the manuscript**

The length of the manuscript (excluding the short content and list of references) for a review paper can be a maximum of 12 pages, for an original paper 10 pages, for professional paper and paper on the history of medicine 8 pages, for previous announcements 4 pages, for a report, book review and letter 2 pages, and for case reports (of patients) up to 6 pages.

**Parts of the paper:** title page, abstract with key words, text of the paper, references, attachments (*tables, graphs, figures*).

**Original and professional papers** should have the following subheadings: Introduction (Aim of the paper should be stated as the last paragraph of the Introduction), Methods, Results, Discussion, Conclusion, References.

**The review paper consists of:** Introduction, Relevant subheadings, Conclusion, References. The review paper must contain at least 5 papers by the author of the article from the narrow field from which the paper is from.

**Patient or case reports consist of:** Introduction (Aim of the paper should be stated as the last paragraph of the Introduction), Patient report, Discussion, References. For other types of papers, the abstract does not have a special structure.

**Preparation of the paper**

The papers should be prepared in accordance with the Vancouver agreement (V Edition, review from 1997), initiated by the International Committee of Medical Journals Editors. ***Uniform Requirements for Manuscripts Submitted to Biomedical Journals***: www.icmje.org – http://www.icmje.org/urm_full.pdf

**Title page**

On a separate page, the title page of the manuscript, the following should be stated:

- A title of the paper without abbreviations;
- Full names and surnames of the authors without titles and indexed by numbers;

- Official name and place of the institutions where the authors work, in the order which matches indexed numbers of the authors;
- At the bottom of the page should be name and surname of the author responsible for correspondence, his address, telephone numbers and e-mail address;
- on this page, at the request of the author, the sources of funding should be indicated, as well as acknowledgements.

**Short summary (abstract) and keywords.** In addition to the original scientific paper, an announcements, review and professional paper and a paper on the history of medicine, a short summary of up to 250 words should be attached on a separate page. It states the objectives and methods, the main results (*if possible, state the numerical data and their statistical significance*) and the basic conclusions of the paper. Finally, list keywords or shorter phrases (3 to 5) relevant to the rapid identification and classification of the article. If possible, use *Medical Subject Headings-MeSH* (http://www.nlm.nih.gov/mesh) to select keywords. It is recommended not to use the words from the title for keywords.

**Title of the paper, full names and surnames of the authors, names of institutions, short summary (abstract) and keywords in English**

On a separate page, type the title of the paper, full names and surnames of the authors, names of institutions, abstract and keywords in English, if the paper is written in Serbian. (For papers written in English, in addition to short summary in English, short summary in Serbian is also required).

**Attachments** are tables, figures (photographs), drawings (schemes, graphs), of which there can be a total of six. Each attachment is submitted as a separate document, marked in the same way as in the text. If tables, graphs, schemes or figures have already been published, indicate the original source and attach written authorization for their use.

**Tables**. Each table should be typed on a separate page. Tables are marked with Arabic numerals according to the order of citation in the text. The title of the table shows its contents and it is typed above the table. Be sure to explain the abbreviations used in the table in the table legend. Work with tables exclusively in Word, through the Table-Insert-Table menu with Instructions to authors defining the exact number of columns and rows that will make up the table grid.

**Figures (photographs).** Submit only original high-quality black-and-white photographs. On the back of each Figure, stick a sticker with its ordinal number, the author's name and the marked top of the Figure. Type the title of the Figure on a separate sheet.

**Drawings (schemes, graphs).** Graphs should be made and submitted in Excel, and then linked to a Word document where the graphs are marked with Arabic numerals in the order in which they appear in the text. Write the titles of the graphs and the legend for each drawing on a separate sheet.

**References.** They are printed on a separate sheet of paper, double-spaced, in Arabic numerals, in the order of their appearance in the text. The number of references should not exceed 30, except in review paper where up to 50 is allowed. Approximately 80% of cited works should be original scientific papers, while the remaining 20% may include books, book chapters or review articles. The majority of the cited articles should not be older than five years, and abstracts should be avoided as references.

References are cited according to so-called Vancouver rules (Vancouver style). Use abbreviated names of journals according to Index Medicus.

**Citation Examples:**

*Journal article:*

Jasselon J, Kuser BY, Wier MR. Hepatitis B surface antigenemia in a chronic hemodialysis program. Am J Kidney Dis 1987;9(6):456-61.

The names of first six authors are to be listed. If there are more than six autors, add 'et al.' after the sixth author.

*Chapter in a book:*

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: Mc-Graw-Hill; 2002. p. 93-113.

*Book:*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

*Article from a congress or meeting:*

Vuković B, Šeguljev Z, Virusni hepatitisi – aktuelan epidemiološki problem 32. Dani preventivne medicine. Niš, 1998. Zbornik rezimea. Institut za zaštitu zdravlja, Niš, 1998; 51-64.

*Dissertation*:

Radosavljević V. Faktori rizika za nastanak malignih tumora mokraćne bešike. Doktorska disertacija. Univerzitet u Beogradu, 1999.

*Journal article in an electronic format:*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

*Web page on the Internet:*

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

**Submitting manuscripts.** Manuscript and all attachments to the paper are submitted exclusively electronically through the application system on the website https://aseestant.ceon.rs/index.php/bioistr

**Note.** Paper that does not meet the requirements of these instructions cannot be submitted for review and will be returned to the authors to supplement and correct it. Adherence to the instructions for the preparation of the paper will significantly shorten the time of the entire process until the publication of the paper in the journal, which will positively affect the quality of articles and the regularity of the journal.

For any additional information, please contact the address and telephone number:

University of East Sarajevo
Faculty of Medicine, Foca
Studentska 5, 73300 Foca
e-mail: biomedicinskaistrazivanja@yahoo.com
tel: 058/210-420; fax: 058/210-007
To the Editorial Board of the Journal ''Biomedicinska istraživanja"