Vol 62, No 1, March, 2023
UDK 61
ISSN 0365-4478 (Printed)
ISSN 1821-2794 (Online)
www.medfak.ni.ac.rs/amm

# ACTA MEDICA MEDIANAE

Naučni časopis
Medicinskog fakulteta Univerziteta u Nišu i
Podružnice Srpskog lekarskog društva u Nišu

AMM

Scientific Journal of the University of Nis Faculty of Medicine
and the Department of the Serbian Medical Society in Niš

*Naučni časopis Medicinskog fakulteta Univerziteta u Nišu i Podružnice Srpskog lekarskog društva u Nišu*

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*Acta Medica Medianae* (UDK 61; ISSN 0365-4478 štampana verzija; ISSN 1821-2794 elektronska verzija) je zvanični časopis Medicinskog fakulteta Univerziteta u Nišu i Podružnice Srpskog lekarskog društva u Nišu pod pokroviteljstvom Ministarstva za nauku i tehnološki razvoj Republike Srbije. Časopis izlazi četiri puta godišnje od 1962 godine. Izdavač je Medicinski fakultet Univerziteta u Nišu, Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija. Sadržaj i celokupan tekst časopisa dostupan je na sajtu Medicinskog fakulteta http://www.medfak.ni.ac.rs/amm. Uputstvo autorima se objavljuje u svakom broju, pri čemu je autor dužan da se pridržava navedenih uputstava prilikom predaje rukopisa.
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Kontakt adresa: Časopis Acta Medica Medianae, Medicinski fakultet, Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija
E-mail: acta@medfak.ni.ac.rs, Tel+381-18-4533001 lok. 122 fax. +381-18-4534336
Tiraž 200 primeraka. Štampa: "Sven", Niš, Srbija.
Acta Medica Medianae je trenutno indeksirana na *Index Copernicus-u, Srpskom citatnom indeksu, DOAJ i EBSCO*


*Acta Medica Medianae* (UDK 61; ISSN 0365-4478 printed version; ISSN 1821-2794 online) is the official Journal of the University of Niš Faculty of Medicine and the Department of the Serbian Medical Society in Niš published with the help of the Ministry of Science and Technological Development of the Republic of Serbia. The Journal has been published four times a year since 1962. The publisher is the University of Niš Faculty of Medicine, Institutional address: dr Zoran Đinđić 81, 18000 Niš, Serbia. Table of contents and full texts of articles are available on the Institutional Home Page at http://www.medfak.ni.ac.rs/amm. Prices are subject to change. All subscriptions start with the first issue of the current year. For payment details contact the Secreteriat at acta@medfak.ni.ac.rs. Instructions for authors appear in every issue. Manuscripts accepted for publication are not returned to the author(s). *Acta Medica Medianae* retains the right for further distribution and printing of the articles.
Editorial correspodence: Journal Acta Medica Medianae, Faculty of Medicine, Dr Zoran Đinđić 81, 18000 Niš, Serbia.
Electronic submission of the papers: acta@medfak.ni.ac.rs, Phone: +381-18-4533001 lok. 113 fax. +381-18-4534336
Printed on acid-free paper; 200 issues. Press: "Sven", Niš, Serbia
*Acta Medica Medianae is currently indexed in Index Copernicus, Serbian Citation Index, DOAJ and EBSCO*

*Naučni časopis Medicinskog fakulteta Univerziteta u Nišu i Podružnice Srpskog lekarskog društva u Nišu*

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http://www.medfak.ni.ac.rs/amm



Autor slike na prednjoj stranici:
Nikola Jovanović

ACTA MEDICA MEDIANAE

Vol 62, No 1, March, 2023



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ACTA MEDICA MEDIANAE

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www.medfak.ni.ac.rs/amm

ACTA MEDICA MEDIANAE

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www.medfak.ni.ac.rs/amm

ACTA MEDICA MEDIANAE

Vol 62, No 1, Mart, 2023


www.medfak.ni.ac.rs/amm

**Original article**

**UDC: 616.853:616.831- 005.1**
**doi: 10.5633/amm.2023.0101**

# RISK FACTORS FOR THE DEVELOPMENT OF SYMPTOMATIC EPILEPSY IN PATIENTS DIAGNOSED WITH STROKE

*Biljana Živadinović[1,2,*], Aleksandra Lučić Prokin[3,4], Jelena Živadinović[5], Aleksandar Stojanov[2]*

Stroke is one of the leading causes of mortality in older population. Little less than 50% of patients with stroke remain with different degrees of disabilities and consequences. Symptomatic epilepsy (PSE) is one of them. The aims of the study were to determine the frequency of PSE in the group of examinees, the difference in the frequency of PSE in the ischemic stroke and intracerebral hemorrhage (ICH) group, the influence of the size and location of the lesion, as well as the influence of comorbidity on the occurrence of PSE.

This prospective study analyzed patients with the first stroke of ischemic and hemorrhagic genesis with the follow up period of two years.

Out of the total of 536 patients, 267 patients (aged 47−92) who had the first stroke, were analyzed. In the control group (n = 246), PSE did not develop after stroke, and the other group (n=21) included patients who had PSE. Cortical and subcortical lesions had a statistically significant ($p < 0.05$) influence on the development of epileptic seizures after stroke. A statistical significance between the size of the lesion as well as the type of stroke and PSE was not determined. The combination of cardiovascular and pulmonary disease was statistically significantly more often associated with the development of PSE after stroke ($p < 0.05$).

The frequency of PSE in the examined group was 7.86%. Younger age, as well as cortical and subcortical lesion, was shown to be statistically significant for the occurrence of PSE. The presence of cardiac and pulmonary disease significantly increases the risk of PSE. Although the significance of ICH and big lesion for the onset of PSE has been described in the literature, we have not found statistical significance regarding their impact on PSE occurrence in our experimental group of patients. *Acta Medica Medianae 2023;62(1):5-14.*

***Key words:*** *risk factors, epilepsy, stroke*

[1]University of Niš, Faculty of Medicine, Department Neurology, Niš, Serbia
[2]University Clinical Center Niš, Clinic of Neurology, Niš, Serbia
[3]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia
[4]University Clinical Center Vojvodina, Clinic of Neurology, Novi Sad, Serbia
[5]University Clinical Center Niš, Clinic of Anesthesiology and Intensive Care, Niš, Serbia

*Contact:* Biljana Živadinović
Faculty of Medicine, University of Niš
81 Dr. Zorana Djindjića Blvd.
18000 Niš, Serbia
Tel: +381631094548
E-mail: biljana.zivadinovic@medfak.ni.ac.rs

## Introduction

Stroke is defined as a sudden loss of brain functions of various degrees, from focal to global, caused by insufficient or complete disruption of blood flow in a specific region of the brain or by bursting of a blood vessel, which causes bleeding (1). It is caused by brain blood vessel occlusion, which is induced thrombosis or embolism, material from the heart or large blood vessels, small blood vessel diseases, systemic hypoperfusion or venous thrombosis. Hemorrhagic stroke is a consequence of bursting of a blood vessel of vascular malformation with intraparenchymal hemorrhage into the chamber system or subarachnoid space. Besides the already present incapacitation related to motoric and non-motoric consequences of the stroke, the development of post stroke symptomatic epilepsy (PSE) significantly contributes and additionally incapacitates the patient (2).

The seizure in symptomatic epilepsy (SE) is a consequence of structural damage of the brain or of certain brain function of various types. Symptomatic epilepsy represents the appearance of epileptic seizures some time after the primary brain disorder without a provoking event. Majority of experts agree that many symptomatic lesions generate permanent predisposition for repeated spontaneous seizure with probability equal to or higher than the probability for new seizure after two spontaneous seizures (≥ 75%) (3). The risk

for developing epilepsy after stroke is considered seven times higher than in normal population (4).

The etiopathogenesis of SE epileptogenesis is explained by pathological changes that develop in the damaged brain tissue after stroke. This process is composed of a cascade of morphological and biological changes in the neurons and glial cells, which leads to hyperexcitability of the nervous tissue (5). The pathogenesis of early seizures depends on local ionic imbalance and the release of high level of excitotoxic neurotransmitters (glutamate), which leads to extended depolarization of the neurons, described in the penumbra zone (6). The inflammation and remodeling of synaptic networks of neurons reduce the convulsion threshold of neurons. Gliosis, the death of potentiating neurons, and repeated seizures cause meningocerebral cicatrix, remodeling of neural networks, hyperexcitability of neurons and are the basis of epileptogenesis and subsequent seizures (7). The very risk of repeated seizures as well as the pathophysiology of the development of early into late seizures are not clearly determined (5, 8, 9).

The recommendations concerning treatment and application of antiepileptic therapy (AET) in PSE are controversial and with the first unprovoked seizures mostly direct to individual approach, without clear evidence that the application on AET after the first unprovoked seizure significantly impacts long-term remission of the diseases (5). Before deciding to include AET, it is important to estimate its iatrogenic effect, the range of the safety profile and contraindications as well as the smaller number of interactions with other drug groups that stroke patients use in everyday treatment (primarily with antiaggregant drugs and anticoagulant therapy).

This paper aimed at determining the risk factors for selecting patients with stroke in whom PSE would develop and who would benefit from AET so that their timely application could prevent severe forms of PSE and enable its successful control and treatment.

## Material and methods

This prospective study included 267 patients with the first stroke, treated between January 1 and December 31, 2016. The follow up of all patients lasted for the following two years. Out of the total number, 246 patients had no symptomatic epilepsy and they composed the control group whereas 21 patients who developed epileptic seizures after stroke during the two-year follow-up period composed the experimental group. All patients and their families were informed about investigation and they gave signed consent for inclusion in this study. Besides, local Ethics Committee approved this study.

A detailed medical history was taken from all patients. Significant information included the beginning of epileptic seizures, whether the seizure was an initial symptom, whether the seizure appeared within the first seven days from the stroke or later. The severity of neurological findings was graded according to the NIHSS Scale of the American National Institute of Health (10). The following steps included standard laboratory testing, computerized tomography (CT) or magnetic resonance imaging (MRI) of the endocranium (in patient with small or undefined lesion as well as a lesion in the area of the brainstem) and the patients were monitored for internal medicine comorbidities.

Both groups were analyzed with regard to gender and age. The study did not include patients with arteriovenous malformations of the brain blood vessels, patients with history of previous epilepsy of any genesis, patients with recurrent stroke, patients with transitory ischemic attacks and with previous alcoholism as well as patients who were taking antiepileptic therapy for other indications or who were taking large doses of benzodiazepine.

The analysis of data obtained after the research was done using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 18.0. Armonk, NY: IBM Corp.

Cluster analysis (k-means clustering method) was used for additional classification of groups based on NIHSS values, i.e. age and NIHSS values. Statistical analysis of data included the use of Chi-squared ($\chi^2$) independence test, Mann-Whitney test and Kruskal-Wallis test. Statistically significant connection was determined if $p < 0.05$.

Binary logistic regression analysis was used to examine the model for the prediction of binary outcome, in our case the appearance of epileptic seizure. The model included independent variables, which had low p values in the previous part of the statistical analysis ($p < 0.4$), which meant that they could significantly influence the appearance of epileptic seizures after stroke.

## Results

Figure 1 shows the age of patients from both the control and the experimental groups. The average age of patients in the experimental group was 67.19 and 75.5 in the control group. Mann-Whitney test showed that the group of patients who developed epileptic seizures after stroke was significantly younger ($p = 0.009$; $Z= -2.618$).

The distribution of patients based on the type of stroke and defined group is shown in Figure 2. Although the presence of PSE in the ICH group was more than twice as big, no statistically significant difference in the number of patients with regard to the type of stroke and the defined group was determined ($\chi^2 = 1.55$; $p = 0.213$, phi = 0.097).

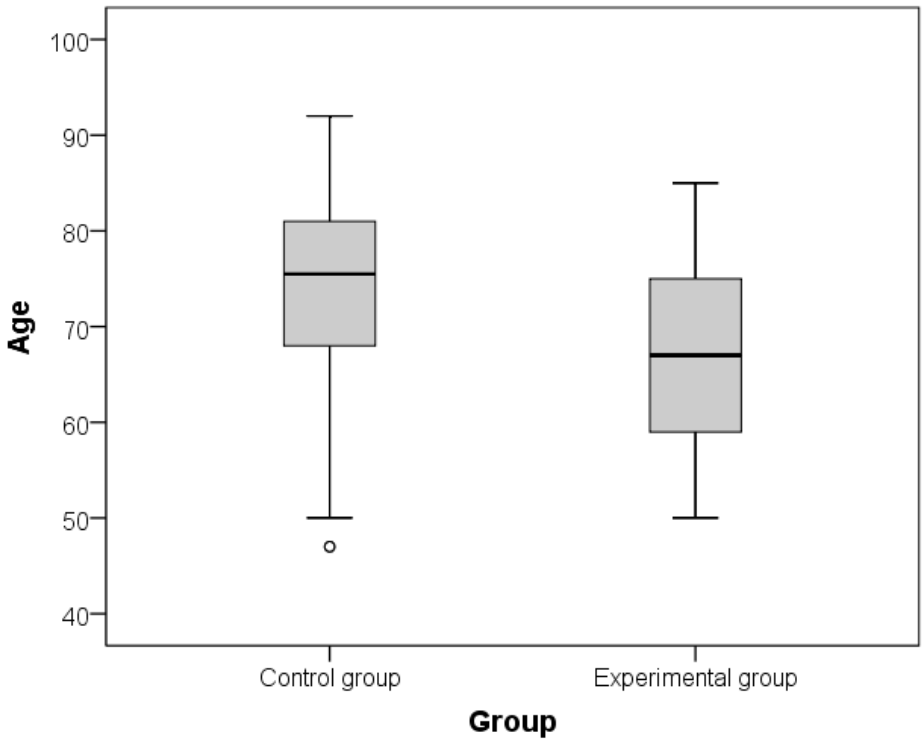



**Figure 1.** Patient age in the control and experimental groups

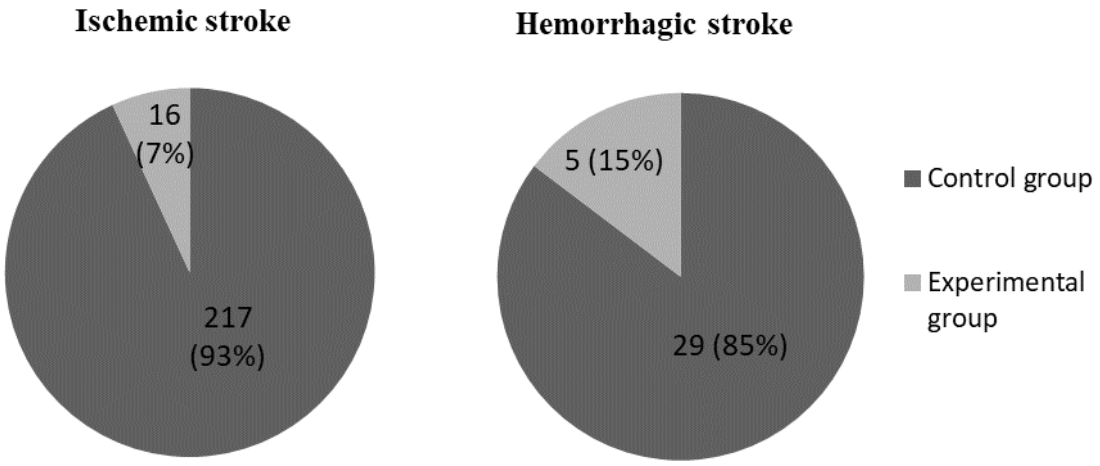



**Figure 2.** Distribution of patients with regard to the type of stroke and the defined group ($\chi^2$ = 0.817; p = 0.366)

With regard to the size, the lesions after stroke were classified into small and big. Small lesions included changes ≤ 3 cm in diameter while big lesions included changes with individual or collective size > 3 cm. No statistical significance was determined between the size of lesions and the appearance of epileptic seizures ($\chi^2$ = 1.536; p = 0.215; phi = 0.09). Figure 3 shows the distribution of patients with regard to the size of lesion after stroke and the defined group. Twice as big number of patients with a big lesion (bigger than 3 cm) was observed in the PSE group.

A detailed analysis of 146 patients with a lesion in the middle cerebral artery flow was done; the lesions were first classified into deep lesions and those with cortical and subcortical location. The distribution of lesions classified in this way, according to the defined groups of patients is

shown in Figure 4. The depth of the lesion was noted to have a statistically significant impact on the development of epileptic seizures after stroke

($\chi^2$ = 3.96; p = 0.047; phi = 0.156) in the sense that the lesions with cortical and subcortical location statistically significantly impacted the development of epileptic seizures after stroke. With the same statistical significance, the deep lesions were more often joined with strokes after which the epileptic seizures did not develop.

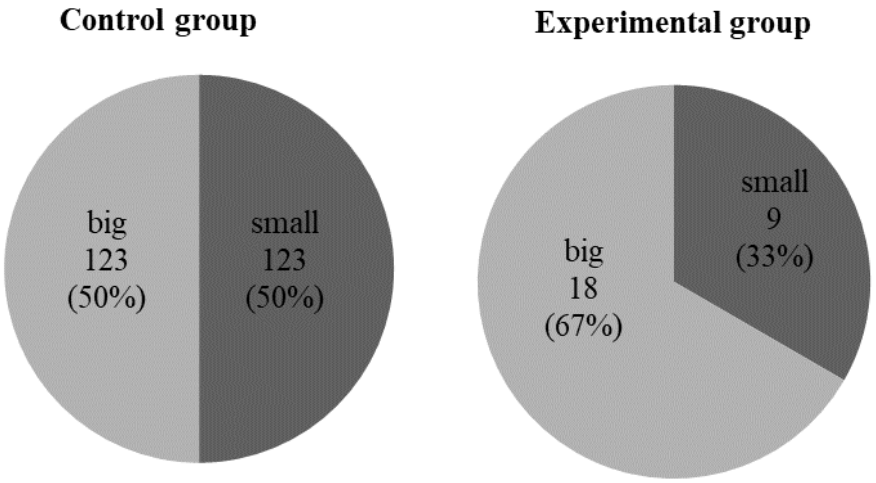



**Figure 3.** Distribution of patients with regard to lesion size after stroke and the defined group ($\chi^2$ = 1.536; p = 0.215)

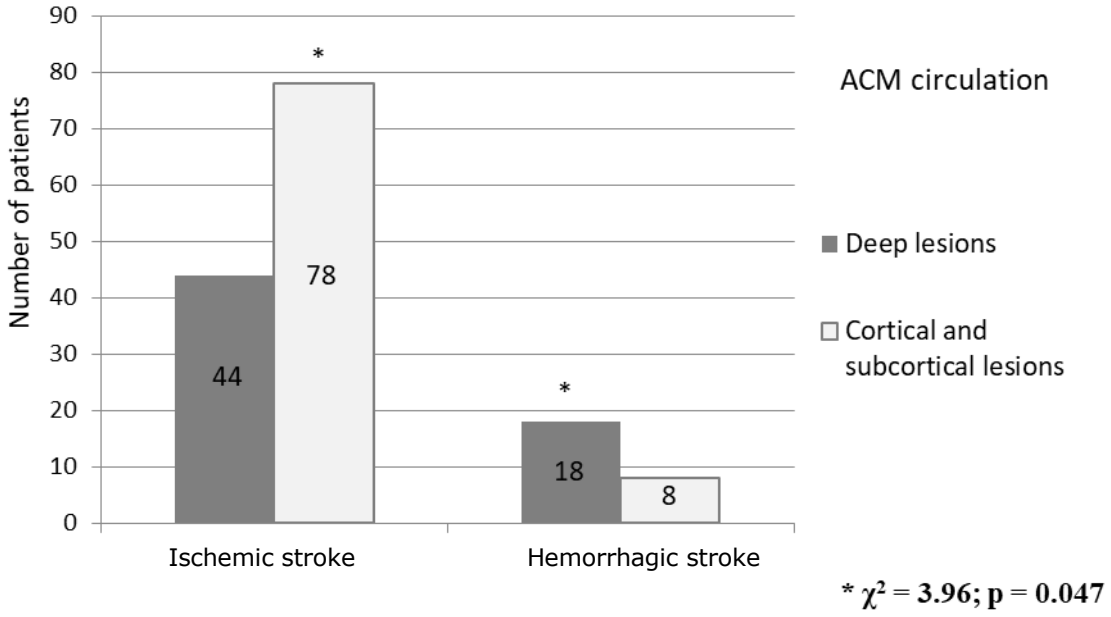



**Figure 4.** Distribution of patients with lesion in the ACM circulation with regard to the depth of lesion and defined group

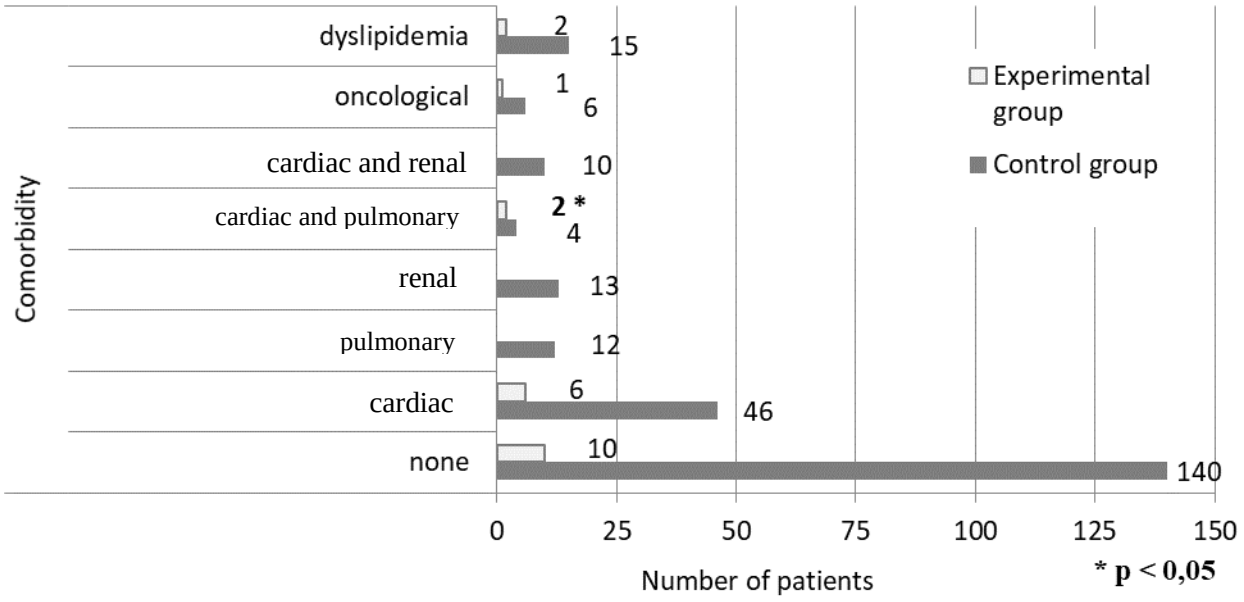



**Figure 5**. Distribution of PSE findings in patients from the control and experimental group with regard to the presence of comorbidities

Figure 5 shows the distribution of patients with regard to comorbidities and the development of epileptic seizures. Comorbidity had no statistical significance in the development of epileptic seizures after stroke ($\chi^2$ = 9.831; p = 0.132, Cramer's V = 0.192). The experimental group had comorbidities of oncological, cardiac, renal and pulmonary origin, as well as co-occurring cardiac and pulmonary morbidity and cardiac and renal morbidity. The co-occurring cardiac and pulmonary morbidity was statistically significantly correlated with epileptic seizures after stroke in the sense that a combination of cardiac and pulmonary disease was statistically significantly more often joined with the development of epileptic seizures after stroke ($p < 0.05$).

Logistic regression analysis was used to determine the impact of several factors on the probability that a patient would develop epileptic seizures after stroke (Table 1). The model contained nine independent variables which had lower p values obtained by the previous analysis (age, type of stroke, the circulation at the location of lesion, lesion size, lesion level with regard to cerebral cortex, type of comorbidity, NIHSS values, group according to cluster analysis) and defined by previous analysis. The whole model with all the predictors was statistically significant, $\chi^2$ (6, n = 267) = 25.523, p = 0.03 which showed that the model differentiated between the examinees who did and those who did not develop epileptic seizures after stroke. The model completely explained between 9.1% (Cox & Snell R square) and 21.5% (Nagelkerke R square) variables and it correctly classified 92.1% of cases.

As shown in Table 1, only one independent variable provided a statistically significant contribution to the model. The strongest predictor of epileptic seizures after stroke was cardiac and pulmonary comorbidity with odds ratio (OR) of 10.191. This showed that the examinees with cardiac and pulmonary comorbidity 10 times more often developed epileptic seizures than those without these two comorbidities along with other factors from the model being equal.

According to the influence, the following factors stood out: age (as binomial variable: > 65 years and ≤ 65 years), location of changes on the level of cerebral cortex and subcortically and group 2 according to cluster analysis which described younger patients with lower NIHSS values.

Age had an OR of 0.341, which showed that patients over 65 years of age developed epileptic seizures after stroke 3 times less often than patients under 65 whereas other factors were equal and controlled.

The next independent variable that statistically significantly influenced the development of epileptic seizures was the location of changes on the level of cerebral cortex and subcortically with OR of 3.411. Epileptic seizures after stroke were 3.411 times more frequent in patients with cortical and subcortical changes than in patients with changes in the deep structures of the central nervous system, when the other factors from the model were equal.

**Table 1**. Probability predictions that a person will develop epileptic seizures after stroke (B - unstandardized coefficient of independent variable; standard error; Wald - contribution of independent variable; No. of deg. of freedom - number of degrees of freedom; OR - odds ratio)

| | ***B*** | **Standard error** | ***Wald*** | **No. of deg. of freedom** | ***p*** | **OR** | **95% confidence interval for quotient probability** | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Upper limit | Lower limit |
| **Age > 65 god.** | -1.076 | 0.572 | 4.042 | 1 | 0.039 | 0.335 | 0.125 | 6.953 |
| **Hemorrhagic stroke** | 1.393 | 0.755 | 3.405 | 1 | 0.065 | 4.027 | 0.917 | 17.682 |
| **ACM circulation** | -0.514 | 0.942 | 0.298 | 1 | 0.585 | 0.598 | 0.094 | 3.787 |
| **Lesion size > 3 cm** | 0.503 | 0.56 | 0.81 | 1 | 0.368 | 1.654 | 0.553 | 4.954 |
| **Cortical and subcortical lesions** | 1.236 | 0.938 | 3.736 | 1 | 0.048 | 3.441 | 0.548 | 21.623 |
| **Diabetes mellitus** | 0.731 | 0.561 | 1.696 | 1 | 0.193 | 2.282 | 0.78 | 6.677 |
| **Without comorbidities** | | | 6.866 | 7 | 0.482 | | | |
| **Cardiac comorbidities** | 0.403 | 0.563 | 0.511 | 1 | 0.474 | 1.496 | 0.496 | 4.514 |
| **Pulmonary comorbidities** | -18.08 | 10297.5 | 0 | 1 | 0.999 | 0 | 0 | . |
| **Renal comorbidities** | -18.942 | 10467.69 | 0 | 1 | 0.999 | 0 | 0 | . |
| **Cardiac and pulmonary comorbidities** | **2.321** | **1** | **5.384** | **1** | **0.02** | **10.191** | **1.434** | **72.411** |
| **Cardiac and renal comorbidities** | -18.415 | 12262.91 | 0 | 1 | 0.999 | 0 | 0 | . |
| **Oncological** | 0.436 | 1.248 | 0.122 | 1 | 0.727 | 1.546 | 0.134 | 17.854 |
| **NIHSS 7-12** | -0.724 | 0.519 | 1.946 | 1 | 0.163 | 0.485 | 0.175 | 1.341 |
| **Cluster 2 (younger and lower NIHSS)** | 0.615 | 0.602 | 2.045 | 1 | 0.05 | 1.85 | 0.569 | 6.021 |
| **Constant** | -4.16 | 0.853 | 23.792 | 1 | 0 | 0.019 | | |

The last independent variable according to significance was the group 2 in cluster analysis which described younger patients with lower NIHSS values. These patients developed epileptic seizures after stroke 1.85 times more often than the older patients with higher NIHSS with other factors from the model being equal. These three factors had a 95% confidence interval which included number 1 (age: 95% CI 0.125-6.953; location of changes in the cortical and subcortical level: 95% CI 0.5-21.6; group 2 in the cluster analysis that described younger patients with lower NIHSS: 95% CI 0.695 - 6.021).

## Discussion

PSE incidence after stroke, which is available in the literature, is within the range of 3–30% (11, 12). In our research, this percentage is 7.86% because out of 267 patients with stroke, 21 had the clinical picture of PSE and composed the experimental group. The remaining 246 patients, who did not develop PSE after the two-year follow up period, composed the control group.

Patients' age in the control group was between 47 and 92, whereas in the experimental group the youngest patients was 50 and the oldest was 85 years old. Younger patients were statistically significantly in the PSI group (Figure 1).

Younger age is described as a separate risk factor for PSE (13 – 16). Cumulative risk for developing PSE in the group of young adults with intracerebral hemorrhage, ischemic stroke and transitory ischemic attack was 31%, 16% and 5% respectively (16). Contrary to increased frequency of PSE in the group of patients under 65 (17, 18), some authors also had other findings where higher frequency of PSE was recorded in patients over 84 years of age (19).

Sarecka et al. (20) showed a higher frequency of PSE in men. Graham et al. (21) found that gender had no impact on PSE development.

Numerous research studies have been conducted to investigate the type of stroke as a risk factor and its relation to PSE. Along these lines, intracerebral hemorrhage is listed as the second most significant risk factor for the development of PSE. It is believed that PSE is more frequent in the group with hemorrhagic compared to ischemic stroke (13, 14, 22). In our research, there is a significantly higher number of patients with PSE in the group with ischemic stroke (15%) compared to patients with ICH (7%) which is in accordance with the literature data (23) (Figure 2).

The size of the lesion is also a significant risk factor for PSE (5, 24). Our patients with stroke were classified into two groups—with lesion bigger than 3 cm and patients with lesion smaller than 3 cm. There was a significantly higher number of patients with PSE with a lesion bigger than 3 cm (67%) compared to 33% of patients with a lesion smaller than 3% but this finding had no statistical significance (Figure 3). The impact of the lesion size on the development of PSE is described by other authors (25, 26), concluding that a bigger lesion represents a higher risk for PSE.

Out of 146 patients with stroke in ACM circulation, the lesions were classified into those with cortical and subcortical presentation while the other group included the patients with lesions in the deep brain structures. Our results show a statistically significant correlation between PSE and subcortical and cortical lesions in the first group while a deep lesion had a lower risk for PSE (Figure 4). Other authors also had similar results pointing out the significance of cortical presentation of stroke for the development of PSE (17, 18). Contrary to that, some research articles showed no significance of cortical lesion for the development of PSE (27, 28).

The presence of other comorbidities (cardiovascular disease, lung disease, malignancy, renal insufficiency, hematological diseases) was significant only in cases with a co-occurring pulmonary (HOBP) and cardiovascular (condition after cardiac arrest, absolute arrhythmia, pacemaker insertion, coronary artery bypass) disease. Independently, all other comorbidities and co-occurring diseases had no statistical significance for the development of PSE after stroke (Figure 5).

Available literature mentions severity of stroke as a significant factor for the occurrence of PSE (13, 18, 29). The design of our study which required a two-year follow up of patients with stroke probably impacted the NIHSS score values where the most severely diseased patient had a score of 14. Patients with higher score died and were not part of the research. A comparison of age and severity of stroke showed that in the PSE group the younger patients with lower NIHSS score were statistically significantly more dominant (Table 1). These results are in accordance with previous research (17, 25).

The precise mechanism for the occurrence of PSE is not completely clarified. It is believed that hyperexcitability is at the basis of the process (24, 30) . The mentioned ischemic cascade which causes cell death is composed of numerous components (energetic metabolism breakdown, excitatory neurotransmitters release, primarily glutamate, disturbance of Ca, Na, Cl, K ion homeostasis, activation of cell enzymes, release of free radicals, damage to cell organelles, cell death). The probable mechanisms are considered inflammatory reaction, perforation of synaptic networks, hereditary predisposition which determines the degree sensitivity of neurons to ischemia and inflammation (9, 18).

Glial cells have an important role in epileptogenesis. They have a direct impact on neural excitability, release of energy, recovery of cells after injuries and infections. The pathology of glial cells is associated with numerous neurologic diseases, first of all mesial temporal epilepsy, hippocampal sclerosis, cortical dysplasia, tuberous sclerosis. The experimental models of epilepsy show a significant abnormality in glial cell activity which is considered a determining factor for the development of epileptogenesis (30).

The understanding of the occurrence of early and late seizures is based on the existence of a latent period from the beginning of the disease as well as the understanding of various risks of recurrent seizures in both patient groups. Some authors consider this to be a 'grace' period or, in terms of stroke treatment - a therapeutic window when antileptic therapy should be introduced (30, 31).

It is believed that a clear answer concerning the risks of recurrent seizures will be provided by research of biochemical parameters that are yet to come. The already mentioned increased risk of PSE in younger patients, those with ICH, cortical lesions, bigger lesions, the fact that a significant number of patients with early seizures develop PSE justifiably poses the question whether the preventive use of current antileptic drugs makes sense and whether it reduces the total risk of recurrent seizures. There is a clear recommendation in the literature concerning the use with ICH (32 – 35).

In a clearly defined situation, such as the occurrence of PSE after the first stroke according to ILAE classification (epileptiform activity on EEG, existence of clear focus in CT or MRI of the brain), as well as in late seizures after stroke, a practitioner has no dilemma about the need to introduce specific treatment (34, 35).

The treatment of PSE represents a great challenge and establishing the correct diagnosis and its adequate treatment are an important task for a neurologist. There are still a number of questions related to epileptogenesis and development of PSE. Numerous undergoing studies will probably in the future provide additional answers

to what is currently still unknown about symptomatic epilepsy after stroke.

## Conclusion

In summary, total PSE frequency in patients treated for stroke is 7.86%. With respect to age, PSE more often occurs in younger patients. Regarding the type of stroke and occurrence of PSE, although the percentage of patients with PSE is higher in the group of patients with ICH compared to ischemic stroke (15.7%), no statistical significance was observed. Patients with stroke in whom CT showed a lesion bigger than 3 cm were more often in the PSE group. Cortical and subcortical lesion in stroke (in the group of patients with stroke and MCA territory) is statistically significantly more often associated with the occurrence of PSE. The presence of associated cardiac and pulmonary comorbidities has been shown to statistically significantly increase the risk of PSE occurrence.

## References


1. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44(7): 2064-89. Erratum in: Stroke 2019; 50(8): e239. [CrossRef] [PubMed]
2. Marciniec M, Popek-Marciniec S, Kulczyński M, Pasterczyk K, Szczepańska-Szerej A, Rejdak K. Prevention of seizures after ischemic stroke: association between statin use and the risk of seizures. World Sci News 2018; 99: 181-92. http://www.worldscientificnews.com/wp-content/uploads/2018/04/WSN-99-2018-181-192.pdf
3. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014; 55(4): 475-82. [CrossRef] [PubMed]
4. Merkler AE, Gialdini G, Lerario MP, Parikh NS, Morris NA, Kummer B, et al. Population-Based Assessment of the Long-Term Risk of Seizures in Survivors of Stroke. Stroke 2018; 49(6): 1319-24. [CrossRef] [PubMed]
5. Van Tuijl JH, Van Raak EPM, Van Oostenbrugge RJ, Aldenkamp AP, Rouhl RPW. The occurrence of seizures after ischemic stroke does not influence long-term mortality; a 26-year follow-up study. J Neurol 2018; 265(8): 1780-8. [CrossRef] [PubMed]
6. Ferro JM, Pinto F. Poststroke epilepsy: epidemiology, pathophysiology and management. Drugs Aging 2004; 21(10): 639-53. [CrossRef] [PubMed]
7. Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. Stroke 2004; 35(7): 1769-75. [CrossRef] [PubMed]
8. Yang H, Rajah G, Guo A, Wang Y, Wang Q. Pathogenesis of epileptic seizures and epilepsy after stroke. Neurol Res 2018; 40(6): 426-32. [CrossRef] [PubMed]
9. Tanaka T, Ihara M. Post-stroke epilepsy. Neurochem Int 2017; 107: 219-28. [CrossRef] [PubMed]
10. Lyden PD, Lu M, Levine SR, Brott TG, Broderick J. NINDS rtPA Stroke Study Group. A modified National Institutes of Health Stroke Scale for use in stroke clinical trials: preliminary reliability and validity. Stroke 2001; 32(6): 1310-7. [CrossRef] [PubMed]
11. Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian county-A population based study. Epilepsia 2015; 56(5): 699-706. [CrossRef] [PubMed]
12. Beleza P. Acute symptomatic seizures: a clinically oriented review. Neurologist 2012; 18(3): 109-19. [CrossRef] [PubMed]
13. De Herdt V, Dumont F, Hénon H, Derambure P, Vonck K, Leys D, et al. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. Neurology 2011; 77(20): 1794-800. [CrossRef] [PubMed]
14. Arntz RM, Maaijwee NA, Rutten-Jacobs LC, Schoonderwaldt HC, Dorresteijn LD, Van Dijk EJ, et al. Epilepsy after TIA or stroke in young patients impairs long-term functional outcome: the FUTURE Study. Neurology 2013; 81(22): 1907-13. [CrossRef] [PubMed]
15. Arntz R, Rutten-Jacobs L, Maaijwee N, Schoonderwaldt H, Dorresteijn L, Van Dijk E,

et al. Post-stroke epilepsy in young adults: a long-term follow-up study. PLoS One 2013; 8(2): e55498. [CrossRef] [PubMed]
16. Arntz RM, Rutten-Jacobs LC, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, et al. Poststroke epilepsy is associated with a high mortality after a stroke at young age: follow-up of transient ischemic attack and stroke patients and unelucidated risk factor evaluation study. Stroke 2015; 46(8): 2309-11. [CrossRef] [PubMed]
17. Conrad J, Pawlowski M, Dogan M, Kovac S, Ritter MA, Evers S. Seizures after cerebrovascular events: risk factors and clinical features. Seizure 2013; 22(4): 275-82. [CrossRef] [PubMed]
18. Misirli H, Ozge A, Somay G, Erdoğan N, Erkal H, Erenoğlu NY. Seizure development after stroke. Int J Clin Pract 2006; 60(12): 1536-41. [CrossRef] [PubMed]
19. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project. BMJ 1997; 315(7122): 1582-7. [CrossRef] [PubMed]
20. Sarecka-Hujar B, Kopyta I. Poststroke epilepsy: current perspectives on diagnosis and treatment. Neuropsychiatr Dis Treat 2018; 15: 95-103. [CrossRef] [PubMed]
21. Graham NS, Crichton S, Koutroumanidis M, Wolfe CD, Rudd AG. Incidence and associations of poststroke epilepsy: the prospective South London Stroke Register. Stroke 2013; 44(3): 605-11. [CrossRef] [PubMed]
22. Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Coté R, et al. Seizures after stroke: a prospective multicenter study. Arch Neurol 2000; 57(11): 1617-22. [CrossRef] [PubMed]
23. Chiu D, Peterson L, Elkind MSV, Rosand J, Gerber LM, Silverstein MD; Glycine Antagonist in Neuroprotection (GAIN) Americas Trial Investigators. Comparison of outcomes after intracerebral hemorrhage and ischemic stroke. J Stroke Cerebrovasc Dis. 2010; 19(3): 225-9. [CrossRef] [PubMed]
24. Di Maio R. Neuronal mechanisms of epileptogenesis. Front Cell Neurosci 2014; 8: 29. [CrossRef] [PubMed]
25. Zelano J. Poststroke epilepsy: update and future directions. Ther Adv Neurol Disord 2016; 9(5): 424-35. [CrossRef] [PubMed]
26. Beghi E, D'Alessandro R, Beretta S, Consoli D, Crespi V, Delaj L, et al. Incidence and predictors of acute symptomatic seizures after stroke. Neurology 2011; 77(20): 1785-93. [CrossRef] [PubMed]
27. Lamy C, Domigo V, Semah F, Arquizan C, Trystram D, Coste J, et al. Early and late seizures after cryptogenic ischemic stroke in young adults. Neurology 2003; 60(3): 400-4. [CrossRef] [PubMed]
28. Reith J, Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Seizures in acute stroke: predictors and prognostic significance. The Copenhagen Stroke Study. Stroke 1997; 28(8): 1585-9. [CrossRef] [PubMed]
29. Jungehulsing GJ, Heuschmann PU, Holtkamp M, Schwab S, Kolominsky-Rabas PL. Incidence and predictors of post-stroke epilepsy. Acta Neurol Scand 2013; 127(6): 427-30. [CrossRef] [PubMed]
30. Boison D, Sandau US, Ruskin DN, Kawamura M Jr, Masino SA. Homeostatic control of brain function - new approaches to understand epileptogenesis. Front Cell Neurosci 2013; 7: 109. [CrossRef] [PubMed]
31. Henshall DC, Engel T. Contribution of apoptosis-associated signaling pathways to epileptogenesis: lessons from Bcl-2 family knockouts. Front Cell Neurosci 2013; 7: 110. [CrossRef] [PubMed]
32. Hamer HM. Epileptische Anfälle und Epilepsien nach "Schlaganfall" [Seizures and epilepsies after stroke]. Nervenarzt 2009; 80(4): 405-14. [CrossRef] [PubMed]
33. Gilad R, Sadeh M, Rapoport A, Dabby R, Boaz M, Lampl Y. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol 2007; 30(4):189-95. [CrossRef] [PubMed]
34. Sykes L, Wood E, Kwan J. Antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Cochrane Database Syst Rev 2014; (1): CD005398. [CrossRef] [PubMed]
35. Qian C, Löppönen P, Tetri S, Huhtakangas J, Juvela S, Turtiainen HM, et al. Immediate, early and late seizures after primary intracerebral hemorrhage. Epilepsy Res 2014; 108(4): 732-9. [CrossRef] [PubMed]

**Originalni rad** **UDC: 616.853:616.831- 005.1**
**doi: 10.5633/amm.2023.0101**

# FAKTORI RIZIKA ZA NASTANAK SIMPTOMATSKE EPILEPSIJE KOD PACIJENATA NAKON MOŽDANOG UDARA

*Biljana Živadinović[1,2,*], Aleksandra Lučić Prokin[3,4], Jelena Živadinović[5], Aleksandar Stojanov[2]*

[1]Univezitet u Nišu, Medicinski fakultet, Katedra za neurologiju, Niš, Srbija
[2]Univerzitetski klinički centar Niš, Klinika za neurologiju, Niš, Srbija
[3]Univerzitet u Novom Sadu, Medicinski fakultet, Novi Sad, Srbija
[4]Univerzitetski klinički centar Vojvodine, Klinika za neurologiju, Novi Sad, Srbija
[5]Univerzitetski klinički centar Niš, Klinika za anesteziju i intenzivnu terapiju, Niš, Srbija

Kontakt: Biljana Živadinovic
Univezitet u Nišu, Medicinski fakultet
Bulevar dr Zorana Đinđića br. 81
18000 Niš, Srbija
E-mail: biljana.zivadinovic@medfak.ni.ac.rs

Moždani udar (MU) jedan je od vodećih uzroka smrtnosti u starijoj populaciji. Oko 50% obolelih od moždanog udara ima neki vid slabosti i posledica. Simptomatska epilepsija (post stroke epilepsy – PSE; eng.) jedna je od njih.

Cilj rada bio je da utvrdi učestalost PSE u ispitivanoj grupi pacijenata nakon MU, razliku u učestalosti PSE u grupi sa hemoragijskim i ishemijskim MU, uticaj veličine i lokalizacije lezije, kao i uticaj postojanja komorbiditeta za nastanak PSE.

U pitanju je bila prospektivna studija, koja je analizirala bolesnike sa prvim MU (ishemijske i hemoragijske geneze) sa periodom praćenja od dve godine.

Od ukupno 536 lečenih bolesnika bilo je analizirano njih 267 (starosti 47 godina do 92 godine), koji su imali prvi MU. U kontrolnoj grupi (n = 246) nije došlo do pojave PSE, dok je njih 21 razvilo PSE u periodu od dve godine nakon MU. Kortikalne i subkortikalne lezije, kao i mlađa životno doba, pokazali su statističku značajnost za pojavu PSE ($p < 0,05$). Nismo dokazali statističku značajnost za nastanak PSE kada je u pitanju veličina lezija i vrsta MU. Udruženo postojanje kardiološkog i plućnog oboljenja statistički je češće bilo povezano sa nastankom PSE nakon MU ($p < 0,05$).

Učestalost PSE u našoj grupi ispitanika bila je 7,86%. Mlađe životno doba, kao i lokalizacija lezije pokazali su statističku značajnost za nastanak PSE, dok veličina lezije i vrsta MU to nisu pokazali u našoj grupi ispitanika. Od značaja za nastanak PSE pokazalo se i postojanje udruženog pulmonalnog i kardiološkog oboljenja. *Acta Medica Medianae 2023;62(1):5-14.*

***Ključne reči:*** *rizik faktori, epilepsija, moždani udar*

**Original article** **UDC: 615.357:616.61**
**doi: 10.5633/amm.2023.0102**

# MELATONIN REDUCES LIPOPOLYSACCHARIDE-INDUCED KIDNEY DAMAGE IN RATS

*Danka Sokolović[1], Milan Lazarević[2,3], Dragan Milić[2,3], Zoran Stanojković[1], Milan N. Petković[2], Nikola M. Stojanović[2], Dušan T. Sokolović[2]*

Lipopolysaccharide (LPS) is a constituent of Gram-negative bacterial cell walls, thus LPS injection has been widely used as a model of experimental acute kidney injury associated with sepsis. LPS-induced sepsis is caused by excessive secretion of pro-inflammatory mediators and reactive oxygen species (ROS). The neurohormone melatonin, which is mainly secreted by the pineal gland, regulates the circadian rhythm, has an anti-inflammatory and immunoregulatory role. Melatonin and its metabolites have been shown to scavenge various free radicals and reactive oxygen intermediates. The aim of this study was to evaluate the effect of melatonin in preventing endotoxemia-induced kidney damage caused by LPS, by analysing the concentration of urea and creatinine in the blood serum of rats. Twenty-eight Wistar albino rats were randomly divided into four groups (n = 7 per group) as follows: 1) Control group, 2) MLT group (50 mg/kg, per os), 3) LPS group (10 mg/kg, i.p.) and 4) LPS + MLT group (10 mg/kg + 50 mg/kg). Serum levels of creatinine and urea were significantly higher ($p<0.05$) in the LPS-treated animals compared with values in the control group. Co-application of LPS and MLT significantly reduced an increase in serum creatinine and urea levels ($p<0.05$). It can be concluded that oral administration of melatonin significantly alleviates LPS-induced acute nephrotoxicity in rats. It is likely that the beneficial effects of melatonin are related to its known antioxidant effects on kidney tissue, and possibly to some other less known/studied effects. *Acta Medica Medianae 2023;62(1):15-20.*

***Key words:*** *melatonin, lipopolysaccharide, kidney, urea, creatinine*

[1]Blood Transfusion Institute Niš, Niš, Serbia
[2]University of Niš, Faculty of Medicine, Niš, Serbia
[3]University Clinical Centre Niš, Clinic for Cardiovascular and Transplant Surgery, Niš, Serbia

*Contact:* Dušan T. Sokolović,
Zorana Đinđića 81, 18000 Niš, Serbia;
Phone number: +381642136478;
e-mail: dusantsokolovic@gmail.com

## Introduction

Acute kidney injury (AKI) is a major public health hazard that adversely affects patient health and results in approximately 1.4 million deaths per year (1). AKI is a very common complication caused by lipopolysaccharide (LPS) (2). In this case, hemodynamical changes occur, reflecting the changes in kidney tissue blood flow and glomerular filtration rate (3). Endotoxemia associated with sepsis has been shown to result in approximately 50% mortality in ICU (4). Sepsis is a dynamic and very complex clinical syndrome caused by the host's systemic inflammatory response to infection, with numerous complications (5). Sepsis is characterized by fever, tachycardia, tachypnea, changes in the number of leukocytes, increased synthesis of acute phase proteins, metabolic disorders, damage to the endothelium, development of shock and multiple organ dysfunction syndrome (6). Sepsis is one of the main causes of AKI and accounts for almost 26%–50% of all AKI in developed countries (7). According to a 2018 WHO report, more than 30 million people worldwide are affected by sepsis every year (8).

It is well known that the injection of LPS which is a molecule part of a Gram-negative bacterial cell wall could be used as a model of experimental AKI associated with sepsis (9). LPS has been proven to be one of the most important sources of sepsis, which can contribute to the "cytokine storm", intense oxidative stress, renal hypoperfusion, low blood pressure and impaired

renal function (10). Lipopolysaccharide-induced sepsis of Gram-negative bacteria is caused by excessive secretion of pro-inflammatory mediators, reactive oxygen and reactive nitrogen species (ROS and RNS, respectively). Inflammation and intense oxidative stress play the most important role in the pathogenesis of sepsis-related AKI (11). ROS production can damage the glomeruli and tubules in the kidneys (12).

The neurohormone melatonin, which is mainly secreted by the pineal gland, has important molecular/biochemical roles when released into the blood (13). Melatonin regulates the circadian rhythm, has an anti-inflammatory and immunoregulatory role, and is also an oncostatic agent (14). Melatonin and its metabolites have been shown to scavenge various ROS and intermediates generated by ROS both *in vitro* and *in vivo*, which may explain its protective effects against LPS toxicity (15). Melatonin has been proven to remove toxins such as hydrogen peroxide, hydroxyl radical, nitric oxide (NO), peroxynitrite anion, hypochlorous acid, singlet oxygen, superoxide anion, and its antioxidant properties are manifested by stimulating superoxide dismutase (SOD), glutathione metabolizing enzymes, as well as by the inhibition of nitric oxide synthase (NOS) (16).

**Aim of the study**

The aim of this study was to evaluate the effect of melatonin in preventing endotoxemia-induced AKI caused by LPS, through the analysis of the concentration of urea and creatinine in the blood serum of rats.

**Materials and methods**

**Animals**

The experimental protocol was approved by the Local Animal Ethics Review Committee of the Faculty of Medicine, University of Niš. All experimental procedures were performed in accordance with the ethical regulations of the European Community guidelines for laboratory animals, as well as those given by the laws of the Republic of Serbia (No. 323–07–08988/2022–05). Experiments were performed on healthy, male Wistar rats (2-2,5 months old) obtained from the Vivarium of the Institute of Biomedical Research, Faculty of Medicine in Niš. The animals were housed under standard housing conditions, and were allowed *ad libitum* food and water.

**Experimental design**

Twenty-eight Wistar rats (weighing from 200 to 250 g) were randomly allocated into four groups (7 animals per group) as follows: 1) Control group, 2) MLT group, 3) LPS group and 4) LPS + MLT group. Septic shock in rats was induced by the application of LPS (obtained from Escherichia coli serotype O111:B4 (Sigma, St. Louis, MO, USA)) in a single dose of 10 mg/kg (17). Melatonin (MLT) (Sigma, St. Louis, MO, USA) solutions were prepared before its administration at a dose of 50 mg/kg (18). Rats were treated as follows: Control group - 8 % ethanol in saline at a dose of 10 ml/kg by oral gavage, MLT group - single 50 mg/kg dose of MLT administered by oral gavage, LPS group - single intraperitoneal (i.p.) injection of LPS at a dose of 10 mg/kg, LPS + MLT group - single 50 mg/kg dose of MLT (per os), followed by a single 10 mg/kg dose of LPS (i.p.). Twelve hours after treatment, the animals were sacrificed with an overdose of ketamine (general anesthetic, Richter Pharma AG - Wells, Austria), after which a blood sample was taken for further biochemical analysis.

**Blood biochemical analysis**

Serum samples from rats were prepared by centrifugation (3,000 rpm for 10 min) and analyzed for the blood biochemistry kidney markers (creatinine and blood urea levels), using an automated biochemical analyzer (Olympus AU680).

**Statistical analysis**

All quantitative values are expressed as mean ± standard deviation (SD). Statistical differences between two groups were examined by one-way ANOVA followed by Tuckey's post hoc test using SPSS version 17.0. Probability values (p) less than 0.05 were considered to be statistically significant.

**Results**

As shown in Figure 1 and 2, serum levels of creatinine (55.2 ± 2.9 vs 38.2 ± 2.1, $p<0.001$) and urea (14.31 ± 1.76 vs 7.83 ± 0.99, $p<0.001$) were significantly elevated in the LPS-treated animals compared with the control group. In the group treated with combined application of LPS and MLT (50 mg/kg), significant reduction of serum creatinine (45.60 ± 2.80; $p<0.05$) and urea (11.95 ± 2.61; $p<0.05$) were noted, however, they were still found to be higher than in the control group.

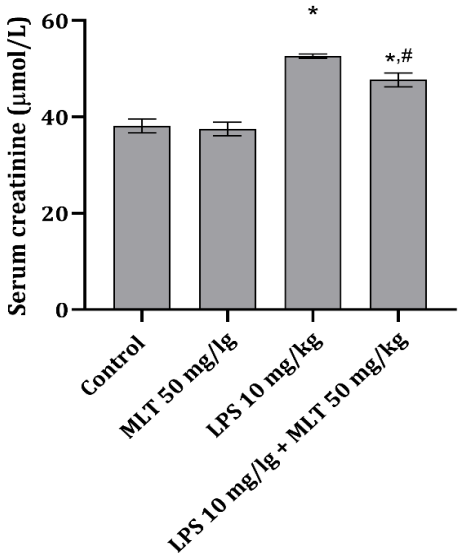



**Figure 1.** Serum levels of creatinine in rats belonging to different experimental groups; Data are given as mean values ± SD (n=7); Comparison was performed using One Way ANOVA followed by Tuckeys post hoc test; *p<0.001 vs control, #p<0.001 vs LPS-treated animals.

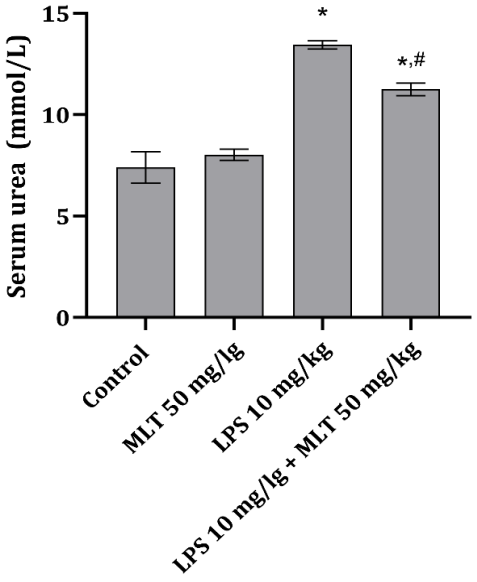



**Figure 2.** Serum levels of urea in rats belonging to different experimental groups; Data are given as mean values ± SD (n=7); Comparison was performed using One Way ANOVA followed by Tuckeys post hoc test; *p<0.001 vs control, #p<0.001 vs LPS-treated animals.

## Discussion

Severe septic conditions are clinically accompanied by azotemia and oliguria, and the renal damage itself can vary from minimal proteinuria to AKI. Decreased diuresis during sepsis is most often a consequence of hypotension. Along with hypotension, the most common pathogenetic mechanisms of AKI are hypovolemia and renal vasoconstriction. In addition to oliguria and azotemia, AKI is also accompanied by hyperkalemia and acidosis, decreased sodium content in urine, elevated levels of urea and creatinine, in the case of primarily prerenal AKI, and in the case of an acute tubular necrosis we could expect an increase in the activity of creatine kinase (CPK) and the presence of cylindrical cysts (19). Lipopolysaccharide (LPS) is an important pro-inflammatory factor, capable

of causing endotoxemia with sepsis, as well as multiple organ dysfunction. Several models of AKI and sepsis in experimental animals have been successfully established by intraperitoneal or intravenous injection of LPS (20).

It has been proven that LPS causes a major disturbance of renal tissue perfusion, apoptosis and renal insufficiency. In this model of AKI, vascular endothelial cell injury (21), neutrophil migration (22), or intravascular coagulation (23) play a significant role in small blood vessel mechanical obstruction leading to AKI and further renal failure.

Serum creatinine and urea levels are important markers of kidney tissue damage (24). A significant increase in serum creatinine and urea levels in LPS-treated rats suggests possible impairment of nephron structural integrity and renal tissue dysfunction (25). Pre-treatment with MLT was found to significantly reduce creatinine and urea levels in serum as well, possibly through the maintenance of cell membrane integrity (26).

Melatonin was revealed to possess significant nephroprotective potential in the present study. Melatonin is widely distributed in the body and can penetrate into every subcellular compartment of the kidney, and to inactivate free radicals. The neurohormone MLT, which can be found in vegetables, fruits, herbs, etc. (27), exhibits a wide range of antioxidant and anti-inflammatory activities, which have been clinically tested in adults and even in premature infants (28).

In both *in vitro* and *in vivo* experimental models, MLT was proven to possess protective effects against oxidative damage caused by various toxic agents in kidney and sepsis-damaged kidneys (28). Melatonin is widely spread, with almost no side effects, readily available and active after oral administration, and it is commonly used in humans to treat insomnia (29).

In this research, by analyzing non-protein nitrogenous compounds (urea and creatinine), we proved that MLT has a protective effect during LPS-induced nephrotoxicity. It was proven that in addition to its antioxidant capacity in kidney tissue MLT is able to neutralize various forms of ROS and to stimulate antioxidant enzymes (SOD and glutathione peroxidase) (28). Several experiments showed that MLT protects against kidney damage (30,31), which is accompanied by a normalization of reduced glutathione (GSH) concentration. Melatonin was shown to reduce tubular necrosis and protect renal function in a model of renal tubular injury, mediated by free radicals (32).

It has been proven that MLT prevents damage to the mitochondria and inhibits an increased expression of iNOS, which is induced by endotoxemia with bacterial LPS. Melatonin prevents multiple organ dysfunction (kidney, liver, lung) and circulatory failure during endotoxemia, protects mitochondria from damage in experimental sepsis, and reduces sepsis mortality. Therefore, it should be kept in mind that in septic patients, the use of MT has a significant role in preserving the mitochondrial energy level in cells (33).

## Conclusion

It can be concluded that a single oral administration of melatonin significantly alleviates lipopolysaccharide-induced acute nephrotoxicity in rats by reducing urea and creatinine levels. It is likely that the beneficial effects of melatonin are related to its known antioxidant effects on kidney tissue and to some of its less known mechanisms of action.

## Acknowledgment

This work is financed by the Science Fund of the Republic of Serbia (IDEAS – project No. 7750154, Acronym NPATPETTMPCB). The authors would also like to thank the Ministry of Education, Science and Technological Development of the Republic of Serbia (Project No. 451-03-68/2022-14/200113) for their assistance in the realization of this work.

## References


1. Jiang W Xu J, Shen B, Wang Y, Teng J, Ding X. Acute kidney injury risk assessment. Contrib Nephrol 2018; 193: 13–20. [CrossRef] [PubMed]
2. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med 2004; 351: 159–69. [CrossRef] [PubMed]
3. Millar CGM, Theimermann C. Intrarenal haemodynamics and renal dysfunction in endotoxaemia: effects of nitric oxide synthase inhibition. Br J Pharmacol 1997; 121: 1824–30. [CrossRef] [PubMed]
4. Shi Y, Hua Q, Li N, Zhao M, Cui Y. Protective effects of evodiamine against LPS-induced acute kidney injury through regulation of ROS-NF-kB-mediated inflammation. Evid Based Complement Alternat Med. 2019 Mar 3; 2019: 2190847. [CrossRef] [PubMed]
5. Chung-Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 101: 1644-55. [CrossRef] [PubMed]
6. Astiz ME, Rackow EC. Septic shock. Lancet 1998; 351: 1501-5. [CrossRef] [PubMed]
7. Alobaidi R, Basu RK, Goldstein SL, Bagshaw SM. Sepsis-Associated Acute Kidney Injury. Semin Nephrol 2015; 35: 2–11. [CrossRef] [PubMed]
8. Kumar S, Tripathy S, Jyoti A, Singh SG. Recent advances in biosensors for diagnosis and detection of sepsis: A comprehensive review. Biosens Bioelectron 2019; 124-125: 205-15. [CrossRef] [PubMed]
9. Chen Y, Luan L, Wang C, Song M, Zhao Y, Yao Y, Yang H, Ma B, Fan H. Dexmedetomidine protects against lipopolysaccharide-induced early acute kidney injury by inhibiting the iNOS/NO signaling pathway in rats. Nitric Oxide 2019; 85: 1–9. [CrossRef] [PubMed]
10. Chen Y, Jin S, Teng X, Hu Z, Zhang Z, Qiu X, Tian D, Wu Y. Hydrogen sulfide attenuates LPS-induced acute kidney injury by inhibiting inflammation and oxidative stress. Oxid Med Cell Longev. 2018; 2018:6717212. [CrossRef] [PubMed]
11. Khajevand-Khazaei MR, Azimi S, Sedighnejad L, Salari S, Ghorbanpour A, Baluchnejadmojarad T, et al. S-allyl cysteine protects against lipopolysaccharide induced acute kidney injury in the C57BL/6 mouse strain: Involvement of oxidative stress and inflammation. Int Immunopharmacol 2019; 69: 19–26. [CrossRef] [PubMed]
12. Ahmadiasl N, Banaei S, Alihemmati A. Combination antioxidant effect of erythropoietin and melatonin on renal ischemiareperfusion injury in rats. Iran J Basic Med Sci 2013; 16: 1209-16. [PubMed]
13. Reiter RJ, Tan DX, Kim SJ, Cruz MH. Delivery of pineal melatonin to the brain and SCN: role of canaliculi, cerebrospinal fluid, tanycytes and Virchow-Robin perivascular spaces. Brain Struct Funct 2014; 219:1873–87. [CrossRef] [PubMed]
14. Manchester LC, Coto-Montes A, Boga JA, Andersen LP, Zhou Z, Galano A, et al. Melatonin: an ancient molecule that makes oxygen metabolically tolerable. J Pineal Res 2015; 59: 403–9. [CrossRef] [PubMed]
15. Galano A, Medina ME, Tan DX, Reiter RJ. Melatonin and its metabolites as copper chelating agents and their role in inhibiting oxidative stress: a physicochemical analysis. J Pineal Res 2014; 58: 107–16. [CrossRef] [PubMed]
16. Reiter RJ, Tan DX, Burkhardt S. Reactive oxygen and nitrogen species and cellular and organismal decline: amelioration with melatonin. Mech Ageing Dev 2002; 123: 1007–19. [CrossRef] [PubMed]
17. Gholamnezhad Z, Fatehi Hassanabad Z. Effects of lipopolysaccharide induced septic shock on rat isolated kidney, possible role of nitric oxide and protein kinase C pathways. Iran J Basic Med Sci 2018;21(10):1073–8. [CrossRef] [PubMed]
18. Potic, M, Ignjatovic, I, Nickovic, VP, Zivkovic JB, Krdzic JD, Mitic JS, et al. Two different melatonin treatment regimens prevent an increase in kidney injury marker-1 induced by carbon tetrachloride in rat kidneys. Can J Physiol Pharm 2019; 97: 422–8. [CrossRef] [PubMed]
19. Kamal F, Snook L, Saikumar JH. Rhabdomyolysis-Associated Acute Kidney Injury With Normal Creatine Phosphokinase. Am J Med Sci 2018; 355(1): 84-7. [CrossRef] [PubMed]
20. Lee S, Kim S, Kang KP, Moon SO, Sung MJ, Kim DH, et al. Agonist of peroxisome proliferator-activated receptor-gamma, rosiglitazone, reduces renal injury and dysfunction in a murine sepsis model. Nephrol Dial Transplant 2005; 20: 1057-65. [CrossRef] [PubMed]
21. Gunnett CA, Chu Y, Heistad DD, Loihl A, Faraci FM. Vascular effects of LPS in mice deficient in expression of the gene for inducible nitric oxide synthase. Am J Physiol Heart Circ Physiol 1998; 275: H416–H421. [CrossRef] [PubMed]
22. Cunningham PN, Dyanov HM, Park P, Wang J, Newell KA, Quigg RJ. Acute renal failure in endotoxemia is caused by TNF acting directly on TNF receptor-1 in kidney. J Immunol 2002; 168: 5817–23. [CrossRef] [PubMed]
23. Schrier RW and Wang W. Acute renal failure and sepsis. N Engl J Med 2004; 351: 159–69. [CrossRef] [PubMed]
24. Doi K, Leelahavanichkul A, Yuen PS, Star RA. Animal models of sepsis and sepsis-induced kidney injury. J Clin Investig 2009; 119: 2868–78. [CrossRef] [PubMed]
25. Coulombe JJ, Favreau L. A new simple semimicro method for colorimetric determination of urea. Clin Chem 1963; 9: 102–8. [CrossRef] [PubMed]
26. Clarkson PM, Kearns AK, Rouzier P, Rubin R, Thompson PD. Serum creatine kinase levels and renal function measures in exertional muscle damage. Med Sci Sports Exerc 2006; 38: 623–27. [CrossRef] [PubMed]
27. Tan D, Manchester LC, Hardeland R, Lopez-Burillo S, Mayo JC, Sainz RM, et al. Melatonin: a hormone, a tissue factor, an autocoid, a paracoid, and an antioxidant vitamin. J Pineal Res 2003; 34: 75–8. [CrossRef] [PubMed]
28. Reiter RJ, Tan DX, Osuna C, Gitto E. Actions of Melatonin in the Reduction of Oxidative Stress. J

Biomed Sci 2000; 7: 444–58. [CrossRef] [PubMed]
29. Brzezinski A. Melatonin in humans. N Engl J Med 1997; 336: 1186-95. [CrossRef] [PubMed]
30. Nava M, Romero F, Quiroz Y, Parra G, Bonet L, Rodriguez-Iturbe B. Melatonin Attenuates Acute Renal Failure and Oxidative Stress Induced by Mercuric Chloride in Rats. Am J Physiol 2000; 279: F910–F918. [CrossRef] [PubMed]
31. Montilla P, Tunez I, Munoz MC, Lopez A, Soria JV. Hyperlipidemic Nephropathy Induced by Adriamycin: Effect of Melatonin Administration. Nephron 1997; 76: 345–50. [CrossRef] [PubMed]
32. Ferraz FF, Kos AG, Janino P, Homsi E. Effects of melatonin administration to rats with glycerol-induced acute renal failure. Ren 2002; 24(6): 735-46. [CrossRef] [PubMed]
33. Escames G, León J, Macías M, Khaldy H, Acuña-Castroviejo D. Melatonin counteracts lipopolysaccharide-induced expression and activity of mitochondrial nitric oxide synthase in rats. FASEB J 2003; 17(8): 932-4. [CrossRef] [PubMed]

**Originalni rad**

**UDC: 615.357:616.61**
**doi: 10.5633/amm.2023.0102**

# MELATONIN SPREČAVA OŠTEĆENJE BUBREGA IZAZVANO LIPOPOLISAHARIDOM KOD PACOVA

*Danka Sokolović[1], Milan Lazarević[2,3], Dragan Milić[2,3], Zoran Stanojković[1], Milan N. Petković[2], Nikola M. Stojanović[2], Dušan T. Sokolović[2]*

[1]Zavod za transfuziju krvi Niš, Niš, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija
[3]Univerzitetski klinički centar Niš, Klinika za kardiovaskularnu i transplatacionu hirurgiju, Niš, Srbija

Kontakt: Dušan T. Sokolović,
Zorana Đinđića 81, 18000 Niš, Srbija;
Telefon: +381642136478;
e-mail: dusantsokolovic@gmail.com

Lipopolisaharid (LPS) je sastavni deo ćelijskih zidova gram -negativnih bakterija, tako da je LPS injekcija široko primenjena kao model eksperimentalne akutne bubrežne insuficijencije povezane sa sepsom. Sepsa indukovana LPS-om uzrokovana je prekomernim lučenjem proinflamatornih medijatora i reaktivnih vrsta kiseonika (ROS). Neurohormon melatonin, koji uglavnom luči epifiza, reguliše cirkadijalni ritam, ima antiinflamatornu i imunoregulatornu ulogu. Pokazalo se da melatonin i njegovi metaboliti uklanjaju različite slobodne radikale i intermedijere reaktivnog kiseonika. Cilj ovog istraživanja bio je da se proceni efekat melatonina u prevenciji endoksemije izazvane oštećenjem bubrega izazvanog LPS -om, analizom nivoa uree i kreatinina u krvnom serumu pacova. Dvadeset osam Wistar albino pacova nasumično je podeljeno u četiri grupe (n = 7 po grupi) na sledeći način: 1) Kontrolna grupa, 2) MLT grupa (50 mg/kg, oralno), 3) LPS grupa (10 mg/kg, i.p.) i 4) LPS + MLT grupa (10 mg/kg + 50 mg/kg). Nivoi kreatinina i uree u serumu ($p < 0,05$) bili su značajno viši kod životinja tretiranih LPS-om u poređenju životinjama iz kontrolne grupe. Zajednički tretman životinja sa sepsom indukovanom LPS-om i MLT značajno je smanjio visok nivo serumskog kreatinina i uree ($p < 0,05$). Može se zaključiti da oralna primena melatonina značajno ublažava akutnu nefrotoksičnost izazvanu LPS-om kod pacova. Verovatno je da su korisni efekti melatonina povezani sa njegovim poznatim antioksidativnim efektima na bubrežno tkivo, a potencijalno i sa nekim drugim manje poznatim mehanizmima dejstva. *Acta Medica Medianae 2023;62(1):15-20.*

***Ključne reči:*** *melatonin, lipopolisaharid, bubreg, urea, kreatinin*

**Original article** **UDC: 617.713-089-035.2**
**doi: 10.5633/amm.2023.0103**

# THE MOST COMMON CONTRAINDICATIONS FOR REFRACTIVE SURGERY

*Maja Živković[1,2]*, Marko Zlatanović[1,2], Nevena Zlatanović[3], Mladen Brzakovic[4], Aleksandra Hristov[4]*

The preoperative examination for refractive surgery is of extreme importance for ensuring optimal outcomes and preventing complications. Aim of this study was to point out the most common contraindications for refractive surgery, laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK).

The study included patients in the process of preoperative examination for refractive surgery who underwent complete standard ophthalmic examinations, as well as corneal topography and ocular biometry. Additional examinations were performed in cases of suspected specific ocular or systemic disease.

Out of 1,238 patients (646 males and 592 females; mean age 32±10.4 years), refractive surgery was performed in 743 patients (60%), LASIK 367 (30%) and PRK in 376 patients (30%). Refractive surgery was contraindicated in 327 patients (26%) while 102 patients cancelled surgery. The most common reasons for not performing surgery were irregular cornea in 106 patients (32%), too steep or too flat corneal curvature in 71 patients (22%), insufficient corneal thickness in 62 patients (19%), high myopia in 28 patients (9%), high hyperopia in 19 patients (6%), dry eye in 13 patients (4%), incipient cataract in 10 patients (3%) and less common ocular and systemic diseases in 18 patients (6%).

According to obtained results, irregular corneal topography, corneal curvature and insufficient corneal thickness are the most common reasons for not performing refractive surgery. *Acta Medica Medianae 2023;62(1):21-26.*

***Key words:*** *corneal curvature, corneal thickness, LASIK, PRK, refractive surgery*

[1]University Clinical Center Niš, Ophthalmology Clinic, Niš, Serbia
[2]University of Niš, Faculty of Medicine, Niš, Serbia
[3]Community Health Center Niš, Niš, Serbia
[4]Special Hospital for Ophthalmology "Clinic Maja", Niš, Serbia

*Contact:* Maja Živković,
University of Niš, Faculty of Medicine, Department of Ophthalmology, Niš, Serbia,
Bulevar dr Zorana Đinđića 81, 18000 Niš, Serbia
Fax: +381 18 4238770; Phone: +381 18 4570029;
e-mail: drzivkovicmaja@gmail.com

## Introduction

Refractive surgery has been used worldwide since 1987 and the first LASIK procedure was performed in 1990. Continuous innovations have led to great progress and improvements in refractive surgery. The satisfaction of patients after the intervention is at a high level and ranges from 82 to 98% (1–4). Patient's satisfaction after the intervention directly correlates with postoperative visual acuity and visual function, but preoperative expectations and psychological characteristics of patients are also of great importance for successful outcome (5, 6, 7).

A thorough screening examination of patients considered for refractive surgery is of extreme importance to ensure optimal outcomes and to prevent complications (8–12). The intervention itself has resulted in time in increased safety and simplicity due to technological developments – introduction of advanced laser generations and surgical instruments. However, despite the advances in refractive surgery equipment, contraindications for the surgery have remained the same. Even though the patients are highly motivated, surgeons are experienced, and the devices and equipment are modern, many patients are not good candidates for refractive surgery, so they still have to wear glasses and contact lenses or decide on some alternative form of intraocular surgery. Contraindications for refractive surgery are numerous.

Referral corneal ***thickness*** is from 530 to 560 μm (13, 14). It is well known that laser ablates the cornea for about 15 μm per diopter, thus the corneal thickness plays an important role in preoperative selection of patients and in the

choice of method. In order to avoid the risk of corneal ectasia, surgeons suggest leaving a minimum residual stromal bed thickness between 250 and 300 μm. Corneal ectasia was first described by Seiler, Koufala and Richter (15) in 1998 as a progressive steepening and thinning of the cornea that is associated with increasing myopic astigmatism and decrease in visual acuity. Risk factors for corneal ectasia include high myopia, forme fruste keratoconus, young age, thin corneas and low residual stromal bed thickness. Randleman et al. designed a scale, ectasia risk score system (ERSS), which includes preoperative parameters to rate post-LASIK ectasia (16). If the cornea is thinner than 500 μm, then PRK is indicated.

Keratoconus or any irregularity of corneal curvature is considered to be an absolute contraindication for refractive surgery. Forme fruste keratoconus (FFK) is described as an atypical or attenuated manifestation of keratoconus, suggesting that the disease has not progressed, or has been aborted at an early stage. The clinical signs are subtle, so it may be difficult to diagnose. Risk factors for FFK include moderate astigmatism, irregular corneal topography, pachymetry less than 500 μm and positive family history of keratoconus (16–20).

Apart from corneal thickness, ***corneal curvature*** is also an important parameter to consider before the intervention. Correction of myopia requires preoperatively a steeper curvature of the cornea, unlike hyperopia correction where a flat cornea is more desirable. Of course, the degree of the curvature change depends on the diopter magnitude to be corrected. Quite often patients have satisfactory corneal thickness, but suboptimal curvature.

"***Dry eye***" is a common postoperative complication, but it decreases over the first year following refractive surgery. Many conditions may contribute to dry eye. They may include postoperative neurotrophic eye disease, tear film instability, local inflammation and corneal exposure (21, 22). Typical symptoms are irritation, pain, and photophobia and visual acuity fluctuations. It is crucial to identify the potential patients at risk of dry eye symptoms in preoperative preparation to ensure postoperative comfort. The results of different studies are controversial regarding the risk factors (depth of ablation, flap thickness, hinge location and size) for postoperative dry eye (23). Most surgeons choose PRK method as a safer procedure in preoperative dry eye, although some studies suggest no postoperative difference in patients regarding different surgical methods (24, 25).

Particular attention at screening should be paid to the most common vision-threatening ***systemic diseases*** that include systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, Grave's disease and Crohn's disease. Nevertheless, refractive surgery may be performed in patients with controlled systemic disease and without ocular involvement (26, 27, 28)

Less common reasons during the screening to refuse patients for refractive surgery include the history of cataract, unstable refraction, amblyopia (not accepting the fact that the intervention could not achieve 100% visual acuity) and immunodeficiency.

The aim was to identify the most common ophthalmic conditions that are contraindication to refractive surgery.

## Methods

This retrospective observational study included 646 male and 592 female candidates for refractive surgery (LASIK or PRK) examined at the Special Hospital for Ophthalmology "Maja Clinic", Niš, Serbia in the period from March 2013 to April 2022. Potential candidates were provided an educational booklet followed by a consultation with the surgeon to discuss any further questions or concerns.

Apart from complete standard ophthalmic examination, all patients underwent refractive error determination (subjective and cycloplegic), best corrected visual acuity in eyes with constricted and dilated pupils, intraocular pressure measurements, examination of anterior and posterior eye segment, determination of tear volume by Schirmer's test, corneal topography using Wavelight Oculyzer® and axial length measurements provided by Wavelight Biograph®. Additional examinations were performed in cases of suspected specific ocular or systemic diseases. Both personal and family medical histories regarding ocular and systemic diseases were noted.

Patients with topographic signs of keratoconus, forme-fruste keratoconus or pellucid marginal degeneration in one eye were excluded from the surgery.

If the preoperative CCT was >500 μm and the residual stromal bed thickness was higher than 300 μm, the patient was considered a candidate for LASIK. In cases where the preoperative CCT was lower than 500 μm or the residual stromal bed thickness was lower than 300 μm, the patient was advised to undergo PRK and not LASIK. In cases where the corneal thickness was <450 μm or the refractive error precluded safe residual corneal thickness, phakic intraocular lens implantation or clear lens extraction was recommended if the corneal topography was normal or had very mild asymmetry.

One or two drops of tropicamide 1% were instilled for mydriasis and cycloplegia. Cataract was detected by slit lamp examination after pupil dilation and any lens opacity was a contraindication for keratorefractive surgery.

## Results

The study enrolled 1,238 patients, 646 male and 592 female, with a mean age of 32 ± 10.4 years. Out of the total of 1,238 patients, refractive surgery was performed in 743 patients (60%). LASIK was done in 367 (30%) and PRK in 376 patients (30%).

Refractive surgery was not performed in 495 patients (40%) who were candidates for the correction of refractive error. Among them 327 (26%) had absolute and relative ophthalmic contraindications for the intervention. In remaining 168 patients, there were no contraindications but they have not had the surgery for personal reasons (want to be sure they are appropriate for refractive surgery and/or plan the intervention according to their schedule). The most common contraindication for the procedure performance was irregular corneal topography in 106 patients (32%), steep or flat corneal curvature in 71 patients (22%), insufficient corneal thickness in 62 patients (19%), high myopia in 28 patients (9%), high hyperopia in 19 patients (6%), dry eye in 13 patients (4%), incipient cataract in 10 patients (3%) and less common ocular and systemic diseases as contraindications in 18 patients (6%) (Table 1).

Less common ophthalmic and systemic diseases included unstable refraction, history of viral herpetic keratitis, corneal dystrophy, uncontrolled glaucoma, diabetes, immunodeficiency disorders and ocular manifestations of rheumatoid diseases.

Corneal curvature as a contraindication to refractive surgery implies too flat cornea in myopia or too steep cornea in hyperopia. Measurements of the corneal curvature after surgery should not be below 36D and above 48D.

Insufficient corneal thickness means that tissue to be removed to treat the diopter at hand will remove more than the allowable removal of corneal tissue. Namely, it is well known that laser ablates the cornea for about 15 μm per diopter, thus the corneal thickness plays an important role in preoperative selection of the patients and in the choice of method. In order to avoid the risk of corneal ectasia surgeons suggest leaving a minimum residual stromal bed thickness between 250 and 300 μm.

High myopia was defined as myopia over -10 Dpt, and high hyperopia as hyperopia greater than +6.0 Dpt.

**Table 1.** The most common contraindications for refractive surgery

| Contraindication | Number of patients (%) |
|---|---|
| Irregular corneal topography | 106 (32%) |
| Corneal curvature | 71 (22%) |
| Insufficient corneal thickness | 62 (19%) |
| High myopia | 28 (9%) |
| High hyperopia | 19 (6%) |
| Dry eye | 13 (4%) |
| Incipient cataract | 10 (3%) |
| Less common ophthalmic and systemic diseases | 18 (6%) |

## Discussion

A thorough screening of patients considered for refractive surgery is of extreme importance to ensure optimal outcomes. According to the results of previous studies, the prevalence of intervention rejection rates after screening is between 25 and 38% (29, 30). Out of all the patients who required the surgery in our sample, 40% of them were contraindicated for refractive surgery.

The main contraindication for the intervention is definitely corneal pathology, namely irregular cornea, too thin cornea, too steep or too flat cornea. It is also important to note that screening for refractive surgery is also the screening process for keratoconus, especially among the populations lacking awareness of this corneal disease. In our sample of patients, corneal irregularity was detected in even 106 patients (32%) and the incidence is far higher than in published results of other studies so far. Regular monitoring of these patients is crucial, since most of them are of young age and progression monitoring is important for timely use of cross-linking method to strengthen the cornea.

Xu et al. studied the sample of 552 patients considered for LASIK in the period from 2005 to 2010 and obtained the following results: 31.7% did not get the intervention, and the most common reasons were low corneal thickness (28.6%), high myopia (15.4%), large pupils (8.0%) and keratoconus (7.4%). The prevalence of rejections of patients decreased from 44.1% in the period from 2005 to 2006 to 3.5% in the period from 2009 to 2010. It is primarily explained by improvements in technology (modern laser eye-tracking system, wave front-guided and femtosecond LASIK technology). This study paid a great deal of attention to consultations with surgeons prior the intervention, 21% of patients changed their minds and refused the surgery after

detailed consultation with the surgeon on possible risks and real postoperative results (29).

Torricelli et al. studied twice as large number of patients where 38.4% of all screened patients did not have the intervention and 12.6% had some contraindication to surgery. The most common reasons to exclude patients were abnormal corneal topography (34.3%) and low corneal thickness (23.1%) followed by high myopia (10.5%), incipient cataract (9.7%), high hyperopia (3.7%), need for wearing reading glasses after the intervention (3.7%), and severe signs of dry eye (3.7%) (30).

A study conducted in India reported suboptimal corneal thickness (55.1%), high myopia (18.4%), keratoconus (9.6%) and high hyperopia (5.9%) as the most common contraindications for LASIK (31). Bamashmus et al. studied the sample of 1,596 examined patients, out of which 405 (25.4%) did not have refractive surgery due to following reasons: suboptimal corneal thickness (25.9%), high myopia (17.0%), keratoconus (15.5%), cataract (11.4%), and suspicious corneal topography (9.4%) (32).

Unfortunately, the number of studies dealing with preoperative screening of patients who request refractive surgery that cannot be performed due to the above mentioned contraindications is scarce. Contraindications are definitely numerous, but adherence to standardized protocols is of utmost importance in performing the intervention. Even though the patients are highly motivated, surgeons are experienced, devices and equipment are highly advanced, still many patients are not appropriate candidates for refractive surgery, so glasses and contact lenses are reasonable alternatives to refractive surgery, or patients may decide on some alternative form of intraocular surgery.

## Conclusion

Contraindications for refractive surgery are diverse. The most common ones include corneal irregularity, corneal curvature and insufficient corneal thickness. Despite highly motivated patients, surgeon's experience and modern devices, a great number of patients have been refused from surgery, so glasses and/or contact lenses appear to be reasonable alternatives for these patients.

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

## References


1. Bamashmus M, Hubaish K, Alawad M, Alakhlee H. Functional Outcome and Patient Satisfaction after Laser In Situ Keratomileusis for Correction of Myopia and Myopic Astigmatism. Middle East Afr J Ophthalmol 2015; 22: 108–14. [CrossRef] [PubMed]
2. Solomon KD, Fernández de Castro LE, Sandoval HP, Biber JM, Groat B, Neff KD, et al. LASIK world literature review: Quality of life and patient satisfaction. Ophthalmology 2009; 116: 691–701. [CrossRef] [PubMed]
3. Tahzib NG, Bootsma SJ, Eggink FA, Nabar VA, Nuijts RM. Functional outcomes and patient satisfaction after laser *in situ* keratomileusis for correction of myopia. J Cataract Refract Surg 2005; 31: 1943–51. [CrossRef] [PubMed]
4. Lazon de la Jara P, Erickson D, Erickson P, Stapleton F. Visual and nonvisual factors associated with patient satisfaction and quality of life in LASIK. Eye. 2011; 25: 1194–01. [CrossRef] [PubMed]
5. Bailey MD, Mitchell GL, Dhaliwal DK, Wachler BS, Olson MD, Shovlin JP, et al. Reasons patients recommend laser in situ keratomileusis. J Cataract Refract Surg 2004; 30: 1861–66. [CrossRef] [PubMed]
6. Sutton G, Lawless M, Hodge C. Laser in situ keratomileusis in 2012: a review. Clin Exp Optom 2014; 97: 18–29. [CrossRef] [PubMed]
7. Price MO, Price DA, Bucci FA Jr, Durrie DS, Bond WI, Price FW Jr. Three-Year Longitudinal Survey Comparing Visual Satisfaction with LASIK and Contact Lenses. Ophthalmology 2016; 123: 1659–66. [CrossRef] [PubMed]
8. Santhiago MR, Smadja D, Wilson SE, Krueger RR, Monteiro ML, Randleman JB. Role of percent tissue altered on ectasia after LASIK in eyes with suspicious topography. J Refract Surg 2015; 31: 258–65. [CrossRef] [PubMed]
9. Randleman JB, Shah RD. LASIK interface complications: etiology, management, and outcomes. J Refract Surg 2012; 28: 575–86. [CrossRef] [PubMed]
10. Henry CR, Canto AP, Galor A, Vaddavalli PK, Culbertson WW, Yoo SH. Epithelial ingrowth after LASIK: clinical characteristics, risk factors, and visual outcomes in patients requiring flap lift. J Refract Surg 2012; 28: 488–92. [CrossRef] [PubMed]

11. De Paula FH, Khairallah CG, Niziol LM, Musch DC, Shtein RM. Diffuse lamellar keratitis after laser in situ keratomileusis with femtosecond laser flap creation. J Cataract Refract Surg 2012; 38: 1014–9. [CrossRef] [PubMed]
12. Gritz DC. LASIK interface keratitis: epidemiology, diagnosis and care. Curr Opin Ophthalmol 2011; 22: 251–255. [CrossRef] [PubMed]
13. Al-Farhan HM, Al-Otaibi WM. Comparison of central corneal thickness measurements using ultrasound pachymetry, ultrasound biomicroscopy, and the Artemis-2 VHF scanner in normal eyes. Clin Ophthalmol 2012; 6: 1037–43. [CrossRef] [PubMed]
14. Guilbert E, Saad A, Grise-Dulac A, Gatinel D. Corneal thickness, curvature, and elevation readings in normal corneas: combined Placido-Scheimpflug system versus combined Placido-scanning-slit system. J Cataract Refract Surg 2012; 38: 1198–06. [CrossRef] [PubMed]
15. Seiler T, Koufala K, Richter G. Iatrogenic keratectasia after laser in situ keratomileusis. J Refract Surg 1998; 14: 312–17. [CrossRef] [PubMed]
16. Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk assessment for ectasia after corneal refractive surgery. Ophthalmology 2008; 115:37–50. [CrossRef] [PubMed]
17. Moshirfar M, Smedley JG, Muthappan V, Jarsted A, Ostler EM. Rate of ectasia and incidence of irregular topography in patients with unidentified preoperative risk factors undergoing femtosecond laser-assisted LASIK. Clin Ophthalmol 2014; 8: 35–42. [CrossRef] [PubMed]
18. Probst LE. LASIK: Advances, Controversies and Customs. Thorofare, New Jersey: Slack Incorporated, 2003.
19. Alió JL, Piñero PD, Alesón A, Teus MA, Barraquer RI, Murta J, Maldonado MJ, *et al*. Keratoconus-integrated characterization considering anterior corneal aberrations, internal astigmatism, and corneal biomechanics. J Cataract Refract Surg 2011; 37: 552–68. [CrossRef] [PubMed]
20. Kozobolis V, Sideroudi H, Giarmoukakis A, Gkika M, Labiris G. Corneal biomechanical properties and anterior segment parameters in formefruste keratoconus. Eur J Ophthalmol 2012; 22: 920–30. [CrossRef] [PubMed]
21. Nettune GR, Pflugfelder SC. Post-LASIK tear dysfunction and dysesthesia. Ocul Surf 2010; 8: 135–145. [CrossRef] [PubMed]
22. Shtein, RM. Post-LASIK dry eye. Expert Rev Ophthalmol 2011; 6: 575–82. [CrossRef] [PubMed]
23. Feng YF, Yu JG, Wang DD, Li JH, Huang JH, Shi JL, Ye T, *et al*. The effect of hinge location on corneal sensation and dry eye after LASIK: a systematic review and meta-analysis. Graefes Arch Clin Exp Ophthalmol 2013; 251: 357–66. [CrossRef] [PubMed]
24. Murakami Y. Manche EE. Prospective, randomized comparison of self-reported postoperative dry eye and visual fluctuation in LASIK and photorefractive keratectomy. Ophthalmology 2012; 119: 2220–24. [CrossRef] [PubMed]
25. Dooley I, D'Arcy F, O'Keefe M. Comparison of dry-eye disease severity after laser in situ keratomileusis and laser-assisted subepithelial keratectomy. J Cataract Refract Surg 2012; 38: 1058–64. [CrossRef] [PubMed]
26. Cobo-Soriano, R, Beltran J, Baviera J. LASIK outcomes in patients with underlying systemic contraindications: a preliminary study. Ophthalmology 2006; 113:1118 e1–8. [CrossRef] [PubMed]
27. Mohammadpour M. Excimer laser refractive surgery in patients with underlying autoimmune diseases. J Cataract Refract Surg 2007; 33: 175–6. [CrossRef] [PubMed]
28. Liang L, Zhang M, Zou W, Liu Z. Aggravated dry eye after laser in situ keratomileusis in patients with Sjögren syndrome. Cornea 2008; 27:120–3. [CrossRef] [PubMed]
29. Xu K, McKee HD, Jhanji V. Changing perspective of reasons for not performing laser-assisted in situ keratomileusis among candidates in a university eye clinic. Clin Exp Optom 2013; 96: 20–4. [CrossRef] [PubMed]
30. Torricelli AA, Bechara SJ, Wilson SE. Screening of refractive surgery candidates for LASIK and PRK. Cornea 2014; 33: 1051–5. [CrossRef] [PubMed]
31. Sharma N, Singhvi A, Sinha R, Vajpayee RB. Reasons for not performing LASIK in refractive surgery candidates. J Refract Surg 2005; 21: 496–8. [CrossRef] [PubMed]
32. Bamashmus M, Saleh MF, Abdulrahman M, Al-Kershy N. Reasons for not performing LASIK in refractive surgery candidates in Yemen. Eur J Ophthalmol 2010; 20: 858–64. [CrossRef] [PubMed]

**Originalni rad** **UDC: 617.713-089-035.2**
**doi: 10.5633/amm.2023.0103**

# NAJČEŠĆE KONTRAINDIKACIJE ZA IZVOĐENJE REFRAKTIVNE HIRURGIJE

*Maja Živković[1,2]*, Marko Zlatanović[1,2], Nevena Zlatanović[3], Mladen Brzakovic[4], Aleksandra Hristov[4]*

1 Univerzitetski klinički centar Niš, Klinika za oftalmologiju, Niš, Srbija
2 Univerzitet u Nišu, Medicinski fakultet, Katedra za oftalmologiju, Niš, Srbija
3Dom zdravlja Niš, Odeljenje za oftalmologiju, Srbija
4 Specijalna bolnica za oftalmologiju „Klnika Maja", Niš, Srbija

Kontakt: Maja Živković,
Univerzitet u Nišu, Medicinski fakultet, Katedra za oftalmologiju, Niš, Srbija,
Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija
Fax: +381 18 4238770; Telefon: +381 18 4570029;
e-mail: drzivkovicmaja@gmail.com

Preoperativni pregled za refraktivnu hirurgiju izuzetno je važan za osiguranje optimalnog ishoda i sprečavanje komplikacija.

Cilj rada jeste da navede najčešće kontraindikacije za refraktivnu hirurgiju, laser-in-situ keratomileuzis (LASIK) i fotorefraktivnu keratektomiju (PRK).

U studiji su obuhvaćeni bolesnici u procesu preoperativnog pregleda za refraktivnu hirurgiju. Svi bolesnici prošli su kompletan oftalmološki pregled, kao i topografiju rožnjače i biometriju oka. Dodatni pregledi izvedeni su u slučajevima sumnje na specifičnu očnu ili sistemsku bolest.

Od 1238 bolesnika (646 muškaraca i 592 žene, srednja starost 32 godine ± 10,4 godine), operacija refraktivne hirurgije obavljena je kod 743 bolesnika (60%), LASIK kod 367 (30%) i PRK kod 376 bolesnika (30%). Refraktivna hirurgija bila je kontraindikovana kod 327 bolesnika (26%), dok su 102 bolesnika otkazala operaciju. Najčešće kontraindikcije za operaciju bile su: nepravilna rožnjača kod 106 bolesnika (32%), previše strma ili suviše ravna zakrivljenost rožnjače kod 71 bolesnika (22%), nedovoljna debljina rožnjače kod 62 bolesnika (19%), visoka miopija kod 28 bolesnika (9%), visoka hipermetropija kod 19 bolesnika (6%), suvo oko kod 13 bolesnika (4%), početna katarakta kod 10 bolesnika (3%) i manje česte očne i sistemske bolesti kod 18 bolesnika (6%).

Na osnovu dobijenih rezultata može se zaključiti da su neregularna topografija rožnjače, zakrivljenost rožnjače i nedovoljna debljina rožnjače najčešće kontraindikacije za refraktivnu hirurgiju. *Acta Medica Medianae 2023;62(1): 21-26.*

***Ključne reči:*** *zakrivljenost rožnjače, debljina rožnjače, LASIK, PRK, refraktivna hirurgija*

**Original article** **UDC: 616.33-006.6**
**doi: 10.5633/amm.2023.0104**

# RISK FACTORS FOR THE DEVELOPMENT OF GASTRIC CANCER: A SINGLE CENTER EXPERIENCE

*Andrija Rančić[1], Vesna Brzački[1,2], Aleksandar Popović[3], Marija Topalović[4]*

Gastric cancer is the fourth most common cancer in the world with over a million new cases per year, and over 750,000 deaths caused by it. The highest incidence is recorded in Japan and China, Eastern Europe and South America, and the lowest is in Africa. The disease is 2 to 3 times more common within male population and people over 60 years of age, but this boundary shifts towards younger age. Five-year survival rate in European countries is 10 to 30%. This is a multifactorial disease and the most important risk factors are: Helicobacter pylori infection, smoking cigarettes, alcohol consumption, male gender, older age, reduced intake of vegetables and fruits, genetic predisposition, diabetes mellitus, etc.

A prospective study was conducted on a selected population of 43 patients diagnosed with the two most common types of stomach cancer: adenocarcinoma and signet ring cell type cancer. Out of the total number of examinees, there were 32 male and 11 female patients, the average age of 68.83±9.26. Among all patients, 39.5% were smokers, 20.9% were alcohol consumers, 62.8% had Helicobacter pylori infection and 16.3% patients had diabetes mellitus. Analysis of the relationship between sex, age, smoking, alcohol intake and diabetes mellitus with the type of cancer did not show statistical significance. The frequency of Helicobacter pylori was statistically significantly different in relation to the type of cancer (p=0.007).

In our study, there was no statistically significant difference between the male gender, the younger population, smokers, chronic alcohol consumers, and patients with diabetes mellitus and a certain type of cancer. Helicobacter pylori infection was found to be a key factor in the development of both types of gastric cancer. This research included a smaller sample of patients and it is necessary to examine a larger number of subjects in the future. *Acta Medica Medianae 2023;62(1):27-35.*

***Key words:*** *gastric cancer, Helicobacter pylori, smoking, alcohol, diabetes mellitus*

[1] University Clinical Center Niš, Gastroenterology and Hepatology Clinic, Niš, Serbia
[2] University of Niš, Medical Faculty, Niš, Serbia
[3] University Clinical Center, Oncology Clinic, Niš, Serbia
[4] University Clinical Center Niš, Pulmonary Diseases Clinic, Niš, Serbia

*Contact:* Andrija Rančić
44 Vase Pelagića St., 18000 Niš, Serbia
E-mail: andrija.m.rancic@gmail.com

## Introduction

Gastric cancer is a multifactorial disease that is mostly caused by environmental factors and more often by genetic polymorphisms (1). Due to insufficiently known pathogenesis, high aggressiveness and heterogeneous nature, today, this disease represents a major health problem (2).

### Epidemiology

Gastric cancer is the fourth most common cancer in the world with an incidence of about 989,500 new cases annually and is the second most common cause of cancer death with about 738,000 cases globally (3). More than 50% of new cases occur in developing countries, such as Europe, East Asia (Japan and China), and parts of Central and South America, while the lowest incidence is in Australia, southern parts of Asia, and North America (4). Gastric cancer occurs 2 to 3 times more often in male population (5). In Japan, five-year survival rate is up to 90% (6), while five-year survival in European countries is only 10 to 30% (7).

### Classification of gastric cancer

The first classification of stomach cancer according to Lauren was adopted in 1965, and according to it, all stomach cancers are divided into intestinal and diffuse type (8). The intestinal type includes tubular and glandular elements, with

different degrees of differentiation, and the diffuse type has weakly cohesive individual cells without the formation of glands, which also includes gastric carcinoma with ring cells (8 - 10). In 2010, the World Health Organization suggested a new division of gastric cancer into adenocarcinoma (which has subtypes – tubular, papillary, mucinous, mixed) and poorly cohesive carcinoma (which includes signet ring cell carcinoma and other poorly cohesive types). According to this classification, the most common is tubular gastric adenocarcinoma (11, 12).

Risk factors

One of the important risk factors is the presence of malignant diseases in the family. It is estimated that only 3% of cancers are truly heritable (13). This form of cancer is known as hereditary diffuse gastric cancer (HDGC) and a mutation in the cadherin-1 (CDH1) gene is thought to be responsible for its development (14). People carrying these mutations have three times higher risk of developing stomach cancer. HDGC occurs more frequently in Asia than in other parts of the world. (15, 16).

The influence of smoking and alcohol consumption in the development of gastric cancer is unavoidable. About 60% of male smokers and 20% of female smokers have a higher risk of developing gastric cancer than non-smokers (17, 18). Smoking status and daily number of smoked cigarettes (over 20 cigarettes/day) are also important, and it shows that former smokers are also at risk of developing gastric cancer (18). Increased alcohol intake is especially associated with the development of non-cardiac types of cancer. Studies indicate a typical ALDH2 genotype in those patients. A higher risk of disease was recorded in the group of former and active drinkers, compared to the group of patients who do not consume alcohol (19).

Gastric infections carry an important role in the development of cancer. Helicobacter pylori (H. pylori) was described by the World Health Organization in 1994 as a first-class carcinogen for the development of gastric cancer (19). Most infected patients are asymptomatic, but gastric cancer appears to develop in 1 to 3% of these cases (20). In addition to H. pylori, the Epstein Barr virus (EBV) is increasingly mentioned as an infectious factor present in 10% of gastric cancers. EBV genome and proteins have been identified in gastric tumor cells. This role of EBV is still not very clear (21).

A higher intake of fresh fruit, green and yellow vegetables rich in vitamin C, B, E and folate is recommended for primary prevention. Beta-carotene is considered the main substance in reducing the risk of cancer (22). All these substances have a strong antioxidant effect (22, 23).

Numerous metabolic diseases can be a risk factor for the development of gastric cancer, and one of the diseases that stands out is diabetes mellitus. The reason is its association with a chronic, systemic inflammatory response, which is why it is associated with the development of pancreatic, liver, colon and uterine tumors (24, 25). The association between diabetes and the occurrence of gastric cancer has not been reliably established, although some studies have proven their connection (26).

**The objective**

The main goal of this research is to determine the relationship between gender, age, smoking cigarettes, alcohol consumption and diabetes mellitus with the appearance of gastric cancer in the observed patient population.

**Materials and methods**

The prospective study research was conducted at the Clinic for Gastroenterology and Hepatology and at the Institute of Pathology of the University Clinical Center in Niš. The research included 43 patients diagnosed with gastric cancer between January and October 2022. All patients underwent a clinical and physical examination, collection of detailed anamnestic data, analysis of blood count and biochemical parameters, and oesophago-gastro-duodenoscopy examination. Information about concomitant diseases and harmful habits were taken from each patient. During the endoscopic examination, biopsy samples were taken of changes suspected of being tumorous. PH verification was performed at the Institute of Pathology by immunohistochemical staining and determination of specific markers in tumor cells (CK7, CK20, MUC5AC, MUC2, CKAE1/AE3, Ki67 proliferation index, presence of acidic mucins in tumor cells, villin, synaptophysin and chromogranin). Two basic types of cancer were taken into account: adenocarcinoma and signet ring cell type cancer, as well as a group of remaining tumor types (MALT lymphomas, Hodgkin lymphomas and metastatic stomach tumors). After the insight into the final pH diagnoses and the obtained anamnestic data, the statistical processing of the data was performed.

**Statistical data processing**

Data are presented in the form of arithmetic mean, standard deviation, minimum and maximum values, and in the form of absolute and relative numbers. A comparison of age in relation to gender and type of cancer was performed by t-test and ANOVA. A comparison of the frequency of risk factors was performed using the Chi-square test and Fisher's test. The hypothesis was tested with a significance threshold of $p<0.05$. Statistical data processing was performed in the software package R and RStudio.

**Results**

This study included 43 patients (32 male and 11 female). The average age of the examinees was 68.83 ± 9.26 (Min 45, Max 87 years); there were

39.5% of smokers, 20.9% of patients who consume alcohol, 62.8% of patients with Helicobacter pylori and 16.3% of patients suffering from diabetes mellitus. From all the patients that were examined, 51.2% had adenocarcinoma, 34.9% had signet ring cell type and 14.0% had other types of tumors (MALT lymphomas, Hodgkin lymphomas and metastatic stomach tumors) (Table 1).

Male patients were older, but there was no statistically significant difference compared to female patients (p = 0.103). The frequency of smoking and alcohol consumption was higher among male participants, but without a statistically significant difference between genders (p = 0.154, respectively p = 0.407). The presence of Helicobacter pylori and the incidence of diabetes did not show statistically significant difference in relation to gender (p = 1.000, or p = 0.106).

There was no statistically significant difference between genders in relation to the type of cancer (p = 0.664) (Table 2).

In relation to the average age of the patients, there was no statistically significant difference in the incidence of a certain type of cancer (p = 0.602). In relation to the type of cancer, there was no statistically significant difference in the frequency of smoking and alcohol consumption (p = 0.766, respectively p = 0.738). The frequency of H. pylori was statistically significantly different in relation to the type of cancer (p = 0.007). H. pylori was present in 59.1% of patients with adenocarcinoma, 86.7% of patients with a signet ring cell type and 16.7% of patients with other types of cancer (Table 3, Chart 1). The occurrence of any of the two types of gastric cancer in patients with diabetes did not show a statistically significant difference (Table 3).

**Table 1.** Demographic and clinical characteristics of the studied population

| Characteristics | Count | % |
|---|---|---|
| Age | 68.83±9.26 | 45-87 years |
| Gender | | |
| Male | 32 | 74.4 |
| Female | 11 | 25.6 |
| Smoking | 17 | 39.5 |
| Alcohol | 9 | 20.9 |
| H. pylori | 27 | 62.8 |
| D. mellitus | 7 | 16.3 |
| **Dg.** | | |
| Adenocarcinoma | 22 | 51.2 |
| Signet ring cell | 15 | 34.9 |
| Other tumor types | 6 | 14.0 |

**Table 2.** Demographic and clinical characteristics in relation to gender

| Characteristics | Male | | Female | | p |
|---|---|---|---|---|---|
| Age | 70.23±8.88 | | 64.91±9.62 | | 0.103[1] |
| Smoking | 15 | 46.9% | 2 | 18.2% | 0.154[2] |
| Alcohol | 8 | 25.0% | 1 | 9.1% | 0.407[2] |
| H. pylori | 20 | 62.5% | 7 | 63.6% | 1.000[2] |
| D. mellitus | 3 | 9.4% | 4 | 36.4% | 0.106 |
| **Dg.** | | | | | |
| Adenocarcinoma | 17 | 53.1% | 5 | 45.5% | 0.664[3] |
| Signet ring cell | 10 | 31.3% | 5 | 45.5% | |
| Other tumor types | 5 | 15.6% | 1 | 9.1% | |

[1] t-test, [2] Fisher's test, [3] Chi-square test

**Table 3.** Demographic and clinical characteristics in relation to cancer type

| Characteristics | Adenocarcinoma | | Signet ring cell | | Other types | | p[1] |
|---|---|---|---|---|---|---|---|
| Age | 70.14±9.07 | | 66.93±10.19 | | 69.00±8.09 | | 0.602[1] |
| Smoking | 9 | 40.9% | 5 | 33.3% | 3 | 50.0% | 0.766[2] |
| Alcohol | 4 | 18.2% | 3 | 20.0% | 2 | 33.3% | 0.738 |
| H. pylori | 13 | 59.1% | 13 | 86.7% | 1 | 16.7% | 0.007[2] |
| D. mellitus | 3 | 13.6% | 3 | 20.0% | 1 | 16.7% | 0.877[3] |

[1] ANOVA, [2] Fisher's test, [3] Chi-square test

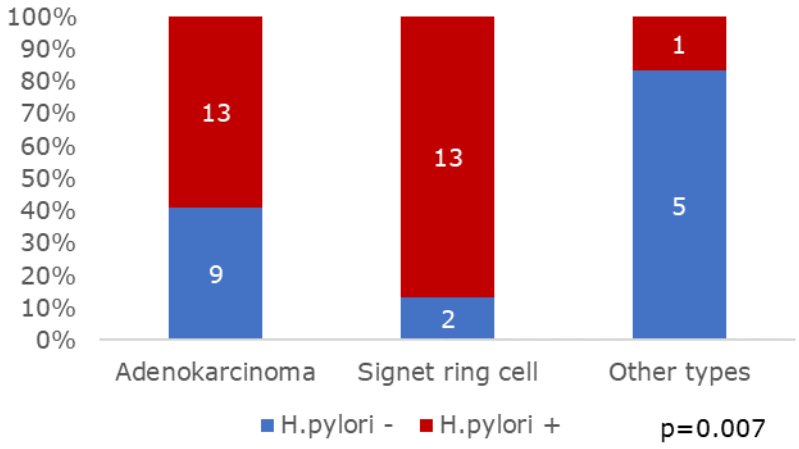



**Chart 1.** Cancer type in relation to H.pylori

## Discussion

Gastric cancer is a major problem today despite attempts of changing lifestyles, eating habits and treatment of Helicobacter pylori infection. There are still many unknown genetic and epigenetic factors that precede the development of this disease (27). The Japanese Association for Gastric Cancer as well as Nakamura and colleagues suggest a division into 5 histological subtypes: tubular adenocarcinoma, papillary adenocarcinoma, poorly cohesive (signet ring cell and other subtypes), mucinous and mixed adenocarcinoma (28). According to ESMO guidelines from July 2022, more than 1 million new cases of this disease were registered during 2020, out of which 768,800 resulted in deaths (29). Despite the large number of patients on a global level, some studies have determined a decrease in the incidence of the disease in the last few decades (27). A large study by Morgan Elleen and colleagues, based on data from the GLOBOCAN database from 185 countries of the world from 2020, indicates that the incidence of the disease is twice higher in male than in female population (15.8 male and 7.0 female per 100,000 cases), with variations between individual countries. The highest incidence is recorded in East Asia (32.5 male and 13.2 female per 100,000), in the male population in Japan (48.1 per 100,000), Mongolia (47.2) and Korea (39.7). The lowest incidence is in Africa with less than 5 developed cancers in 100,000 cases (30). In our observed population of 43 patients, there was no statistically significant difference in morbidity in relation to gender, although world studies record a higher incidence of morbidity in males. Arnold M and colleagues in their study deny the decline in incidence and indicate an increase in the number of patients under 50 years of age. This is probably due to the expansion of obesity and bad eating habits (31). A large cohort study by Wong Martin and colleagues examined the global incidence and mortality of gastric cancer and showed a decrease in the average of patients from 59.1 years (in 1980.) to 56.8 years (in 2018) (32). This supports the previous research conducted by Arnold, which indicated an increase in incidence in younger patients. Also, Wong Martin and colleagues point to a drastically faster death outcome and shorter survival rate, ranging from 1.3 to 25.8 years (in 1980.) to only 1.5 to 18.5 years (in 2018.). This study indicates an increase in the number of

patients under the age of 40 in certain countries, primarily Sweden, Great Britain and Ecuador (32). In the group of patients we examined, the recorded average age of developing cancer ranged from 70.14 ± 9.07 for gastric adenocarcinoma, to 66.93 ± 10.19 for signet ring cell carcinoma. Although we recorded a slightly younger age for developing signet ring cell type cancer, the results do not follow the trend of boundary moving towards a younger age of life, which is currently recorded in some countries. Although the incidence of the disease is different around the world, the population of Japan and Korea still lead in the number of developed gastric cancers. The reasons are probably eating habits, hygiene and higher prevalence of the East Asian form of CagA (cytotoxin-associated genes) compared to the American countries where the western variant of CagA Helicobacter pylori is usually present (33). It is considered that Helicobacter pylori is an unavoidable factor in the development of gastric cancer. In 1982, Warren and Marshall discovered the association of Helicobacter pylori with the development of chronic gastritis (34). It is estimated that 85% of patients with developed gastric cancer also have a positive test for Helicobacter pylori (20). A large meta-analysis of 7 randomized studies by Ford and colleagues showed that eradication of Helicobacter pylori reduces the risk of disease by about 30.5% (35). This bacterium usually acts in two main ways: indirect effect on the gastric mucosa and potential inflammation, but also a direct action in the form of changing the function of epithelial cells, dominantly through the bacterial antigen CagA. Probably, both of these pathways are involved in the development of gastric cancer (36). Research in Shandong indicates that the use of proton pump inhibitors (PPIs) and amoxicillin significantly reduces the incidence of gastric cancer by 39% (in follow-up studies of 14.7 years). This confirms the effectiveness of antibiotic therapy against Helicobacter pylori (37). The recommendations of the last Maastricht VI from 2022 suggest that Helicobacter pylori is a key etiological factor for the development of proximal adenocarcinoma and carcinoma of the gastroesophageal junction (38). In our selected examined population, the presence of this bacterium was found in 59.1% of patients with gastric adenocarcinoma and in 86.7% patients with signet ring cell carcinoma. These results were statistically significant in relation to a certain type of cancer, which confirms the importance of this bacterium in the development of the disease. The eradication of H. pylori reduces the chance of further progression of atrophic gastritis towards metaplasia and dysplasia up to gastric cancer (38). In addition to H. pylori infection, the role of smoking and increased alcohol consumption in the development of cancer is huge (39). Cigarettes smoking is a known carcinogen responsible for the development of tumors in more than 20 locations. From all of 5200 known components of smoke, over 60 of them have direct carcinogenic effects tested in rodents and for over 10 components, there is strong evidence of carcinogenesis in humans (40). A study of the etiology of gastric cancer conducted in Shanghai by Cheng Xiao found an 80% higher risk of developing gastric cancer in smokers compared to a group of non-smokers (39). A meta-analysis of 32 studies conducted by Lopes-Ladeiras and co-workers indicates a 60% higher risk of disease in smokers compared to non-smokers (40). Ramos Marcus Fernando and colleagues studied the importance of smoking experience in the development of cancer and found that the risk of the disease was higher if the smoking status was longer and more cigarettes were smoked throughout the years (when the index number of cigarettes smoked-years is greater than 38) (41). Lindblad and co-workers noted that the former smoking status was important only in female smokers, while they did not establish such an association with gastric cancer in male population (30). In our examined patient population, a higher frequency of smoking was recorded in male patients (46.9%) compared to females (18.2%). Although there were more sick male smokers, there was no statistically significant difference in developing a certain type of cancer in these patients. Female smokers were equally likely to develop any type of gastric cancer. Nishino and colleagues confirm the hypothesis that smoking status increases the risk of the disease in both male and female, which was also the case with our examinees (42). In addition to smoking, alcohol consumption is an inevitable factor in the development of gastric cancer. A large cohort study done in Europe on a sample of 444 cases of gastric cancer found a positive association of frequent alcohol consumption with the occurrence of cancer, but this risk was significantly lower in people who drank less than 60 grams of alcohol per day. Alcohol is considered a risk factor for the development of primary non-cardiac gastric cancer (43). According to a survey conducted in Brazil by the World Health Organization (WHO), 20.4% of cancer patients were former alcohol users, while 58% of patients consumed alcohol at the time of diagnosis (44). A meta-analysis by Ma Ke and colleagues supports the hypothesis of an increase in gastric cancer incidence with increased alcohol intake (45). However, an increase in stomach and oesophageal cancer has been reported in the first two years after stopping alcohol consumption. The reason is probably the quitting of alcohol consumption only at the time of diagnosis or during the appearance of symptoms, which is why patients are identified as former drinkers (46). Out of a total of 43 of our respondents, 8 were male and only 1 was a female. The incidence of a certain type of cancer in these 9 patients was uniform and there was no statistically significant difference in relation to the type of developed cancer. In addition to the mentioned factors, some systemic diseases can be related to gastric cancer. Diabetes can be a predisposition to the development of cancer in several ways. Hyperglycemia can lead to direct DNA damage or the production of free radicals (47). This activates oxidative stress, which can result in mutations in oncogenes and tumor-suppressor genes. This kind of damage can be explained by the synergistic effect of diabetes and H. pylori infection

(48). A large cohort study conducted in 2020 by Yang Hyo-Joon and colleagues showed that diabetes can lead to mucosal atrophy and the development of intestinal metaplasia, which can be the basis for the development of cancer. This study also suggests more frequent endoscopic check-ups in those patients (49). In our observed population, there were only 7 patients (16.3%) suffering from diabetes mellitus, 3 male and 4 female patients. Although all these patients had a diagnosis of gastric cancer, it was not statistically significantly different according to the type of cancer. This indicates that diabetes can be a risk factor, but the number of such subjects is relatively small. Tseng Chin and colleagues, in their study of the potential relationship between diabetes and gastric carcinoma, indicate a positive correlation of this disease with the occurrence of cancer, more often in females in the Asian population (50). Research on this topic conducted in 2021 by Dabo Bashir and colleagues did not establish the relationship between diabetes and the occurrence of gastric cancer (51). These studies and the obtained connections between diabetes and the occurrence of gastric cancer are inconsistent, which is also the case with our patient population, so further research on this topic is required. Other risk factors and protective factors include: poor socioeconomic status (associated with a higher mortality rate) (52), frequent use of non-steroidal anti-inflammatory drugs (NSAIDs, especially aspirin usage) (53), use of statins (they reduce the risk of disease by about 30%) (54), high body-mass index (BMI of 30-35, the risk of disease is 2 times higher, BMI over 40, the risk of disease is more than 3 times higher) (55), increased physical activity (reduces the risk of developing cancer by 21%) (56) and gastroesophageal reflux disease (2 to 4 times more common gastric cardia malignancy) (57, 58).

## Conclusion

The purpose of this study of the selected population of patients was to determine the relationship between gender, age, Helicobacter pylori infection, smoking cigarettes, alcohol consumption and diabetes mellitus with the occurrence of two basic types of gastric cancer - adenocarcinoma and signet ring cell type. Although numerous worldwide studies indicate higher incidences of gastric cancer in male and more often in younger population, in smokers, chronic alcohol consumers and patients with diabetes mellitus, our study did not show statistically significant difference in relation to the type of cancer. Helicobacter pylori infection is one of the key factors in the development of both types of gastric cancer. Further research on a larger population of patients should aim at discovering important genetic factors, obtaining more precise data on the intake of vegetables, fruits and vitamins, analyzing the role of obesity and the role of systemic and inflammatory diseases. This would be necessary in order to clarify the etiology of gastric cancer in patients where the most common risk factors are not present.

## References


1. Yusefi AR, Lankarani KB, Bastani P, Radinmanesh M, Kavosi Z. Risk factors for gastric cancer: A systematic review. Asian Pac J Cancer Prev 2018; 19: 591–603. [CrossRef] [PubMed]
2. Zhang XY, Zhang PY. Gastric cancer: Somatic genetics as a guide to therapy. J Med Genet 2017; 54(5): 305–12. [CrossRef] [PubMed]
3. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomark Prev 2010; 19(8): 1893–1907. [CrossRef] [PubMed]
4. Ang TL, Fock KM. Clinical epidemiology of gastric cancer. Singap Med J 2014; 55(12): 621–8. [CrossRef] [PubMed]
5. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127(12): 2893–917. [CrossRef] [PubMed]
6. Stock M, Otto F. Gene deregulation in gastric cancer. Gene 2005; 360(1): 1–19. [CrossRef] [PubMed]
7. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics 2002. CA Cancer J Clin 2005; 55(2): 74–108. [CrossRef] [PubMed]
8. Lauren, P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965; 64: 31–49. [CrossRef] [PubMed]
9. Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO Classification of tumours of the digestive system. 4th ed. Lyon: IARC; 2010.
10. Vogelaar IP, Van der Post RS, Jm van Krieken JH, Spruijt L, Ag van Zelst-Stams W, Kets CM, et al. Unraveling genetic predisposition to familial or early onset gastric cancer using germline whole-exome sequencing. Eur J Hum Genet 2017; 25(11): 1246–52. [CrossRef] [PubMed]
11. Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: Classification, histology and application of molecular pathology. J Gastrointest Oncol 2012; 3(3): 251–61. [CrossRef] [PubMed]
12. Werner M, Becker K, Keller G, Höfler H. Gastric adenocarcinoma: Pathomorphology and molecular pathology. J Cancer Res Clin Oncol 2001; 127(4): 207–16. [CrossRef] [PubMed]
13. Lauwers GY, Mullen JT, Schreiber KEC, Chung DC. Familial Gastric Cancers. Pathol Case Rev 2014; 19: 66–73. [CrossRef] [PubMed]
14. Pinheiro H, Oliveira C, Seruca R, Carneiro F. Hereditary diffuse gastric cancer – pathophysiology and clinical management. Best Pract Res Clin Gastroenterol 2014; 28(6): 1055–68. [CrossRef] [PubMed]
15. Zhang X-L, Cui Y-H. GSTM1 null genotype and gastric cancer risk in the Chinese population: an updated meta-analysis and review. Onco Targets Ther 2015; 8: 969-75. [CrossRef] [PubMed]
16. Felipe AV, Silva TD, Pimenta CA, Kassab P, Forones NM. Interleukin-8 gene polymorphism and susceptibility to gastric cancer in a Brazilian population. Biol Res 2012; 45(4): 369-74. [CrossRef] [PubMed]
17. Moy KA, Fan Y, Wang R, Gao Y-T, Yu MC, Yuan J-M. Alcohol and tobacco use in relation to gastric cancer: A prospective study of men in Shanghai, China. Cancer Epidemiol Biomark Prev 2010; 19(9): 2287–97. [CrossRef] [PubMed]
18. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control 2008; 19(7): 689–701. [CrossRef] [PubMed]
19. Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: A state of the art review. Gastroenterol Hepatol Bed Bench 2015; 8: S6–S14. [PubMed]
20. Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med 2002; 347(15): 1175–86. [CrossRef] [PubMed]
21. Lizasa H, Nanbo A, Nishikawa J, Jinushi M, Yoshiyama H. Epstein-Barr Virus (EBV)-associated Gastric Carcinoma. Viruses 2012; 4(12): 3420-39. [CrossRef] [PubMed]
22. Nomura AM, Hankin JH, Kolonel LN, Wilkens LR, Goodman MT, Stemmermann GN. Case-control study of diet and other risk factors for gastric cancer in Hawaii (United States). Cancer Causes Control 2003; 14(6): 547–58. [CrossRef] [PubMed]
23. Tavani A, Malerba S, Pelucchi C, Dal Maso L, Zucchetto A, Serraino D, et al. Dietary folates and cancer risk in a network of case-control studies. Ann Oncol 2012; 23(10): 2737–42. [CrossRef] [PubMed]
24. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005; 293(2): 194–202. [CrossRef] [PubMed]
25. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a largescale population-based cohort study in Japan. Arch Intern Med 2006; 166(17): 1871–7. [CrossRef] [PubMed]
26. Ikeda F, Doi Y, Yonemoto K, Ninomiya T, Kubo M, Shikata K, et al. Hyperglycemia increases risk of gastric cancer posed by Helicobacter pylori infection: a population-based cohort study. Gastroenterology 2009; 136(4): 1234–41. [CrossRef] [PubMed]
27. Sitarz R, Skierucha M, Mielko J, Offerhaus GJA, Maciejewski R, Polkowski WP. Gastric cancer: Epidemiology, prevention, classification, and treatment. Cancer Manag Res 2018; 10: 239–48. [CrossRef] [PubMed]
28. Nakamura K, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. Gan 1968; 59(3): 251-8. [PubMed]
29. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014; 23(5): 700-13. [CrossRef] [PubMed]
30. Lindblad M, Rodriguez LAG, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a

nested case-control study. Cancer Causes Control 2005; 16(3): 285–294. [CrossRef] [PubMed]
31. Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram. Is gastric cancer becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut 2020; 69(5): 823-9. [CrossRef] [PubMed]
32. Wong MCS, Huang J, Chan PSF, Choi P, Lao XQ, Chan SM, et al. Global Incidence and Mortality of Gastric Cancer, 1980-2018. JAMA Netw Open 2021; 4(7): e2118457. [CrossRef] [PubMed]
33. Shah SC, McKinley M, Gupta S, Peek Jr RM, Martinez ME, Gomez SL. Population-Based Analysis of Differences in Gastric Cancer Incidence Among Races and Ethnicities in Individuals Age 50 Years and Older. Gastroenterology 2020; 159(5): 1705-14. [CrossRef] [PubMed]
34. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983; 1(8336): 1273–5. [CrossRef] [PubMed]
35. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ 2014; 348: g3174. [CrossRef] [PubMed]
36. Chiba T, Marusawa H, Seno H, Watanabe N. Mechanism for gastric cancer development by Helicobacter pylori infection. J Gastroenterol Hepatol 2008; 23: 1175–81. [CrossRef] [PubMed]
37. Ma JL, Zhang L, Brown LM, Li J-Y, Shen L, Pan K-F, et al. Fifteen year effects of Helicobacter pylori, garlic and vitamin treatments on gastric cance incidence and mortality. J Natl Cancer Inst 2012; 104(6): 488-92. [CrossRef] [PubMed]
38. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou J-M, Schulz C, et al. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut 2022: gutjnl-2022-327745. [CrossRef] [PubMed]
39. Cheng XJ, Lin JC, Tu SP. Etiology and prevention of gastric cancer. Gastrointest Tumors 2016; 3(1): 25-36. [CrossRef] [PubMed]
40. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer Causes Control 2008; 19(7): 689-701. [CrossRef] [PubMed]
41. Ramos MFKP, Junior UR, Viscondi JKY, Zilberstein B, Cecconello I, Eluf-Neto J. Risk factors associated with the development of gastric cancer - case-control study. Rev Assoc Med Bras 2018; 64(7): 611-19. [CrossRef] [PubMed]
42. Nishino Y, Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, et al. Tobacco smoking and gastric cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2006; 36(12): 800–7. [CrossRef] [PubMed]
43. Duell EJ, Travier N, Lujan-Barroso L, Clavel-Chapelon F, Boutron-Ruault M-C, Morois S, et al. Alcohol consumption and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Am J Clin Nutr 2011; 94(5): 1266-75. [CrossRef] [PubMed]
44. WHO Global status report on alcohol and health 2018. Geneva 2018.
45. Ma K, Baloch Z, He T-T, Xia X. Alcohol consumption and gastric cancer risk: A meta-analysis. Med Sci Monit 2017; 23: 238-46. [CrossRef] [PubMed]
46. Jarl J, Heckley G, Brummer J, Gerdtham UG. Time characteristics of the effect of alcohol cessation on the risk of stomach cancer: a meta-analysis. BMC Public Health 2013; 13: 600. [CrossRef] [PubMed]
47. Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, et al. Oxidative damage to DNA in diabetes mellitus. Lancet 1996; 347 (8999): 444–5. [CrossRef] [PubMed]
48. Olefson S, Moss SF. Obesity and related risk factors in gastric cardia adenocarcinoma. Gastric Cancer 2015; 18(1): 23–32. [CrossRef] [PubMed]
49. Yang H-J, Kang D, Chang Y, Ahn J, Ryu S, Cho J, et al. Diabetes mellitus is associated with an increased risk of gastric cancer: a cohort study. Gastric Cancer 2020; 23(2): 382-390. [CrossRef] [PubMed]
50. Tseng C-H, Tseng F-H. Diabetes and gastric cancer: the potential links. World J Gastroenterol 2014; 20(7): 1701-11. [CrossRef] [PubMed]
51. Dabo B, Pelucchi C, Rota M, Jain H, Bertuccio P, Bonzi R, et al. The association between diabetes and gastric cancer: results from the Stomach cancer pooling project consortium. Eur J Cancer Prev 2022; 31(3): 260-9. [CrossRef] [PubMed]
52. Camargo MC, Kim W-H, Chiaravalli AM, Kim K-M, Corvalan AH, Matsuo K, et al. Improved survival of gastric cancer with tumour Epstein-Barr virus positivity: an international pooled analysis. Gut 2014; 63(2): 236–43. [CrossRef] [PubMed]
53. Yang P, Zhou Y, Chen B, Wan H-W, Jia G-Q, Bai H-L, et al. Aspirin use and the risk of gastric cancer: a meta-analysis. Dig Dis Sci 2010; 55(6): 1533–9. [CrossRef] [PubMed]
54. Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. Ann Oncol 2013; 24(7): 1721–30. [CrossRef] [PubMed]
55. Hoyo C, Cook MB, Kamangar F, Freedman ND, Whiteman DC, Bernstein L, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol 2012; 41(6): 1706–18. [CrossRef] [PubMed]
56. Singh S, Varayil JE, Devanna S, Murad MH, Iyer PG. Physical activity is associated with reduced risk of gastric cancer: A systematic review and meta-analysis. Cancer Prev Res 2014; 7(1): 12–22. [CrossRef] [PubMed]
57. Farrow DC, Vaughan TL, Sweeney C, Gammon MD, Chow WH, Risch HA, et al. Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. Cancer Causes Control 2000; 11(3): 231–8. [CrossRef] [PubMed]
58. Engel LS, Chow W-H, Vaughan TL, Gammon MD, Risch HA, Stanford JL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 2003; 95(18): 1404–13. [CrossRef] [PubMed]

**Orginalni rad** **UDC: 616.33-006.6**
**doi: 10.5633/amm.2023.0104**

# FAKTORI RIZIKA ZA RAZVOJ KARCINOMA ŽELUCA – ISKUSTVO JEDNOG CENTRA

*Andrija Rančić[1], Vesna Brzački[1,2], Aleksandar Popović[3], Marija Topalović[4]*

[1] Univerzitetski klinički centar Niš, Klinika za gastroenterologiju i hepatologiju, Niš, Srbija
[2] Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija
[3] Univerzitetski klinički centar Niš, Klinika za onkologiju, Niš, Srbija
[4] Univerzitetski klinički centar Niš, Klinika za pulmologiju, Niš, Srbija

*Kontakt:* Andrija Rančić
Vase Pelagića 44, 18000 Niš, Srbija
E-mail: andrija.m.rancic@gmail.com

Karcinom želuca je četvrti najčešći karcinom na svetu, sa preko milion novih slučajeva godišnje i preko 750 000 smrtnih ishoda od karcinoma. Najviša incidencija beleži se u Japanu i Kini, istočnoj Evropi i Južnoj Americi, a najniža u Africi. Bolest je dva do tri puta češća kod muškaraca i kod osoba starijih od 60 godina, ali se granica pomera ka mlađem uzrastu. Petogodišnje preživljavanje u evropskim zemljama je od 10% do 30%. Ovo je multifaktorijalna bolest, a najvažniji faktori rizika su: infekcija bakterijom Helicobacter pylori, pušenje, konzumiranje alkohola, muški bol, starije životno doba, smanjen unos povrća i voća, genetska predispozicija, šećerna bolest i dr.

Prospektivno istraživanje sprovedeno je na odabranoj populaciji od 43 bolesnika sa dijagnozom dva najčešća tipa karcinoma želuca: adenokarcinom i signet ring cell tip karcinom. Od ukupnog broja ispitanika bilo je 32 muškarca i 11 žena, prosečnih godina starosti 68,83 godine ± 9,26 godina. Među obolelima bilo je 39,5% pušača, 20,9% konzumenata alkohola, 62,8% ispitanika sa nalazom Helicobacter pylori i 16,3% obolelih od šećerne bolesti. Analiza povezanosti pola, godina, pušenja, unosa alkohola i šećerne bolesti sa tipom karcinoma nije pokazala statističku značajnost. Učestalost H. pylori statistički se značajno razlikovala u odnosu na tip karcinoma ($p = 0,007$).

U našem ispitivanju nije bilo statistički značajne razlike između muškog pola, mlađe populacije, pušača, hroničnih konzumenata alkohola i bolesnika sa šećernom bolešću i oboljevanja od određenog tipa karcinoma. Infekcija bakterijom Helicobacter pylori pokazala se kao ključan faktor u razvoju oba tipa karcinoma želuca. Ovo istraživanje obuhvatilo je manji uzorak ispitanika, te je neophodno ispitivanje na većem broju bolensika. *Acta Medica Medianae 2023;62(1): 27-35.*

***Ključne reči:*** *karcinom želuca, Helicobacter pylori, pušenje, alkohol, diabetes mellitus*

**Original article** **UDC: 616.833.58- 009.7:[616.98:578.834**
**doi: 10.5633/amm.2023.0105**

# SCIATICA AND LUMBAGO IN HOSPITALIZED COVID-19 PATIENTS

*Jovan Ilić[1*], Aleksandar Kostić[1,2], Nikola Stojanović[1], Marija Djordjević[2], Emina Kostić[2], Vesna Nikolov[1,2], Radisav Mitić[1]*

Clinical symptoms in patients infected with COVID-19 can vary from asymptomatic and very mild conditions to severe multi-organ failure, severe pneumonia and septic shock. Although relatively common in the non-COVID population, lumbago and sciatica in hospitalized COVID-19 patients have not been sufficiently investigated and reported in the scientific literature. Therefore, the aim of our research was to examine the frequency of sciatica and lumbago, as well as their characteristics in hospitalized COVID-19 patients. The research included 119 patients with confirmed COVID-19 infection with a Real-Time Polymerase Chain Reaction assay for SARS-Cov-2. The presence of sciatica and lumbago were assessed based on the anamnestic data, available medical records of patients and clinical examination. In our study a total number of 39 patients (68.42%) with a previous history of sciatica and lumbago had recurrence of lower back pain. On the other hand, in the group of patients without a previous history of sciatica and lumbago, 30 patients (48.38%) experienced lower back pain for the first time. There was a statistically significant relationship between a previous history of sciatica and lumbago and the recurrence in hospitalized Covid-19 patients (LR = 25.317; p = 0.000). Low back pain and sciatica in hospitalized COVID-19 patients correlate with the length of hospitalization, patient age and vaccination status. There was a high probability that patients with a previous history of lumbago and sciatica may experience a relapse during COVID-19 hospitalization. *Acta Medica Medianae 2023;62(1):36-41.*

***Key words:*** *COVID-19, sciatica, low back pain, COVID-19 vaccines*

[1]Department of Neurosurgery, University Clinical Center of Niš, Niš, Serbia
[2]Faculty of Medicine, University of Niš, Niš, Serbia

*Contact:* Jovan Ilić
112/12 Vizantijski Blvd., 1800 Niš, Serbia
E-mail: jovanilic94@gmail.com

## Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious viral disease with variable clinical symptoms caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). Globally, there have been more than 600 million confirmed cases of COVID-19 since the beginning of the pandemic, while the World Health Organization has reported more than 6 million deaths from COVID-19 (3). Despite the rapid development of vaccines against SARS-CoV-2 with different mechanisms of action, the virus is prone to genetic evolution and adaptation to human hosts by mutations, which significantly hinders progress in the fight against the pandemic (1, 2).

Clinical symptoms in patients infected with COVID-19 vary from asymptomatic and very mild conditions to severe multi-organ failure, severe pneumonia and septic shock (2).

Patients are commonly present with fever, cough, shortness of breath, fatigue, dyspnea, dysgeusia, anorexia, nausea, malaise, myalgia, sputum production and headache. Furthermore, other clinical signs such as rhinorrhea, chest pain, hemoptysis, conjunctival congestion and vomiting are considered to be rare symptoms (4, 5).

The clinical diagnosis of sciatica (radicular pain or lumbosacral radicular syndrome) is based on pain that radiates along one or both legs, and may be accompanied by neurological deficit (6). It can be caused by nerve root compression that forms the sciatic nerve (L4-S1) due to a herniated intervertebral disc as well as the resulting inflammatory response. Less common etiological factors are spinal trauma, foraminal stenosis, synovial cysts and tumors (7, 8). Pain in the lower back (lumbago) can be neuropathic, nociceptive and nociplastic pain, while clinically, it can be manifested as non-specific pain in this area (9).

Given that the COVID-19 pandemic caused unprecedented changes in healthcare systems, the number of patients who underwent elective lumbar spine surgery was drastically lower during the pandemic, and patients had higher number of comorbidities and overall complications (10).

Although it is relatively common in the non-COVID population, low backache and sciatica in

hospitalized COVID-19 patients have not been sufficiently investigated and reported in the scientific literature. Therefore, the aim of our research was to examine the frequency of sciatica and lumbago, as well as their characteristics in hospitalized COVID-19 patients.

## Patients and methods

The research was conducted as a prospective study at the COVID hospital-object 4 in the period from March 15, 2021 to January 4, 2022.

The research included 119 patients with confirmed COVID-19 infection with a Real-Time Polymerase Chain Reaction assay for SARS-Cov-2. The previously signed informed consent was obtained for each patient.

The patients included in the research were patients with a mild clinical presentation and without serious comorbidities (hospitalized patients with SpO2 > 90%, with X-ray signs of pneumonia, with or without signs of hypoxia on admission). They were under constant medical supervision, including regular measurement of body temperature, oxygen saturation, respiratory rate and diuresis. All patients included in the study were hospitalized for a minimum of 7 days.

Based on the presence of sciatica, the patients were divided into the following groups:

Group I: patients with a previous history of sciatica and lumbago

Group II: patients with the first onset of sciatica and lumbago

The presence of sciatica and lumbago were assessed based on the anamnestic data, available medical records of patients and clinical examination, which included straight leg raising test (Lazarevic/Lasegue test), Mingazzini test, dorsiflexion and plantar flexion of the foot, Neri's test, Menell's test, the presence of paresthesia along the legs and other sensibility disorders as well as loss of bowel or bladder control. The characteristics of sciatic pain and lumbago were assessed based on a numerical scale from 0 (no pain) to 10 (worst possible pain), while the patients self-reported the degree of pain.

All the patients were treated conservatively for their symptoms of sciatica and lumbago. Further diagnostic procedures due to back pain and sciatica and other therapeutical options were left for a period after the patients' recovery from the COVID-19 infection.

## Statistical data processing

Data entry, tabulation and graphical presentation were performed by using MS Office 2016 Excel program. The results of statistical analysis are presented in tables. Statistical calculations were performed using SPSS program (version 26). Among the basic descriptive statistical parameters, standard statistical methods were used for qualitative and quantitative assessment of the results: absolute numbers, relative numbers (%), arithmetic mean ($\bar{x}$), standard deviation (SD), minimum and maximum values. The normality of the distribution of individual values was examined by Kolmogorov-Smirnov test. The $\chi^2$ test was used to test the statistical significance of absolute frequency differences between samples. The statistical hypothesis was tested at the level of significance for the risk of $\alpha = 0.05$, i.e. the difference between the samples is considered significant if $p < 0.05$. Comparison of the arithmetic means of the two samples was performed by t-test. Multiple logistic regression analysis was used to assess the influence of multiple risk factors on the occurrence of lumbago and sciatica.

## Results

In the study group of 119 COVID-19 infected patients who were hospitalized, we tried to determine the frequency and some characteristics of ishilagia and lumbago. The average age of the patients was 66.14 years (min 29; max 89), while there were 69 (58.98%) male and 50 (42.02%) female patients. The total number of unvaccinated patients was 109 (91.6%), while 6 patients were vaccinated with 2 doses of vaccine (5%) and 4 with only one dose of vaccine (3.4%) (Table 1.).

**Table 1.** Vaccination status of patients

| Variable | Frequency | Percent |
|---|---|---|
| Fully vaccinated, but does not know which vaccine he/she received | 2 | 1.7 |
| No vaccines | 109 | 91.6 |
| Pfizer-BioNTech COVID-19 Vaccine 1 dose | 1 | 0.8 |
| Sinopharm [Vero Cell]-Inactivated 1 dose | 2 | 1.7 |
| Sinopharm [Vero Cell]-Inactivated 2 doses | 4 | 3.3 |
| The Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine) COVID-19 vaccine- 1 dose | 1 | 0.8 |
| Total | 119 | 100 |

In our study, a total of 39 patients (68.42%) with a previous history of sciatica and lumbago had recurrence of lower back pain. On the other hand, in the group of patients without a previous history of sciatica and lumbago, 30 patients (48.38%) experienced lower back pain for the first time (Table 2). There was a statistically significant relationship between a previous history of sciatica and lumbago and the recurrence in hospitalized Covid-19 patients (LR = 25.317; p = 0.000). The degree of sciatica and lower back pain did not change significantly in relation to the Covid-19 infection and hospitalization (t = 1.909; p = 0.59).

**Table 2.** Presence of current sciatica and lumbago versus the previous history

| Variable | The patient has current sciatica and lumbago | The patient without current sciatica and lumbago | Total |
|---|---|---|---|
| Previous history of sciatica and lumbago | 39 | 18 | 57 |
| The patient has never had sciatica and lumbago | 30 | 32 | 62 |
| Total | 69 | 50 | 119 |

**Table 3**. Comparison of vaccination status and previous history of sciatica and lumbago with the currently present sciatica and lumbago

| Variables | Vaccination status | | Hospitalization in patients with the previous history of sciatica/lumbago | |
|---|---|---|---|---|
| | F† | p | t‡ | p |
| Current degree of sciatica/lumbago | 1.884 | 0.103 | 1.909 | 0.59 |

**Table 4.** The influence of the tested parameters on the development of sciatica and lumbago (multiple logistic regression analysis)

| Variable | OR | 95%CI | p |
|---|---|---|---|
| Fever | 0.754 | 0.181-3.453 | 0.790 |
| Pharyngitis | 0.815 | 0.183-3.641 | 0.789 |
| Nonproductive cough | 0.775 | 0.239-2.517 | 0.672 |
| Productive cough | 0.714 | 0.178-2.866 | 0.634 |
| Fatigue | 26.644 | 2.285-310.718 | **0.009** |
| Dyspnea | 0.718 | 0.186-2.764 | 0.630 |
| Dysgeusia | 14.840 | 0.594-370.931 | 0.100 |
| Anosmia | 0.042 | 0.001-1,324 | 0.072 |
| Nausea | 1.970 | 0.548-7.088 | 0.299 |
| Myalgia | 1.252 | 0.432-3.631 | 0.678 |
| Headache | 6.486 | 1.754-23.986 | **0.005** |
| Neck pain | 6.314 | 1.484-26.862 | **0.013** |
| Diarrhea | 0.497 | 0.081-3.039 | 0.449 |
| Vomiting | 1.083 | 0.079-14.900 | 0.952 |
| Oxygen saturation | 1.050 | 0.940-1.173 | 0.384 |
| C-reactive protein | 0.992 | 0.984-1.000 | 0.065 |
| Previous use of favipiravir in the outpatient setting | 0.813 | 0.129-5.138 | 0.825 |
| Oxygen flow through the mask | 1.062 | 0.909-1.214 | 0.446 |

The vaccination status of patients did not vary significantly between the group of patients with a previous history of sciatica and lumbago and the group of patients with current sciatica and lumbago (F = 1.884; p = 0.103) during hospitalization (Table 3).

Multiple logistic regression analysis showed a statistically significant influence of fatigue (p = 0.009), headache (p = 0.005) and neck pain (p = 0.013) on the occurrence of sciatica and lumbago (Table 4).

**Discussion**

Considering the available scientific literature in the Internet databases (MEDLINE, PubMed, Embase, ClinicalTrials.gov) and to the best of our knowledge, we did not come across any research that investigated the frequency of sciatica and

lumbago, as well as their characteristics in hospitalized COVID-19 patients.

It has been observed that older male patients, as well as obese patients, have an increased risk of hospitalization due to Covid-19 infection (11, 12, 13). It is assumed that elderly patients are more affected by viral infections due to a weaker immune system (14). On the other hand, the exact mechanism why men have a more severe COVID-19 infection during hospitalization is still not clarified, but it is suggested to be multifactorial (15). Some authors have noted that obese patients are hospitalized more often and have a worse clinical outcome (16). According to other authors, the risk of hospitalization was 17 times higher in the unvaccinated population (17).

The average age of the patients in our study was 66.14 years, while there were 69 (58.98%) male and 50 (42.02%) female patients. The total number of unvaccinated patients was 109 (91.6%), while 6 patients were vaccinated with 2 doses of vaccine (5%) and 4 with only one dose of vaccine (3.4%). These results of our research are consistent with the results of the aforementioned researches. The relationship between aging, degenerative processes, and lumbago with sciatica is still unclear. Aging-related degeneration of the intervertebral disc involves numerous inflammatory mediators and cytokines (18).

We found a statistically significant influence of fatigue ($p = 0.009$), headache ($p = 0.005$) and neck pain ($p = 0.013$) on the occurrence of sciatica with lumbago (Table 4). Headache, fatigue and neck pain are common symptoms of COVID-19 (4), but they are non-specific symptoms that also occur during other viral infections. Our results can be applied to all bed-rest related illnesses, where locomotor system is minimally active for a substantial period of time. The patients from our study were hospitalized for a minimum of 7 days, average 11.6. days. Both obesity and low level of physical activity are independent risk factors of radiating low back pain (19).

There was a high probability that patients with a history of sciatica and lumbago may experience it again during their stay in Covid Hospital and that patients without it would not (LR = 25.317; $p = 0.000$).

Patients with degenerative diseases of the lumbar spine, such as disc herniation, have elevated levels of IL-6, TNF-α and IFN-γ, but their increased values can also be found in patients with rheumatological diseases (20). In addition to the mechanical compression of lumbar nerve roots and sensory root ganglia by herniated discs, there is a chemical stimulus for creating pain in the sciatic leg, which could be prescribed to elevated concentrations of IL-1α and consequently Prostaglandin E2, after which the tissue becomes more sensitive to bradykinin (21). It has been proven that as a result of COVID-19 infection, the epithelium is damaged while IL-1α and IL-1β concentration increases. Elevated levels of IL-6, TNF-α and IFN-γ in COVID-19 patient could be significant in forming an overacting immune response, especially IL-6 (22). Despite this connection in elevated values of IL-6, IL-1α, TNF-α and IFN-γ the pathophysiological mechanism remains not fully elucidated, because their values are elevated in many other diseases. The correlation between systemically elevated cytokine values and local pain in patients is also unclear. On the other hand, some authors suggest that in disc herniation and neuropathic pain, the intensity of pain is proportional to the local elevation of cytokines (20).

In one study on sciatic nerves in animal models, it was shown that during infection with COVID-19, HCoV-OC43 polypeptides are secreted and lead to molecular mimicry of the myelin basic protein and consequent mechanical hypersensitivity of the sciatic nerve. The same authors therefore propose this mechanism of action of the COVID-19 virus as a potential pathophysiological explanation for the neuropathic effect (23). The authors of one case report reported a case of acute denervation in the left tibialis anterior muscle due to COVID-19 sciatic mononeuropathy (24).

Therefore, additional research is needed to clarify the pathophysiological association between lumbago and sciatica in patients with COVID-19.

## Conclusion

Low back pain and sciatica in hospitalized COVID-19 patients correlate with the length of hospitalization, patient age and vaccination status. There was a high chance that patients with a previous history of lumbago and sciatica may experience a relapse during COVID-19 hospitalization. Additional research is needed in order to clarify in detail the pathophysiological mechanism of the sciatic pain and lumbago in COVID-19 patients.

**References**


1. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MMG, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. Cochrane Database Syst Rev 2022, Issue 5. Art. No.: CD013665. [CrossRef] [PubMed]
2. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). [PubMed]
3. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Washington: 2022. Available from: URL: https://covid19.who.int/
4. Şahin T, Ayyildiz A, Gencer-Atalay K, Akgün C, Özdemir HM, Kuran B. Pain Symptoms in COVID-19. Am J Phys Med Rehabil 2021; 100(4): 307-12. [CrossRef] [PubMed]
5. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. Morb Mortal Wkly Rep 2020; 69(24): 759-65. [CrossRef] [PubMed]
6. Valat JP, Genevay S, Marty M, Rozenberg S, Koes B. Sciatica. Best Pract Res Clin Rheumatol 2010; 24: 241-52. [CrossRef] [PubMed]
7. Ailianou A, Fitsiori A, Syrogiannopoulou A, Toso S, Viallon M, Merlini L, et al. Review of the principal extra spinal pathologies causing sciatica and new MRI approaches. Br J Radiol 2012;85:672-81. [CrossRef] [PubMed]
8. Konstantinou K, Dunn KM, Ogollah R, Vogel S, Hay EM. Characteristics of patients with low back and leg pain seeking treatment in primary care: baseline results from the ATLAS cohort study. BMC Musculoskelet Disord 2015; 16(1): 332. [CrossRef] [PubMed]
9. Knezevic NN, Candido KD, Vlaeyen JWS, Van Zundert J, Cohen SP. Low back pain. Lancet 2021; 398(10294): 78-92. doi:10.1016/S0140-6736(21)00733-9. [CrossRef] [PubMed]
10. Song J, Katz A, Virk S, Sarwahi V, Silber JS, Essig DA. P132. Lumbar fusion during the COVID-19 pandemic: greater rates of morbidity and longer procedures. Spine J 2022;22(9):S190. [CrossRef] [PubMed]
11. Imam Z, Odish F, Armstrong J, Elassar H, Dokter J, Langnas E, et al. Independent correlates of hospitalization in 2040 patients with COVID-19 at a large hospital system in Michigan, United States. J Gen Intern Med 2020; 35(8): 2516-7. [CrossRef] [PubMed]
12. Ebinger JE, Achamallah N, Ji H, Claggett BL, Sun N, Botting P, et al. Pre-existing traits associated with Covid-19 illness severity. PLoS One 2020; 15(7): e0236240. [CrossRef] [PubMed]
13. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966. [CrossRef] [PubMed]
14. Vahey GM, McDonald E, Marshall K, Martin SW, Chun H, Herlihy R, et al. Risk factors for hospitalization among persons with COVID-19-Colorado. PloS one 2021; 16(9): e0256917. [CrossRef] [PubMed]
15. Jutzeler CR, Bourguignon L, Weis CV, Tong B, Wong C, Rieck B, et al. Comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatment strategies, and outcomes in adult and pediatric patients with COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020; 37: 101825. [CrossRef] [PubMed]
16. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. Clin Infect Dis 2020; 71(15): 896–97. [CrossRef] [PubMed]
17. Havers FP, Pham H, Taylor CA, Whitaker M, Patel K, Anglin O, et al. COVID-19-Associated Hospitalizations Among Vaccinated and Unvaccinated Adults 18 Years or Older in 13 US States, January 2021 to April 2022. JAMA Intern Med 2022; 182(10): 1071-81. [CrossRef] [PubMed]
18. Podichetty VK. The aging spine: the role of inflammatory mediators in intervertebral disc degeneration. Cell Mol Biol 2007; 53(5): 4-18. [PubMed]
19. Shiri R, Solovieva S, Husgafvel-Pursiainen K, Telama R, Yang X, Viikari J, et al. The role of obesity and physical activity in non-specific and radiating low back pain: the Young Finns study. Semin Arthritis Rheum 2013; 42(6): 640-50. [CrossRef] [PubMed]
20. Andrade P, Hoogland G, Garcia MA, Steinbusch HW, Daemen MA, Visser-Vandewalle V. Elevated IL-1β and IL-6 levels in lumbar herniated discs in patients with sciatic pain. Eur Spin J 2013; 22(4): 714-20. [CrossRef] [PubMed]
21. Takahashi H, Suguro T, Okazima Y, Motegi M, Okada Y, Kakiuchi T. Inflammatory cytokines in the herniated disc of the lumbar spine. Spine 1996; 21(2): 218-24. [CrossRef] [PubMed]
22. Shekhawat J, Gauba K, Gupta S, Purohit P, Mitra P, Garg M, et al. Interleukin-6 perpetrator of the COVID-19 cytokine storm. Indian J Clin Biochem 2021; 36(4): 440-50. [CrossRef] [PubMed]
23. Shubayev VI, Dolkas J, Catroli GF, Chernov AV. A human coronavirus OC43-derived polypeptide causes neuropathic pain. EMBO Rep 2022; 23(6): e54069. [CrossRef] [PubMed]
24. Acharya S, Thibault M, Lee J, Taha O, Morpurgo AJ, Kshetree BK, et al. COVID-19-Induced Left Sciatic Neuropathy Requiring Prolonged Physical Medicine and Rehabilitation. Cureus 2021; 13(6): e15803. [CrossRef] [PubMed]

**Originalni rad** **UDC: 616.833.58- 009.7:[616.98:578.834**
**doi: 10.5633/amm.2023.0105**

# LUMBOISCHIALGIA KOD HOSPITALIZOVANIH BOLESNIKA ZARAŽENIH VIRUSOM COVID-19

*Jovan Ilić[1]*, Aleksandar Kostić[1,2], Nikola Stojanović[1], Marija Đordjević[2], Emina Kostić[2], Vesna Nikolov[1,2], Radisav Mitić[1]*

[1]Univerzitetski klinički centar Niš, Klinika za neurohirurgiju, Niš, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija

Kontakt: Jovan Ilić
Vizantijski bulevar 112/12, 1800 Niš, Srbija
E-mail: jovanilic94@gmail.com

Klinička slika bolesnika sa infekcijom izazvanom virusom COVID-19 varira od asimptomatskih i veoma blagih stanja do oštećenja više organa, teške pneumonije i septičkog šoka. Iako se relativno često javlja u populaciji koja nije obolela od virusa COVID-19, nema dovoljno podataka o lumboischialgiji kod hospitalizovanih COVID-19 bolesnika u naučnoj literaturi. Stoga je cilj našeg istraživanja bio da ispitamo učestalost lumboischialgije, kao i njene karakteristike kod hospitalizovanih bolesnika zaraženih virusom COVID-19. Istraživanje je obuhvatilo 119 bolesnika sa potvrđenom infekcijom izazvanom viursom COVID-19 PCR testom za SARS-Cov-2. Prisustvo lumboischialgije procenjivano je na osnovu anamnestičkih podataka, dostupne medicinske dokumentacije i kliničkog pregleda bolesnika. U našoj studiji ukupno 39 pacijenata (68,42%) sa prethodnom istorijom lumboischialgije imalo je recidiv ove bolesti. Sa druge strane, u grupi bolesnika koji nikada ranije nisu imali lumboischialgiju, 30 bolesnika (48,38%) prvi put doživelo je ovu bolest. Utvrđena je statistički značajna veza između prethodne istorije lumboischialgije i recidiva lumboischialgije kod hospitalizovanih bolesnika sa COVID-19 virusom (LR = 25,317; p = 0,000). Bol sa lumboischialgičnim karakteristikama kod hospitalizovanih pacijenata sa COVID-19 virusom korelirao je sa dužinom hospitalizacije, uzrastom bolesnika i vakcinalnim statusom. Rezultati našeg istraživanja ukazuju na veliku šansu da bolesnici sa prethodnom istorijom lumboischialgije mogu doživeti recidiv tokom hospitalizacije zbog infekcije izazvane virusom COVID-19. *Acta Medica Medianae 2023;62(1): 36-41.*

***Ključne reči:*** *COVID-19, lumboischialgia, COVID-19 vakcine*

**Original article** **UDC: 616.98:578.834]:616-051(497.11)**
**doi: 10.5633/amm.2023.0106**

# PREVALENCE OF DEPRESSIVE SYMPTOMS IN EMPLOYEES IN A TERTIARY HEALTHCARE INSTITUTION IN BELGRADE DURING THE COVID-19 PANDEMIC

*Sonja Giljača[1], Slavica Maris[1], Milica Ranković – Janevski[2], Marko Stojanović[3]*

Increased work engagement during COVID-19 pandemic has certainly damaged the health of workers in healthcare institutions. The aim of this paper was to determine the quality of life of employees and the presence of depressive symptoms after contracting Covid-19. A panel longitudinal study was conducted (following two times periods in 2020 and 2021 from March to May) among employees at the Belgrade Institute of Neonatology, using the following questionnaires: Patient Health Quality 9 (PHQ-9) for self-assessment of depressive symptoms; EuroQol-visual analogue scale (EQ VAS) for self-assessment of health condition and socio-descriptive characteristics of respondents were collected through a general questionnaire. Only fully completed questionnaires were included in the study, and that number was 138. There were a total of 138 participants (6 men and 132 women). Women were more represented (95.6%) and (66.0%) respondents were married and had a university education. The average value of the score of the PHQ-9 questionnaire for all employees in 2020 was 5.54 + 4.9. We determined that more than half of the employees, 77 (56.0%), had no depressive symptoms, that is, they had a score in the interval of 0-4 points, 30 employees (21.3%) had a score of 5 − 9, 22 employees (16.0%) scored 10 − 14, 7 employees (5.1%) 15 − 19 and score ≥20 had two employees (1.4%). In 2021, average value of the score of the PHQ-9 questionnaire for all employees was 3.8 + 5.12. Without depressive symptoms, there were 70.30% of employees with a score of 0 − 4, which is significantly more ($p < 0.01$) than in 2020. In all categories, from the mildest subclinical upper score of 5 − 9 to the most severe ≥ 20, depressive symptoms were almost 50% less prevalent among employees in 2021. *Acta Medica Medianae 2023;62(1):42-49.*

***Key words:*** *COVID-19, healthcare workers, symptoms of depression*

[1]Institute of Public Health of Belgrade, Republic of Serbia
[2]Institute of Neonatology, Belgrade, Republic Serbia
[3]Institute of Public Health Niš, Republic of Serbia

*Contact:* Sonja Giljaca*
54 a Despota Stefana Blvd., Belgrade
E-mail: sonja.giljaca@zdravlje.org.rs

## Introduction

The importance of the well-being and mental health of health workers as one of the risk occupational groups was in focus even before the COVID-19 pandemic occurred. Numerous studies have been conducted (1, 2) in which it was found that health workers are more exposed to stressors related to work compared to other professions. Some of these stressors include: long hours, extensive workloads, the growing intensity and complexity of the job, relentless contact with patient, high level of responsibility, rapid change within healthcare, institutional constraints such as discrimination and intimidation, lack of autonomy, low levels of support, loss of job satisfaction, low morale and inability to attend to their personal lives (1).

On January 30 2020, the world health organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a Public Health Emergency of International Concern, its highest level of alarm. An unparalleled global response followed, with local and national "lockdowns", quarantines, travel restrictions, and physical distancing measures introduced in attempts to curb transmission rates (3).

Scholars have found that healthcare workers suffered significant mental health problems during the COVID-19 outbreak. For example, medical workers were more likely to develop psychosocial

problems than non-medical workers were. Moreover, the front-line medical staff in close contact with infected patients were more likely to suffer anxiety and depression than administrative staff and the general public. However, there is a lack of evidence in the literature regarding the mechanism of those risk factors on mental health problems among healthcare workers (4).

The new infectious disease, Covid-19, first appeared on the territory of the Republic of Serbia on March 6, 2020. Medical and non-medical staff in the conditions of the COVID-19 did not have much information, but health workers were required to provide maximum physical engagement and to learn daily about personal protection equipment, its use, as well as to familiarize with the method of treatment and care of patients with COVID-19. In their daily work in COVID as well as in non COVID zones, employees were in risk of contracting infection with the new coronavirus SARS-CoV-2 (COVID-19) and death. Increased work engagement has certainly impaired the health of employees , significantly changed the organization of work and lifestyle, and the main goal of this research is to determine some of the consequences of these changes, such as the presence of symptoms of depression.

## Material and methods

The research was conducted as a panel longitudinal study (following two time periods in 2020 and 2021, March-May) in the period from July 28, to September 24, 2022 and the population of respondents was represented by all employees of the Belgrade Institute of Neonatology. The criteria for inclusion of respondents in the research were the following: adults (> 18 years), permanent employment in the mentioned institution and voluntary consent to participate in the study. Exclusion criteria: workers who were in the process of resolving their work status or obtaining a license, discontinuity in work for more than a year, and persons who refused to participate. Before the start of the research, a meeting was held where all respondents were informed in detail about the purpose of the research and consent was obtained for conducting the research by the Ethics Committee of the Institute of Neonatology No: 2487/3 date 12.07.2021. The data for this study were obtained by voluntary filling of anonymous questionnaires by the respondents.

For the purpose of this research, a general questionnaire was constructed and two more were used: PHQ-9 and EQ VAS.

The general questionnaire contains 20 questions and was used to collect the basic socio-descriptive data of the respondents (gender, age, marital status, education level, length of service/ higher position in institution, shift work, satisfaction with working conditions, number of hours of sleep, illness from COVID-19).

The PHQ-9 contains 9 questions to which respondents answer by circling one of the provided answers. The answer to each question out of 9 questions on a four-point Likert scale is scored 0 – 3 (not at all = 0, a few days = 1, more than half a day = 2, almost every day = 3), the points are also added depending on the height score, the severity of depressive episode is assessed (0 – 4 no depressive symptoms, 5 – 9 subclinical form of depression, 10 – 14 mild depressive episode, 15 – 19 moderately severe and > 20 indicates severe depressive episode).

The EQ VAS scale is an instrument used for self-assessment of health status. To help respondents rate how good or bad their health is, we drew a scale (which looks like a thermometer) on which we marked the best imaginable state with 100 and the worst imaginable state with 0. We asked respondents to show us on a scale how good or bad their state of health was at the time of the study by drawing a line from the black cube that says "Your state of health today" to a point on the scale that best describes how good or bad their state of health is. The obtained values of the EQ VAS scale in the respondents for the period March-May in 2020 and 2021 were processed using the analysis of variance for repeated measurements.

## Statistical analysis

Statistical analysis of data was done using statistical package SPSS 20.0 for Windows. All continuous variables are given as means ± standard deviations (SD). Average values of continuous variables in the two tested groups were compared by means of Student's t-test and Chi-square test was used to examine the differences of categorical variables. Spearman's correlation coefficient (ρ) was used for measurement of the strength and direction of association between two ranked variables. Assessment error less than 5% ($p < 0.05$) was accepted as the threshold of statistical significance.

## Results

A total of 138 respondents (6 men and 132 women) participated in the study. Women were more represented (95.6%) than men (4.4%) and the difference was statistically significant. The average age of all respondents was 40.10 + 11.4 years and ranged from 21 to 66 years, and the most respondents were in the age group 20 - 39 77 (55.8%).

The highest percentage of employees were married (66.0%), i.e. 91 of them, 27 (19.4%) were single, five (3.6%) were divorced, two (1.4%) were widows and 12 (8.6%) did not give an answer. Ninety-one employees (66.0%) had a university education, one (1%) completed three-year high school, 12 (9%) completed four-year high school, 15 (11%) had Bachelor's degree, 10

(7%) had specialization, 5 (3%) had subspecialty training, one (1%) had academic title and 3 (2%) did not give any answer. The average length of service for all employees was 15.2 years ± 11.2 and ranged from 1 month to 42 years. The largest number of respondents, 49 (35.5%), had a length of service of less than ten years, followed by a total of 45 employees (32.6%) with a length of service of 10 to 19 years, and the least respondents, only two (1.4%) were with 40 to 49 years of work experience. Only 17 (13.7%) respondents held a managerial position.

Most respondents worked in shifts, 94 (68.1%). 46 respondents (33.4%) did not answer about the length of the shift, and 91 (65.9%) respondents worked from 6 to 12 hours, and one (0.72%) stated that they worked 18 hours. The average working time of the employees was 7.84 hours ± 5.64 and ranged from 0 to 18 hours. The largest number of employees, 88 (63.7%), were satisfied with the working conditions, while there was the same number of employees — 25 (18.1%) who did not give a precise answer to this question and were unsatisfied with the working conditions (Table 1).

**Table1.** Socio-descriptive characteristics of employees

| Socio-descriptive characteristics | | N | (%) |
|---|---|---|---|
| Gender | Male | 6 | 4.4 |
| | Female | 132 | 95.6 |
| Age | 20 – 39 | 77 | 55.8 |
| | 40 – 59 | 54 | 39.1 |
| | ≥ 60 | 7 | 5.0 |
| Marital status | Married | 91 | 65.5 |
| | Single | 27 | 19.4 |
| | No answer | 12 | 8.6 |
| | Divorced | 5 | 3.6 |
| | Widow/widower | 2 | 1.4 |
| Education | Three-year high school | 1 | 1.0 |
| | Four-year high school | 12 | 9.0 |
| | Bachelor | 15 | 11.0 |
| | College | 91 | 66.0 |
| | Academic title | 1 | 1.0 |
| | Specialization | 10 | 7.0 |
| | Subspecialty | 5 | 3.0 |
| | No answer | 3 | 2.0 |
| Occupation | Medical doctor | 21 | 15.3 |
| | Nurse/medical technician | 111 | 80.4 |
| | Tech staff | 3 | 2.3 |
| | Administrative workers | 1 | 0.7 |
| | No answer | 2 | 1.4 |
| Higher position in company | Yes | 17 | 13.7 |
| | No | 121 | 86.3 |
| Working in shifts | Yes | 94 | 68.1 |
| | No | 44 | 31.8 |
| Duration of working hours | No answer | 46 | 33.4 |
| | 6 - 12* | 91 | 65.9 |
| | ➢ 12 | 1 | 0.72 |
| Satisfaction with working conditions | Yes | 88 | 63.7 |
| | No | 25 | 18.1 |
| | Neither | 25 | 18.1 |
| Hours of sleep | < 6 hours | 45 | 32.6 |
| | 6 - 8 hours | 92 | 66.7 |
| | > 8 hours | 1 | 0.7 |
| Length of vacation per year | < 20 | 8 | 5.8 |
| | ≥ 20 | 4 | 2.9 |
| | ≥ 30 | 70 | 50.7 |
| | ≥ 40 | 56 | 40.6 |
| Years of employment | > 10 | 49 | 35.5 |
| | 10 - 19 | 45 | 32.6 |
| | 40 - 49 | 2 | 1.4 |

*Length of working time in hours

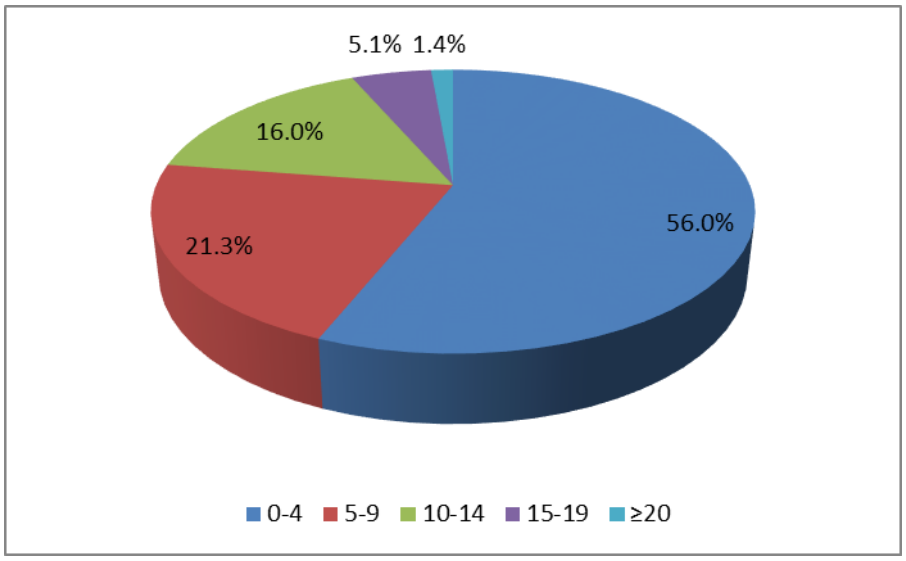



**Figure 1.** Distribution of employees according to the score in the PHQ-9 questionnaire in March, April and May of 2020

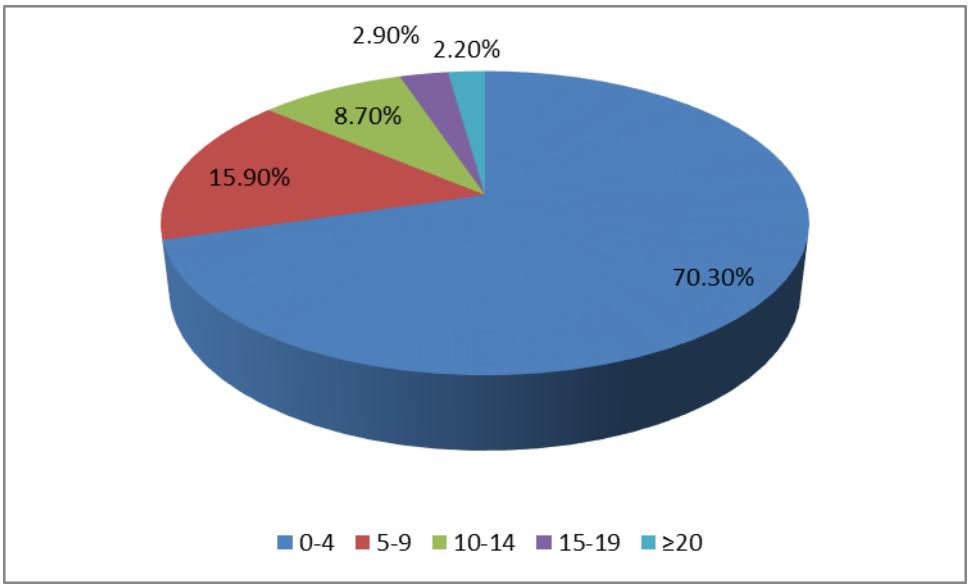



**Figure 2**. Distribution of employees according to the score in the PHQ-9 questionnaire in March, April and May 2021

The average length of vacation was 35.90 days ± 7.42 and ranged from 0 to 49 days. The largest number of employees, 92 (66.7%), slept 6 – 8 hours during 24 hours, and only one person slept more than 8 hours. Twenty-one respondents were infected with COVID-19. Fifteen point three percent were doctors, 80.4% were nurses/technicians, 2.3% were members of technical staff, 0.7% were administrative workers and 1.4% did not give an answer regarding their occupation. Eighty-seven respondents (63.4%) were vaccinated against COVID-19.

The average value of the score in the PHQ-9 questionnaire for all employees in 2020 was 5.54 ± 4.9. After analyzing the responses of employees from the first three months of 2020, it was determined that more than half of the employees, 77 (56.0%), had no depressive symptoms, that is, they had a score in the interval (0 – 4 points), 30 employees had a score of 5 – 9 (21.3%), 22 employees (16.0%) had a score of 10 – 14, 7 employees (5.1%) had a score of 15 – 19 and two employees (1.4%) had a score ≥ 20 (Figure 1).

The average of the score in the PHQ-9 questionnaire for all employees in 2021 was 3.8 ±

5.12. Without depressive symptoms, there were 70.30% of employees with a score of 0 – 4, which is significantly more ($p < 0.01$) than in 2020. In all categories, from the mildest subclinical upper score of 5 – 9 to the most severe ≥20, depressive symptoms were almost 50% less prevalent among employees in 2021 (Figure 2) than in 2020 (Figure 1).

The average PHQ-9 score in 2021 was 3.8 ± 5.12 and the decrease in the average PHQ-9 score compared to 2020 in health workers was statistically significant ($p = 0.0036$). Using Spearman's correlation, the average score of the EQ VAS questionnaire and the length of the duration of the COVID-19 pandemic of the employees was determined to have a statistically significant positive correlation of $r = 0.185$; $n = 138$; $p = 0.001$.

In the period of the first three months of 2020 and 2021, the number of employees without symptoms of depression increased significantly. No statistically significant positive correlation was found between the average score of depression symptoms in the PHQ-9 questionnaire and age, length of service, length of working hours, shift work, and length of rest.

The analysis of variance for repeated measurements showed that during the test, there was no statistically significant increase in EQ VAS values, and only in May 2020, when the smallest number of employees rated their health as the best possible (score 100) that year (Table 2). An increase in EQ VAS scores was recorded from April 2021 compared to 2020, the determined difference was not statistically significant.

**Table 2**. Average values of the EQ VAS scale among employees in March, April and May 2020 and 2021

| Period | Average values EQ VAS | | |
|---|---|---|---|
| | 2020 | 2021 | p |
| March | 74.27 ± 24.80 | 74.50 ± 25.76 | 0.929 |
| April | 74.38 ± 24.71 | 76.11 ± 25.63 | 0.562 |
| May | 77.40 ± 24.01 | 78.26 ± 25.70 | 0.758 |

## Discussion

We applied a panel study in order to analyze the quality of life of employees in a tertiary healthcare institution and the prevalence of depressive symptoms in two different years. Using two specific and one general questionnaire for data collection, we determined that the average PHQ-9 score for all employees in 2021 was significantly lower, and that two thirds of employees were without symptoms of depression than in 2020.

Healthcare workers (HCWs) worldwide face a high risk of developing mental health problems during COVID-19, in particular frontline, and a large number of studies confirmed that (3, 4, 5), whereas only a few studies were conducted related to this issue among the population of non-frontline HCWs (5, 6, 7). Because of the above, our study was conducted in a health facility where work non-frontline HCWs, all with the aim of contributing to a better understanding of the impact and consequences of COVID-19 on the mental health of the above mentioned population.

The socio-descriptive characteristics of the respondents of our study indicate that there were more women (95.6%). The average age of all respondents was 40.10 + 11.4 years, and the largest percentage of respondents 77 (55.8%) belonged to the age group of 20 – 39 years. Ninety-one respondents (66%) were married and had university education. Forty-nine respondents (35.5%) had less than 10 years of work experience, and 94 respondents (68.1%) worked in shifts. Health workers (doctors, nurses) made up to 95.7% of respondents, 1.4% did not answer and the other 3% of respondents were technical and administrative workers. Eighty-seven respondents (63.04%) were vaccinated against COVID-19.

An administrative cross-sectional survey was conducted by Osaka local government from May 27, to July 23, 2020. All 1269 HCWs (1060 non-frontline, 209 frontline) from three hospitals in Osaka participated in the survey. The majority of the respondents (44%) were 30 – 49 years of age, (75%) female, (7%) and (55%) physicians and nurses and 610 (48%) had a career length > 10 years. Socio-descriptive characteristics of the respondents in this study are similar to ours, except for the length of work experience. The majority of respondents in this study were without depressive symptoms 1088 (86%), while 181 (14%) exhibited depressive symptoms (PHQ-9 > 10) (5). In our study, in 2021, 97 (70.30%) respondents were without symptoms and 41 (29.7%) had symptoms from subclinical to severe depression form.

The cross-sectional study was conducted between May 1, 2021 and August 31, 2021. Participants were psychiatric HCWs working at the Department of Psychological Medicine, University Malaya Medical Centre (UMMC). This online survey was completed by 177 (132 non-frontline, 41 frontline) HCWs. The mean age of the respondents was 36.5 years old (SD = 8.1). Most respondents were female, married, doctors, nurses and 5% of respondents were administrative staff members. More than four-fifths of the respondents received their COVID-19 vaccination. These data correspond to the results of our research. Depressive symptoms (HADS > 8) were reported by 29 psychiatric HCWs (16.7%). Respondents who were experiencing financial hardship were unvaccinated and those who had a shorter duration of service in the psychiatric department had a higher level of depressive symptoms (6). In our research, no connection was established between the socio-descriptive characteristics respondents and the increased level of depressive symptoms.

A comparative cross-sectional study was conducted in two government hospitals managing COVID-19-related cases in Kelantan, Malaysia from May to July 2020, in which 306 healthcare providers (146 non-frontline, 160 frontline) participated. The majority of the healthcare providers were, like in our study, female 141 (88.1%), had diploma education 134 (83.8%) and were married 133 (83.1). But unlike our respondents, they did not work in shifts. The level of depressive symptoms (HADS score > 8) was 27.5% for the frontline healthcare providers and 37.7% for the non-frontline healthcare providers. The mean depressive symptoms score for the non-frontline healthcare providers was 0.75 points higher than that of frontline healthcare providers after adjusting gender, duration of employment and social support (7).

One of the first repeated multi country analysis of the mental wellbeing of medical doctors (n = 5,275) was conducted in Catalonia, Italy and UK at two time points during the COVID-19 pandemic (June 2020 and Novembar/Decembar 2020) in order to understand the prevalence of anxiety and depression, as well as associated risk factors. Rate of depression were highest in Italy (20.1%), second highest in Catalonia (17.4%) and lowest in the UK (13.7%). Across all countries, higher risk of anxiety and depression symptoms were found among women, individuals below 60 years old, those felling vulnerable/exposed at work, and those reporting normal/below-normal health (8).

In a healthcare setting in Oman, a cross-sectional study was conducted during COVID-19 pandemic, from April 8 to 17, 2020, in which a mental health status of 1,139 healthcare workers (574 frontline) and (565 non-frontline) was assessed. Healthcare workers reported to have depression (32.3%), anxiety (34.1%), stress and insomnia (23.8% and 18.5%). No significant differences in depression status were found between the frontline and non-frontline groups (9).

Between March 27 and March 31, 2020 in Italy, during COVID-19 pandemic, a cross-sectional study was conducted in healthcare workers to assess mental health outcomes (PTSS, depression, anxiety, insomnia, perceived stress). Fifty-two point five seven percent of frontline and 27.35% of second-line HCWs were included in study. Results are in line with previous reports from China, confirming a substantial proportion of mental health issues, particularly among young women and frontline HCWs (10).

A scoping review regarding mental healthcare consequences for HCWs found that high number of depression symptoms and anxiety was present at HCWs. Further, there were differences in symptoms by sex, age, and HCW role, with female, younger-age, frontline workers, and non-physician workers being affected more than other subgroups (11).

In the period from July 25 to August 25, 2021, a survey was conducted among primary care health workers from Sarajevo canton and other cantons of Bosnia and Herzegovina. The results of this study confirmed the existence of increased stress, anxiety, depression and fear among HCWs. A great influence on the mental health of employees was working with some of colleagues who had had a more severe form of COVID-19 (70%), and one of most significant stressors that influenced HCWs mental health was the death of a colleague during COVID-19 pandemic (24%) (12).

Survey conducted about characteristics of work-related COVID-19 in Croatian HCWs (between May 1, 2020 and November 12, 2020) suggest that this disease is most common in hospital nurses, laboratory technicians and takes a mild form (13).

During the COVID-19 outbreak in Serbia, a study was conducted with the aim to assess the impact of outbreak-related information and public trust in the health system and preventive measures in 2020 on the levels of anxiety and depression in education, army and healthcare professionals. Among healthcare workers, average level of anxiety and the frequency of perceiving outbreak-related information available in public media as disturbing were higher compared to the group of army professionals. The lack of public trust was associated with higher levels of depression (14).

Between April 18, and May 24, 2020, an international cross-sectional study was conducted in 41 countries, including China, UK and USA. Of all participants (2,527), 1,343 (57.1%) were aged 26 to 40 years, 2,021 (80.0%) were female, 874 (34.6%) were doctors and 1,367 (54.1%) were nurses. Factors associated with an increased likelihood of depressive symptoms were working in the UK and the US, being female, being a nurse and caring for a COVID-19 positive patient who subsequently died (15).

As we can see, many studies reported depression as one of the parameters of mental health problems among healthcare providers during the COVID-19 pandemic. The reported pooled prevalence of depression among healthcare providers in 11 studies from China, West Bengal, India and Singapore was 30.2% and 22.8% in 10 studies conducted in China and Singapore (7).

The reasons of significantly increased number of respondents without symptoms of depression in 2021 compared to 2020 in our study can be various: purchase of personal protection and its constant use, introduction of mandatory preventive measures, new treatment protocols, vaccination etc.

## Conclusion

According to the presented results, a significantly smaller number of employees had symptoms of depression. Despite the duration of the pandemic, there was a decrease in the average prevalence of depressive symptoms among employees.

Based on all of the above, we can conclude that mental health problems in the form of depressive symptoms are also present in the non-frontline healthcare workers. In some studies, the connection between the increased level of depressive symptoms and certain socio-descriptive characteristics of this population of respondents was determined. In our opinion, the obtained results indicate the need for further detailed research on the impact of COVID-19 on the mental health of non-frontline healthcare workers and the possible connection of the socio-descriptive characteristics of respondents with more frequent occurrence of depressive symptoms.

**References**


1. Outhoff K. Depression in doctors: A bitter pill to swallow. South African Family Practice 2019; 61(1): S11-S14. [CrossRef]
2. Bulut A. The Prevalence of Chronic Fatigue Syndrome in Emergency Healthcare Professionals and the Associated Factors. International Journal of Caring Sciences 2018;11(2): 868
3. Johns G, Samuel V, Freemantle L, Lewis J, Waddington L. The global prevalence of depression and anxiety among doctors during the covid-19 pandemic: Systematic review and meta-analysis, Journal of Affective Disorders 298 2020; 431-41. [CrossRef] [PubMed]
4. Peng R, Zhou W, Zhou D, Chu M, Ling L. The Mediating Health and its Associated Factors: Evidence From Chinese Healthcare Workers During the COVID-19 Pandemic. Front Psychiatry 12: 665992. [CrossRef] [PubMed]
5. Takada H, Ae R, Ogawa M, Kagomoto T. Depression prevention in healthcare workers during the COVID-19 pandemic. Occupational Medicine 2022; 72; 207-14. [CrossRef] [PubMed]
6. Kumar M, Kumar N, Francis B, Hashim AH, Zainal NZ, Rashid RA, GuanNg C, et al. Prevalence of Anxiety and Depression among Psychiatric Healthcare Workers during the COVID-19 Pandemic: A Malaysian Perspective. Healthcare 2022; 10: 532. [CrossRef] [PubMed]
7. Norhayati MN, Yusof RC, Azman MY. Depressive symptoms among frontline and non-frontline healthcare providers in response to the COVID-19 pandemic in Kelantan, Malaysia: A cross sectional study.PLoS ONE 16(8):e0256932. [CrossRef] [PubMed]
8. Quintana-Domeque C , Lee I, Zhang A, Proto E, Battisti M, Ho A. Anxiety and depression among medical doctors in Catalonia, Italy, and the UK during the COVID-19 pandemic. PLoS ONE 16(11): e0259213. [CrossRef] [PubMed]
9. Alshekaill M, Hassan W, Al Said N, Al Sulaimani F, Jayapal SK, Al-Mawaliet A, et al. Factors associated with mental health outcomes across healthcare settings in Oman during COVID-19: frontline versus non-frontline healthcare workers. BMJ Open 2020; 10: e042030. [CrossRef] [PubMed]
10. Rossi R, Socci V, Pacitti F, Di Lorenzo G, Di Marco A, Siracusano A, et al. Mental Health Outcomes Among Frontline and Second-Line Health Care Workers During the Coronavirus Disease 2019 (COVID-19) Pandemic in Italy. JAMA Network Open 2020; 3(5): e201,0185. [CrossRef] [PubMed]
11. Moitra M, Rahman M, Collins PY, Gohar F, Weaver M, Kinuthia J, et al. Mental Health Consequences for Healthcare Workers During the COVID-19 Pandemic: A Scoping Review to Draw Lessons for LMICs. Front. Psychiatry 12: 602614. [CrossRef] [PubMed]
12. Durmišević D, Hrustemović Dž, Salihagić S, Savić N. The COVID-19 Influence on Mental Health of Healthcare Employees in the Primary Health Care. PHARM-HEALTH 2: 77-85.
13. Žaja R, Kerner I, Macan J, Milošević M. Characteristics of work-related COVID-19 in Croatian healthcare workers: a preliminary report. 2021; 72(1): 36-41. [CrossRef] [PubMed]
14. Marković I, Nikolovski S, Milojević S, Živković D, Knežević S, Mitrović A et al. Public Trust and media influence on anxiety and depression levels among skilled workers during the COVID-19 outbreak in Serbia. Vojnosanit Pregl 2020; 77(11): 1201-9. [CrossRef]
15. Khajuria A, Tomaszewski W, Liu W, hua Chen J, Mehidan R, Fleming S, et al. Workplace factors associated with mental health of healthcare workers during the COVID-19 pandemic: an international cross-sectional study. BMC Health Services Research (2021) 21:262. [CrossRef] [PubMed]

**Originalni rad** **UDC: 616.98:578.834]:616-051(497.11)**
**doi: 10.5633/amm.2023.0106**

# ZASTUPLJENOST DEPRESIVNIH SIMPTOMA KOD ZAPOSLENIH U ZDRAVSTVENOJ USTANOVI TERCIJARNOG TIPA U BEOGRADU TOKOM PANDEMIJE VIRUSA COVID-19

*Sonja Giljača[1], Slavica Maris[1], Milica Ranković – Janevski[2], Marko Stojanović[3]*

[1]Gradski zavod za javno zdravlje Beograd, Beograd, Srbija*
[2]Institut za neonatologiju Beograd, Srbija
[3]Instutut za javno zdravlje Niš, Niš, Srbija

Kontakt: Sonja Giljaca*
Bulevar. Despota Stefana 54a, Beograd, Srbija
E-mail: sonja.giljaca@zdravlje.org.rs

Povećano radno angažovanje tokom pandemije virusa COVID-19 sigurno je narušilo zdravlje zaposlenih u zdravstvenim ustanovama. Cilj ovoga rada jeste da se utvrde neke od posledica navedenih zdravstvenih promena. Sprovedena je panel longitudalna studija (za dva vremeska perioda: 2020. i 2021. godinu od marta do maja meseca) kod zaposlenih u Institutu za neonatologiju Beograd, primenom upitnika PHQ-9 za samoprocenu depresivnih simptoma, EQVAS za samoprocenu zdravstvenog stanja i opštim upitnikom prikupljeni su socijalni podaci ispitanika, dati deskriptivno. Ukupna vrednost skora PHQ-9 upitnika za sve zaposlene u 2020. godini iznosila je 5,54 + 4,9, a u 2021. godini 3,8 + 5,12. Zastupljenije su bile žene (95,6%), a 66,0% ispitanika bilo je u braku i univerzitetskog obrazovanja. *Acta Medica Medianae 2023;62(1): 42-49*.

***Ključne reči:*** *COVID-19, zdravstveni radnici, simptomi depresije*

**Case report** **UDC: 616.833-002:[616.98:578.834**
**doi: 10.5633/amm.2023.0107**

# COMORBIDITY OF GUILLAIN-BARRE SYNDROME AND COVID-19 INFECTION: A CASE REPORT AND A REVIEW OF THE CURRENT LITERATURE

*Radomir Damjanović[1,2], Aleksandar Stojanov[1,2], Ninoslava Simić[1,3], Andrija Jović[1,4], Dejan Popović[1,5]*

Guillain-Barre syndrome is an immunologically mediated polyradiculoneuropathy characterized by a monophasic course, with a clinical peak within 4 weeks of disease onset. There have been several reports ofGuillain-Barré syndrome, related to COVID-19, days or weeks after the onset of respiratory symptoms. In contrast to that, we describe a case of acute sensorimotor demyelinating polyradiculoneuropathy, followed by COVID-19 infection. Our patient was successfully treated with intravenous immunoglobulins while COVID-19 was treated according to the latest clinical management protocol. In our case, neuropathy symptoms showed aparainfectious profile rather than a post-infectious one, which is uncommon inGuillain-Barré syndrome. *Acta Medica Medianae 2023;62(1):50-55.*

***Key words:*** *Guillain-Barré syndrome (GBS), Coronavirus disease 2019 (COVID-19), weakness*

[1]University Clinical Center Niš, COVID hospital, Niš
[2]University Clinical Center Niš, Neurology Clinic, Niš,
[3] University Clinical Center Niš, Mental Health Protetction Center, Department for Child and Adolescent Psychiatry Niš, Serbia
[4] University Clinical Center Niš, Dermatovenerology Clinic, Niš, Serbia
[5] University Clinical Center Niš,Cardiovascular Deases Clinic, Niš, Srbija

*Contact:* Radomir Damjanović
48 Dr. Zoran Djindjića Blvd., 18000 Niš, Serbia
Tel: +381 61 44 86424
E-mail: rdamjanovic@gmail.com

## Background

The World Health Organization declared the Coronavirus disease (COVID-19) pandemic on March 11, 2020, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). From then tonow, COVID-19 has aroused great interest of the scientific public all around the world, both due to the various presentations of the disease itself and due to the growing number of data about the connection of this respiratory infection with various organ systems (1). Although the most commonly described manifestations are mainly within the respiratory and gastrointestinal systems, COVID-19 may be associated with various neurological symptoms, such as headache, syncope, anosmia and ageusia (2, 3). Severe neurological diseases associated with COVID-19, including stroke, encephalopathies, encephalitis and immune neuropathies like Guillain-Barré syndrome (GBS) have also been reported (4, 5).

GBS is an immunologically mediated polyradiculoneuropathy characterized by a monophasic course, with a clinical peak within 4 weeks of disease onset (6). There have been several reports of GBS, related to COVID-19, days or weeks after onset of respiratory symptoms (7). In contrast to that, herein we present a patient with clinical symptoms characteristic for GBS, followed by COVID-19 infection.

## Case presentation

A 36-year-old previously healthy man was admitted to the Clinic for Neurology at the University Clinical Center of Niš, Serbia, due to numbness of limbs, followed by weakness of lower limbs. The symptoms started while he was preparing for the job earlier that day. After a while, the patient also had weakness of his hands. On the admission, neurological examination showed the mild proximal weakness of upper and lower limbs, symmetrically reduced deep tendon reflexes of all four limbs and numbness of hands and foot. He had no comorbid conditions. There was no history of known respiratory or gastrointestinal infection, nor vaccination against COVID-19. According to the

protocol for admission of patients to our institution, an antigenic test for SARS Cov-2 was performed, which was negative. A standard set of biochemical analyzes was performed and elevated values of AST, ALT, and g-GT were marked off the findings. The blood count was of no clinical significance (Table 1). The next day, an MRI of the endocranium was performed and it showed reductive changes of the brain parenchyma as well as an MRI of the cervical spine,which was normal. Electrophysiological studies revealed acute sensorimotor demyelinating polyradiculoneuropathy, which, with albumin-cytologic dissociation (cerebrospinal fluid proteins 0.63 g/L) found at the cerebrospinal fluid examination, confirmed the diagnosis of GBS (Table 2).On the fourth day after admission, the patient had a fever (37.8°C) and cough, which indicated general biochemical analyzes to be performed (CRP 15 mg/L, AST 50 U/L, ALT 176 U/L, g-GT 70 U/L), as well as blood count (WBC 12.0 (10^9/L), NE 10.55 (10^9/L) (Table 1). X-ray of the chest showed inflammatory changes in the lower parts of the right and left lungs (Figure 1a).

**Table 1.** Oxygen saturation, haematological and biochemical parameters of our patient on admission, ICU admission and control analyses two weeks after onset of symptoms (the tenth day of treatment at the ICU).

| | On admission | ICU admission | Control (10th day at the ICU) | Units and normal range |
|---|---|---|---|---|
| SpO2 | 97% | 90% | 98% | |
| WBC | 8.7 | 15.8 | 18.6 | Cells/L (4.0-9.0*10^9) |
| Lymphocytes | 2.03 | 1.86 | 0.78 | Cells/L (1.0-4.0*10^9) |
| Platelets | 846 | 604 | 604 | Cells/L (120-380*10^9) |
| RBC | 5.02 | 4.81 | 4.20 | Cells/L (4.30-5.80*10^12) |
| Hemoglobin | 135 | 136 | 124 | g/L (120-180) |
| Hematocrit | 0.430 | 0.435 | 0.365 | L/L (0.410-0.560) |
| CRP | 8.9 | 138.2 | 31.8 | mg/L (0.0-5.0) |
| GGT | 55 | 78 | 164 | U/L (0-55) |
| AST | 35 | 42 | 135 | U/L (10-37) |
| ALT | 40 | 90 | 230 | U/L (10-42) |
| Albumin | 44 | 31 | 28 | g/L (35-52) |
| D-dimer | 230 | 704 | 560 | ng/mL (<250) |

**Table 2.** Motor nerve conduction studies on upper and lower extremities

| Nerve | Distal latency (ms) | CMAP amplitude (mV) | Conduction Velocity (m/s) |
|---|---|---|---|
| Median, L | 6.40 | 3.8 | 35.50 |
| Ulnar, L | 5.70 | 5.8 | 44.60 |
| Median, R | 7.20 | 3.7 | 37.40 |
| Ulnar, R | 5.50 | 5.4 | 40.10 |
| Peroneal, L | 12.75 | 1.2[a] | 26.90 |
| Tibial, L | Absent | Absent | Absent |
| Peroneal, R | 11.50 | 1.3[a] | 26.30 |
| Tibial, R | Absent | Absent | Absent |

a–temporal dispersion and conduction block

According to the indication of the Infectologist, a PCR test for SARS Cov-2 from a nasopharyngeal swab was done and found positive. The patient was transferred to the COVID-19 Department of the University ClinicalCenter in Niš, where he was connected to oxygen support (5L/min) due to oxygen saturation (SpO2) valueof90%. Further, there was a worsening of his neurologic symptoms reflected in examination findings of flaccid, areflexicquadriparesis, speech and swallowing difficulties.

The sixth day after admission, further deterioration
of respiratory function due to bulbar weakness occurred.

The patient was transferred to the Intensive Care Unit (ICU), intubated and connected to mechanical respiratory support (Mechanical ventilation–MV) with continuous analgesia with midazolam and remifentanil. Meanwhile, he was managed with five cycles of intravenous human immunoglobulins (0.6 g/kg/day). The value of C-reactive protein rose and blood count also worsened in terms of leukocytosis and neutrophilia.

On the twelfth day after admission, MV support (CPAP, FiO2 = 40%, SpO2 = 97%), with continuous infusion of remifentanil was resumed. He opened his eyes to the call and verbal contact was also possible.

Two days after (the fourteenth day after admission), the patient was disconnected from the MV, extubated and connected to oxygen support of 10L/min (SpO2 = 97%).

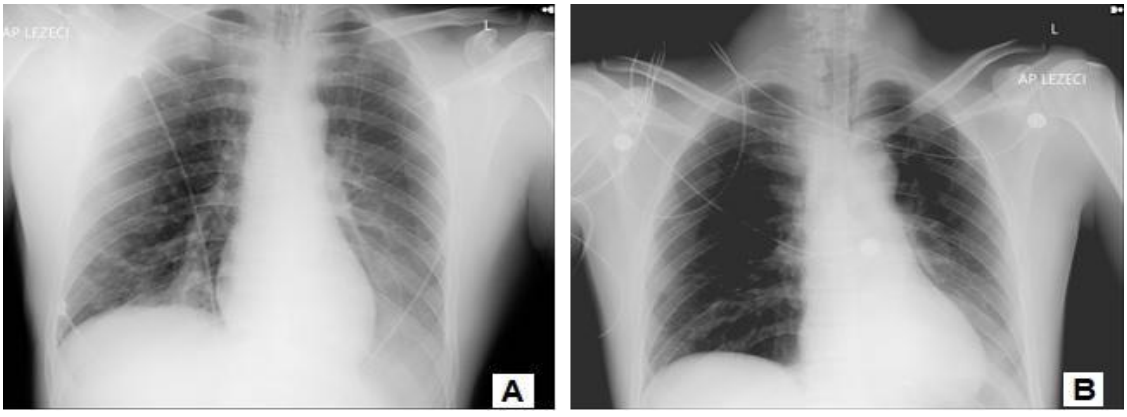



**Figure 1.** X-ray of the chest on the fourth day (A) and four weeks after admission (B)

On the twenty-first day after admission, the patient was in good general condition, with SpO2 = 98% and no oxygen support. He became SARS Cov-2 PCR negative, and the next day, he was discharged with a suggested physical rehabilitation program. Improvement of neurological findings was identified—mild quadriparesis with generally reduced muscle tendon reflexes and discrete bulbar symptomatology. During his hospitalization at the Covid-19 Department and Covid-19 Intensive Care Unit, the patient was treated according to the latest clinical management protocol for patients with Covid-19 infection (oxygen support, antiviral therapy, low molecular weight heparin, corticosteroid, gastroprotective and vitamin therapy). At the follow-up performed 30 days after discharge, the presented neurological examination showed difficulty with balance and coordination, while walking was possible only with support or mobility aid. Control chest X-ray four weeks after admission shows partial radiographic resolution of the lung opacities (Figure 1b).

## Discussion and review of the literature

COVID-19 is caused by SARS-CoV-2, a single stranded RNA beta coronavirus. Numerous neurological manifestations have been associated with SARS-CoV-2 infection, such as acute cerebrovascular diseases, seizures, meningitis, encephalitis and skeletal muscle involvement (8,9). A study conducted in the Chinese population revealed that 36.4% of patients have some neurological symptoms during COVID-19 infection (10). There are case reports which describe GBS after COVID-19 infection or after vaccination against the SARS-CoV-2 virus (11 – 14). More accurately, GBS has been reported in less than 0.5% of SARS-CoV-2 infections (15). In this study, we reported a patient with GBS in which neurological symptoms (weakness, tingling and numbness of limbs, reduced deep tendon reflexes…) preceded symptoms of COVID-19 infection (fever, cough). Filosto et al. associated Covid-19 with the development of both postinfectious and parainfectious GBS (16). In our case, neuropathy symptoms showed a parainfectious profile rather than a postinfectious one, which is uncommon in GBS. Also, our patient does not have any history of an infection or vaccination a few weeks before the onset of symptoms. A review of the literature showed that the time from onset of the COVID-19 symptoms to the clinical GBS manifestations ranged between 3 and 28 days (in some patients, the onset of GBS preceded by a few days the first manifestations of COVID-19) (17). SARS-CoV-2 infection in its most severe form includes three stages: early infection, pneumonia and hyperinflammatory response (16). According to Siddiqi and Mehra, active viraemia occurs in the first two stages (18). Since the incubation period of SARS-CoV-2 is up to 14 days, it is difficult to determine at what stage GBS occurs. Searching through the literature, we found that neuropathy symptoms preceding Covid-19 were a rarity, although the parainfectous profile of GBS associated with COVID-19 was described in some papers (19, 20). Even in those papers in which neuropathy symptoms preceding COVID-19 symptoms,favourable outcome of GBSwas a rarity. A group of authors from the UK, interestingly, findno epidemiological or phenotypic clues of SARS-CoV-2 being causative of GBS, although they donot entirely rule out the possibility of that link (21). In addition, they have found that the intubation was more frequent in the Covid-19-related GBS, likely related to respiratory involvement. Our case (intubation on sixth day after admission), excellently depicts these findings.The same authors showed no significant homology of SARS-CoV-2 genetic or protein structure and human protein structures, which indicates that molecular mimicry is less likely. Mary et al. noted that posttranslational modification in viral capsid by the host cells could occur, which implicates the generation of immunogenic surface glicomolecules (22). We need more research to examine precisely this causal relationship. A group of authors from Canada described through a systematic review patients with GBS and concomitant Covid-19, following the Preferred reporting items for systematic reviews and meta-analysis statement (PRISMA) (23). They identified 1,450 records and 81 studies, and after applying exclusion criteria, a total number of patients was 99 cases, after PCR or serologic testing. A high level of diagnostic certainty for GBS (Brighton Criteria 1 or 2) fulfilled 77 patients. In those groups, the sensorimotor variant was reported in 64 cases, Miller-Fisher syndrome in 9, and other variants in the remainder. Authors marked male predominance (male to female ratio 2.5:1), which, according to previously reported risk factors for severe Covid-19 outcome, including increased age and male gender, could reflect the male predominance in this series of patients. AIDP was the most frequent electrophysiological profile in Covid-19-related GBS, which also expresses data reported by Dotes etal. (24). The treatment of GBS includes either IVIG or plasma exchange, despite still unclear mechanisms of their action (25). Although both treatment options have shown to be equally effective, a stronger effect could be obtained if treatment is administered within two weeks after disease onset (26–28).

## Conclusion

Covid-19 is a multisystem disease that causes not only respiratory symptoms but also the neurologic ones. The concurrence of COVID-19 with GBS can increase the likelihood of neuromuscular respiratory failure, autonomic dysfunction, and other life-threatening symptoms. Given the growing number of reported cases of COVID-19-related GBS and its association with a severe disease course, it is important to emphasise the significance of early diagnosis and treatment of GBS in COVID-19 patients. In addition, no less effort should be made to elucidate the causal mechanism between the two diseases.

## References


1. Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, et al. Organ-specific manifestations of COVID-19 infection. Clin Exp Med 2020;20(4):493-506. [CrossRef][PubMed]
2. Suri V, Pandey S, Singh J, Jena A. Acute-onset chronic inflammatory demyelinating polyneuropathy after COVID-19 infection and subsequent ChAdOx1 nCoV-19 vaccination. BMJ Case Rep 2021;14(10):e245816. [CrossRef][PubMed]
3. Needham EJ, Chou SH, Coles AJ, Menon DK. Neurological implications of COVID-19 infections. Neurocrit Care 2020;32:667–671. [CrossRef][PubMed]
4. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol 2021;268:1133–70. [CrossRef][PubMed]
5. Caress JB, Castoro RJ, Simmons Z, Scelsa SN, Lewis RA, Ahlawat A, et al. COVID-19–associated Guillain-Barré syndrome: the early pandemic experience. Muscle Nerve 2020;62:485–91. [CrossRef][PubMed]
6. Van der Meché FG, Van Doorn PA, Meulstee J, Jennekens FG; GBS-consensus group of the Dutch Neuromuscular Research Support Centre. Diagnostic and classification criteria for the Guillain-Barré syndrome. Eur Neurol 2001;45:133–9. [CrossRef][PubMed]
7. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, et al. Neurological manifestations of COVID-19: a systematic review. Crit Care 2020;24:421. [CrossRef][PubMed]
8. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683–9. [CrossRef][PubMed]
9. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Rev Neurol 2020;70:311–22. [CrossRef][PubMed]
10. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):683–90. [CrossRef][PubMed]
11. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci 2020;76:233-235. [CrossRef][PubMed]
12. Hirayama T, Hongo Y, Kaida K, Kano O. Guillain-Barré syndrome after COVID-19 in Japan. BMJ Case Rep 2020;13(10):e239218. [CrossRef][PubMed]
13. Hasan T, Khan M, Khan F, Hamza G. Case of Guillain-Barré syndrome following COVID-19 vaccine. BMJ Case Rep 2021;14(6):e243629. [CrossRef][PubMed]
14. Bouattour N, Hdiji O, Sakka S, Fakhfakh E, Moalla K, Daoud S, et al. Guillain-Barré syndrome following the first dose of Pfizer-BioNTech COVID-19 vaccine: case report and review of reported cases. Neurol Sci 2022;43(2):755-761. [CrossRef][PubMed]
15. Guilmot A, Maldonado Slootjes S, Sellimi A, Bronchain M, Henseeuw B, Belkhir L, et al. Immune-mediated neurological syndromes in SARSCoV-2-infected patients. J Neurol 2021;268:751-7. [CrossRef][PubMed]
16. Filosto M, Cotti Piccinelli S, Gazzina S, Foresti C, Frigeni B, Servalli MC, et al. J Neurol Neurosurg Psychiatry 2021;92(7):751-756. [CrossRef][PubMed]
17. Zito A, Alfonsi E, Franciotta D, Todisco M, Gastaldi M, Cotta Ramusino M, et al. COVID-19 and Guillain-Barré Syndrome: A Case Report and Review of Literature. Front Neurol 2020;11:909. [CrossRef][PubMed]
18. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. J Heart Lung Transplant 2020;39:405–7. [CrossRef][PubMed]
19. Abolmaali M, Heidari M, Zeinali M, Moghaddam P, Ramezani Ghamsari M, Jamshidi Makiani M, et al. Guillain-Barré syndrome as a parainfectious manifestation of SARS-CoV-2 infection: A case series. J Clin Neurosci 2021;83:119-122. [CrossRef][PubMed]
20. Kajumba MM, Kolls BJ, Koltai DC, Kaddumukasa M, Kaddumukasa M, Laskowitz DT. COVID-19-Associated Guillain-Barre Syndrome: Atypical Para-infectious Profile, Symptom Overlap, and Increased Risk of Severe Neurological Complications. SN Compr Clin Med 2020;21:1-13. [CrossRef][PubMed]
21. Meyer Sauteur PM, Huizinga R, Tio-Gillen AP, Roodbol J, Hoogenboezem T, Jacobs E, et al. Mycoplasma pneumoniae triggering the Guillain-Barré syndrome: a case-control study. Ann Neurol 2016;80:566–80. [CrossRef][PubMed]
22. Mary B, Maurya S, Arumugam S, Kumar V, Jayandharan GR. Post-translational modifications in capsid proteins of recombinant adeno-associated virus (AAV) 1-rh10 serotypes. FEBS J 2019;286(24):4964-4981. [CrossRef][PubMed]
23. Aladawi M, Elfil M, Abu-Esheh B, Abu Jazar D, Armouti A, Bayoumi A, et al. Guillain Barre Syndrome as a Complication of COVID-19: A Systematic Review. Can J Neurol Sci 2022;49(1):38-48. [CrossRef][PubMed]
24. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological complications during treatment of middle east respiratory syndrome. J Clin Neurol 2017;13:227–33. [CrossRef][PubMed]
25. Kaeley N, Kabi A, Pillai A, Shankar T, Ameena S. Post-COVID-19 Guillain-Barré Syndrome: A Case Report With Literature Review. Cureus 2022;14(1):e21246. [CrossRef][PubMed]
26. Chevret S, Hughes RA, Annane D: Plasma exchange for Guillain-Barré syndrome. Cochrane Database Syst Rev 2017;2:CD001798. [CrossRef][PubMed]
27. Plasmapheresis and acute Guillain-Barré syndrome. The Guillain-Barré syndrome Study Group. Neurology 1985;35(8):1096-104. [CrossRef][PubMed]
28. Appropriate number of plasma exchanges in Guillain-Barré syndrome. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Ann Neurol 1997;41:298-306. [CrossRef][PubMed]

**Pregledni rad** **UDC: 616.833- 002:[616.98:578.834**
**doi: 10.5633/amm.2023.0107**

# KOMORBIDITET SINDROMA GUILLAIN–BARRE I INFEKCIJE VIRUSOM COVID-19 – PRIKAZ SLUČAJA I PREGLED LITERATURE

*Radomir Damjanović[1,2], Aleksandar Stojanov[1,2], Ninoslava Simić[1,3], Andrija Jović[1,4], Dejan Popović[1,5]*

[1] Univerzitetski klinički centar Niš, COVID bolnica, Niš, Srbija
[2] Univerzitetski klinički centar Niš, Klinika za neurologiju, Niš, Srbija
[3] Univerzitetski klinički centar Niš, Centar za zaštitu mentalnog zdravlja, Departman za dečiju i adolescentsku psihijatriju, Niš, Srbija
[4] Univerzitetski klinički centar Niš, Klinika za dermatovenerologiju, Niš, Srbija
[5] Univerzitetski klinički centar Niš, Klinika za kardiovaskularne bolesti, Niš, Srbija

*Kontakt:* Radomir Damjanović
48 Dr. Zoran Djindjića Blvd., 18000 Niš, Serbia
Tel: +381 61 44 86424
E-mail: rdamjanovic@gmail.com

GBS je imunološki posredovana poliradikuloneuropatija koju karakteriše monofazni tok, a klinički pik dostiže unutar četiri nedelje od početka bolesti. Do sada je opisano nekoliko slučajeva GBS-a povezanog sa infekcijom izazvanom virusom COVID-19, nekoliko dana ili nedelja nakon početka respiratornih tegoba. Za razliku od toga, mi opisujemo slučaj akutne senzomotorne poliradikuloneuropatije, koja je praćena infekcijom izazvanom virusom COVID-19. Naš bolesnik uspešno je lečen intravenskim imunoglobulinima, dok je COVID-19 tretiran prema poslednjem kliničkom protokolu za lečenje bolesti izazvane ovim virusom. U ovom prikazu simptomi neuropatije imaju parainfektivni, a ne postinfektivni karakter, što je neuobičajeno za GBS. *Acta Medica Medianae 2023;62(1): 50-55.*

***Ključne reči:*** *Guillain–Barré sindrom (GBS), COVID-19 virus, mišićna slabost*

**Review article**

**UDC: 615.212.015:616-053.2**
**doi: 10.5633/amm.2023.0108**

# INFLUENCE OF PATIENT-RELATED FACTORS ON FENTANYL PHARMACOKINETICS IN CHILDREN

*Jelena Lilić[1], Vesna Marjanović[1,2], Ivana Budić[1,2], Ivana Mitić[1], Maja Zečević[3], Gorana Nedin-Ranković[4]*

Fentanyl is commonly used in a hospital setting for achieving sedation and analgesia in children. The aim of this review was to clarify the pharmacokinetic aspects of the intravenous fentanyl use in children.

In general, drug pharmacokinetics is altered in children at all levels, but there is a significant variability between children of different age, as well. After intravenous drug administration, the difficulties related to oral route and gastrointestinal absorption are avoided. Changes in drug distribution, metabolism and elimination are due to differences in the volume of extracellular and total body water compartments, organ perfusion, acid-base balance, membrane permeability and cardiac, liver and kidney function. Nevertheless, the greatest impact is attributed to the body size.

Children are the most vulnerable population. Therefore, it is of extreme importance to dose fentanyl safely, but efficiently as well. Common weight-based dosing strategy may not always be the optimal, due to numerous covariates of the fentanyl pharmacokinetics. In a certain clinical setting, beside hidden factors such as genetics, age and gestational age, obesity and potential drug interactions are the first to be taken into account. *Acta Medica Medianae 2023;62(1):56-61.*

***Key words:*** *fentanyl, pharmacokinetic, children*

[1] University Clinical Center Niš, Anesthesiology and Intensive Care Clinic, Niš, Serbia
[2] University of Niš, Medical Faculty, Niš, Serbia
[3] University Clinical Center Niš, Pediatric Surgery and Orthopedics Clinic, Niš, Serbia
[4] University of Nis, Medical faculty, Department Pharmacology with Toxicology, Niš, Serbia

*Contact:* Jelena Lilić
48 Dr Zoran Djindjić Blvd., 18000 Niš, Serbia
E-mail: jjeca8451@gmail.com

## Introduction

The importance of pain management lies in the fact that it is one of the most common acute symptoms and, therefore, one of the most common complaints. Primarily, it protects the organism from further damage, but this cannot be related to all types of pain. On the other hand, irrespectively on the type of pain, it affects the patient's quality of life. Managing pain in children is of the same importance, even though, historically, it was thought that the nervous system in neonates was not developed enough to sense pain. When the opiophobia is added into concern, for long, opioid analgesics were avoided in the pediatric population.

Nociceptive circuits are not like other sensory networks, dependant on external stimulation, so infants born even before 35 weeks of gestation have nervous system functional enough to sense pain stimuli (1). Nevertheless, it undergoes postnatal maturation, both peripherally and centrally. Therefore, its functionality greatly depends on the child's age. These changes also involve the endogenous opioid system. In adults, pain perception becomes modulated by mu-opioid receptors (MOR) activation, unlike in the younger age, so this type of signaling is stronger in children. Opioidergic stimulation, by endogenous or exogenous MOR agonists, has an important role in neuronal migration, differentiation and maturation (2). It is supposed that this process includes the development of supraspinal control over the spinal activity. The reaction of neonates to pain greatly differs form the one in the adults, and is described as either exaggerated or inappropriate, due to high activity of excitatory and low activity of the inhibitory neurons in the dorsal horns. The MOR is expressed in neonates both superficially and in deeper laminas of the dorsal horns. The later ones disappear with

age. These differences cause the age-dependent variability in sensitivity and selectivity of the opioid pharmacological actions (3, 4). Increased sensitivity may be explained by the expression of MOR in both A and C-fibres nociceptors, while they are, with age, confined to solely C-fibres (5).

Fentanyl is commonly used in a hospital setting for achieving sedation and analgesia in children. There is a wide range of fentanyl formulations, including parenteral, transmucosal and transdermal preparations. In the pediatric population, especially in the intensive care units, the preferred route of administration is parenteral (6). Therefore, the aim of this review is to clarify the pharmacokinetic aspects of the intravenous fentanyl use in children.

**Fentanyl pharmacokinetics**

As a relatively new opioid analgesic, introduced in 1963, the main difference from the previously used opioids was its lipophilicity. Greater lipophilicity provided faster absorption and greater distribution into brain tissue, leading to quicker and stronger effects, more than 100 times greater in comparison to morphine. It is primarily a MOR agonist, while it has lower affinity for kappa- and delta-opioid receptors. The half-life of the distribution into the central nervous system is 5 – 6 min, predominantly via passive diffusion enabled by its physical characteristics, but also by active transport. Primary distribution involves highly vascularized tissues, while during redistribution it may accumulate in muscle and adipose tissue, causing long elimination half-life (estimated at 3 – 8h). As a consequence of these pharmacokinetic properties, its pharmacological effects depend on the way of administration, bolus injection or continuous infusion (6, 7). Prolonged continuous infusion of fentanyl increases the context-sensitive half-time (8). Only 20% of fentanyl dose is available to distribution into tissues, due to high affinity for binding to plasma proteins. It is metabolized in liver by CYP3A4/5, therefore the inducers/inhibitors of this izoenzyme may affect the drug concentrations. Fentanyl metabolites are mostly excreted renally (6, 7).

**Factors influencing fentanyl pharmacokinetics in children**

In general, drug pharmacokinetics is altered in children at all levels, but there is a significant variability between children of different age, as well. After intravenous drug administration, the difficulties related to oral route and gastrointestinal absorption are avoided. Changes in drug distribution, metabolism and elimination are due to differences in the volume of extracellular and total body water compartments, organ perfusion, acid-base balance, membrane permeability and cardiac, liver and kidney function (9). Nevertheless, the greatest impact is attributed to the body size (10). The importance of elucidating factors affecting fentanyl pharmacokinetics in children lies in its relatively narrow therapeutic window. Concentrations inducing mild analgesia are estimated at 0.6 ng/ml, while 1.2-3 ng/ml concentrations are associated with substantial analgesia (11).

Both the volume of distribution (Vd) and fentanyl clearance decrease with age. Previous studies reported a wide range of Vd and clearance values in different age group. They are not all comparable due to different clinical settings and ways of drug administration, but their values gradually decreased with age in all the studies (12 – 18). The volume of distribution decreases form around 6 l/kg in neonates and infants to 2 - 4 l/kg in children above the age of 12. The clearance of fentanyl approaches the adult level after the age of 13 (12). Age-dependency is explained by higher metabolic elimination (larger liver volume and more intense blood flow through liver), but also by age-related differences in liver enzymes activity and fentanyl binding to proteins (8, 12). In preterm neonates, Vd was found to be higher than in at-term neonates, which is attributed to differences in body water/fat ratio and albuminemia (8). Clearance is lower in preterm neonates, increasing gradually after birth until it stabilizes after 10 – 15 days, emphasizing the importance of gestational age for the maturation of enzymatic activity (19).

Fentanyl is a highly lipophilic drug. Due to its distribution into adipose tissue, weight based dosing may be problematic and cause overdosage. Obesity is associated with higher Vd and lower weight-normalized clearance of fentanyl, but higher overall clearance. With similar weight-adjusted doses, higher concentrations were achieved in obese, but it took longer time to achieve steady state due to longer drug half-life. The differences between obese and non-obese are more prominent in older children. In these cases, the dosing strategy, without weight adjustments, resulted in similar steady state concentrations, but still with prolonged time to achieve maximum in the obese. The clearance increase is less than proportional to the body weight, due to non-weight-dependent clearance mechanisms (protein binding, intrinsic clearance). For lipophilic drugs such as fentanyl, some have proposed to use total body weight for loading doses and ideal body weight for maintenance doses. Therefore, the obese children would need lower doses adjusted for weight (12, 20). The same weight-based fentanyl dosing may not be optimal for each age—in an twice older infant with the same weight, equal dosing would lead to more than twice lower fentanyl concentration (10).

In adults, factors affecting liver function were confirmed to impact achieved fentanyl concentrations since CYP3A4/5 mediated metabolism is the primary route of fentanyl elimination (18). In children, this has not be confirmed due to low number of cases, but there were individual case reports or small studies describing the potential impact (8). It is assumed

that half of the adult's level of enzyme activity is reached at the age of 6-12 months (10). Increased intraabdominal pressure, present after abdominal surgery, decreases liver perfusion, and, therefore, diminishes drug clearance. Known CYP3A4 inhibitors, such as azole antifungal drugs, may increase fentanyl levels and risk of toxicity (18). The interactions confirmed in children leading to increased fentanyl metabolism include CYP3A4/5 inducers fosphenytoin and phenobarbital, often used in critically ill children (11). Genetic factors are described as a cause of interindividual variability in fentanyl metabolism, in children as well. Intermediate and poor metabolism, in carriers of CYP3A5*3 and CYP3A5*6 alleles (heterozygous and homozygous, respectively), were associated with significant decrease in fentanyl clearance (21). Other possible SNPs, confirmed in adult patients, include CYP2D6*9, CYP2D6*29 and CYP3A4*1B (22). Decreased fentanyl metabolism and increased availability may also be present in patients with decreased liver function, the state characterized by hypoalbuminemia, as well.

The relevance of albuminemia is questionable. Even though fentanyl has high affinity for albumin, not many studies have confirmed the influence of hypoalbuminemia, such as in burn patients. In children, neither liver nor renal failure were associated with changes in fentanyl pharmacokinetics (8).

Genetic and ontogenetic factors have strong impact on fentanyl pharmacokinetics, as previously described CYP3A4 polymorphisms. Fentanyl is a substrate of P-glycoprotein. This efflux transporter is involved in limiting the distribution of morphine and other opioids, besides fentanyl, to brain (9). The efflux via P-glycoprotein expressed at blood-brain barrier is lower in newborns leading to higher drug concentrations in the brain tissue and an increased sensitivity to opioids. This may last for 3 – 6 months, when the density of P-glycoprotein increases to the adult level (2, 23). Genetic variability of ABCB1 gens (rs1045642 AA genotype) was associated with lower fentanyl dose needed, due to low activity of the transporter (24).

**Critically ill children**

Pharmacokinetic analysis in critically ill children on mechanical ventilation has shown age-dependant variability in Vd, clearance and elimination half-life, similar to the other studies, but with greater interindividual variability (16). There is still a large percentage of unexplained variability in pharmacokinetic factors. In adult critically ill patients, the highest influence was in the following factors: liver disease, congestive heart failure and weight (11). The rate of fentanyl liver extraction has not been studied. On the other hand, commonly used drugs in critically ill children, such as anticonvulsive drugs phenobarbital, phenytoin, and its prodrug fosphenytoin, induce fentanyl metabolism in the liver, by inducing the transcription of CYP3A4/5 genes. The effect of co-administration of these drugs and metabolism induction is the most prominent after the end of fentanyl infusion, decreasing the half-life up to 30% and accelerating the drug clearance from the central nervous system. These facts imply the need of higher doses or infusion rates in patients administered CYP3A4/5 inducers, but extremely cautiously because of the high interindividual variability in fentanyl pharmacokinetics. At some instances, the achievement of lower steady-state concentrations may be even beneficial, when only moderate analgesia is needed, because of the lower risk of depressant adverse effects. On the contrary, depressant fentanyl effect is desirable in patients with severe lung disease or ventilator asynchrony, if used to facilitate mechanical ventilation (11). We can assume numerous other factors that may affect fentanyl pharmacokinetics in these circumstances, but up today, there are no valid evidence. They might include other inducers and inhibitors of CYP3A4/5 enzyme, other drug interactions involving drug transporters and plasma proteins, pharmacogenomics, vasopressor use, hepatic disease and intraabdominal pressure (11).

During cardiovascular procedures involving extracorporeal circulation, numerous factors change the pharmacokinetics of intravenous fentanyl. Hemodilution increases Vd, affects protein binding and increases elimination half-life. Liver function, both enzyme activity and perfusion, is decreased due to hypothermia and changes in Vd (25). Fentanyl may also be sequestrated in lungs. Besides, drug molecules may bind to extracorporeal circuit components diminishing fentanyl availability, even up to 60 – 90% (8, 26, 27). It is supposed that the membrane oxygenator is the primary point of the drug binding, while the siliconized tubes have lesser importance. The proportion of the drug sequestered is a lot higher in children, compared to only 10% in the adults, due to higher circulation rate (26).

Drug pharmacokinetics changes greatly in patients with burns. There is a substantial increase in the volume of intra and extracellular fluid due to increased capillary permeability, but because of the fluid administration as well. Consequently, interstitial edema occurs, and the drug abundantly diffuses into the extracellular compartment, especially in the burned area (28). Within hours after the injury, the volume of the interstitial fluid is doubled. This increase lasts for 36 – 48h until the unburnt tissues have been affected by proinflammatory mediators. Systemic consequences of the burn injury are seen in all patients with more than 25% of body surface affected (29). One week after the burn injury, and during the following month, fentanyl Vd is increased with lower plasma concentrations achieved, which is partially influenced by the increased clearance and increased cardiac output (22, 28). The hypermetabolic state in burn patients is associated with decreased systemic vascular resistance, increased cardiac output, and therefore, the increased blood flow through the elimination organs and increased clearance by almost 50%. On the other hand, liver function is often impaired after

major burns (28). This may explain smaller impact of fentanyl clearance on its plasma concentration. Decreased albuminemia in this second phase leads to an increase in free drug concentrations enabling it to be easily distributed and eliminated (29). This clinical situation increases the risk of pharmacokinetic interactions with fentanyl, since there is a great need for the antimicrobial treatment, especially with drugs that are expected to induce or inhibit fentanyl metabolism. All these pharmacokinetic changes have not been confirmed in pediatric population with burn injuries, but previous studies have shown great variability in the pharmacokinetic parameters. The impact of all the proposed factors is yet to be determined (18).

## Conclusion

Children are the most vulnerable population. Therefore, it is of extreme importance to dose fentanyl safely, but efficiently as well.

Due to the ethical problems, as well as to the great intragroup variability, previous studies are not consistent in estimating the pharmacokinetic parameters, as well as in determining the significance of the factors influencing fentanyl pharmacokinetics. Common weight-based dosing strategy may not always be the optimal, due to numerous covariates of the fentanyl pharmacokinetics. In a certain clinical setting, beside hidden factors such as genetics, age and gestational age, obesity and potential drug interactions are the first to be taken into account.

## Acknowledgement

The work resulted from a project led by Prof. Dr. Goran Marjanović, approved by the Ethics Committee, entitled: "The influence of immunomodulatory and pharmacokinetic properties of fentanyl and alfentanil on the variability of the therapeutic response in the postoperative period in pediatric patients".

## References

1. Verriotis M, Chang P, Fitzgerald M, Fabrizi L. The development of the nociceptive brain. Neuroscience 2016;338:207-19. [CrossRef][PubMed]
2. van den Hoogen NJ, de Kort AR, Allegaert KM, Joosten EA, Simons SHP, Tibboel D, et al. Developmental neurobiology as a guide for pharmacological management of pain in neonates. Seminars in Fetal and Neonatal Medicine 2019;24(4):101012. [CrossRef][PubMed]
3. Kwok CHT, Devonshire IM, Bennett AJ, Hathway GJ. Postnatal maturation of endogenous opioid systems within the periaqueductal grey and spinal dorsal horn of the rat. PAIN 2014;155(1):168-78. [CrossRef][PubMed]
4. Brewer CL, Baccei ML. The development of pain circuits and unique effects of neonatal injury. J Neural Transm 2020;127:467–79. [CrossRef][PubMed]
5. Fitzgerald M. The development of nociceptive circuits. Nature Reviews 2005;6:507-20. [CrossRef][PubMed]
6. Schug SA, Ting S. Fentanyl Formulations in the Management of Pain: An Update. Drugs 2017;77(7):747-763. [CrossRef][PubMed]
7. Choi L, Ferrell BA, Vasilevskis EE, Pandharipande PP, Heltsley R, Ely EW, et al. Population Pharmacokinetics of Fentanyl in the Critically Ill. Crit Care Med 2016;44(1):64-72. [CrossRef][PubMed]
8. Ziesenitz VC, Vaughns JD, Koch G, Mikus G, van den Anker JN. Pharmacokinetics of Fentanyl and Its Derivatives in Children: A Comprehensive Review. Clin Pharmacokinet 2018;57(2):125-149. [CrossRef][PubMed]
9. Thigpen JC, Odle BL, Harirforoosh S. Opioids: A Review of Pharmacokinetics and Pharmacodynamics in Neonates, Infants, and Children. Eur J Drug Metab Pharmacokinet 2019;44(5):591-609. [CrossRef][PubMed]
10. Lim SY, Miller JL, Henry E, Heltsley R, Woo S, Johnson PN. Analysis of fentanyl pharmacokinetics, and its sedative effects and tolerance in critically ill children. Pharmacotherapy 2021;41:359-369. [CrossRef][PubMed]
11. Hagos FT, Horvat CM, Au AK, Conley Y, Li L, Poloyac S, et al. Factors Contributing to Fentanyl Pharmacokinetic Variability Among Diagnostically Diverse Critically Ill Children. Clin Pharmacokinet 2019;58**:**1567–76. [CrossRef][PubMed]
12. Lim SY, Woo S, Miller JL, Skrepnek GH, Henry ED, Johnson PN. Prediction and Comparison of Fentanyl Infusion Pharmacokinetics in Obese and Nonobese Children. Pediatr Crit Care Med 2019;20(12):e556-e564. [CrossRef][PubMed]
13. Johnson KL, Erickson JP, Holley FO, Scott JC. Fentanyl pharmacokinetics in the pediatric population. Anesthesiology 1984; 61:1. [CrossRef]

14. Singleton MA, Rosen JI, Fisher DM. Pharmacokinetics of fentanyl for infants and adults. Anesthesiology 1984;61:A440. [CrossRef]
15. Vaughns JD, Ziesenitz VC, Williams EF, Mushtaq A, Bachmann R, Skopp G, et al. Use of fentanyl in adolescents with clinically severe obesity undergoing bariatric surgery: A pilot study. Paediatr Drugs 2017;19:251–257. [CrossRef][PubMed]
16. Katz R, Kelly HW. Pharmacokinetics of continuous infusions of fentanyl in critically ill children. Crit Care Med 1993;21:995–1000. [CrossRef][PubMed]
17. Clotz MA, Nahata MC, Jones PR, Anglin DL. Variability of fentanyl clearance in pediatric patients undergoing sedation. J Appl Ther Res 1998;2:59–61.
18. Grimsrud KN, Lima KM, Tran NK, Palmieri TL. Characterizing Fentanyl Variability Using Population Pharmacokinetics in Pediatric Burn Patients, Journal of Burn Care & Research 2020;41(1):8–14. [CrossRef][PubMed]
19. Völler S, Flint RB, Andriessen P, Allegaert K, Zimmermann LJ, Liem KD, et al. Rapidly maturing fentanyl clearance in preterm neonates. Archives of Disease in Childhood-Fetal and Neonatal Edition 2019;104(6):F598-F603. [CrossRef][PubMed]
20. Maharaj AR, Wu H, Zimmerman KO, Speicher DG, Sullivan JE, Watt K, et al. Dosing of Continuous Fentanyl Infusions in Obese Children: A Population Pharmacokinetic Analysis. J Clin Pharmacol 2020;60(5):636-47. [CrossRef][PubMed]
21. Williams ML, Kannankeril PJ, Breeyear JH, Edwards TL, Van Driest SL, Choi L. Effect of CYP3A5 and CYP3A4 Genetic Variants on Fentanyl Pharmacokinetics in a Pediatric Population. Clin Pharmacol Ther 2022;111(4):896-908. [CrossRef][PubMed]
22. Stapelberg F. Challenges in anaesthesia and pain management for burn injuries. Anaesthesia and Intensive Care 2020;48(2):101-13. [CrossRef][PubMed]
23. Lam J, Baello S, Iqbal M, Kelly LE, Shannon PT, Chitayat D, et al. The ontogeny of P-glycoprotein in the developing human blood–brain barrier: implication for opioid toxicity in neonates. Pediatr Res 2015;78:417–421. [CrossRef][PubMed]
24. Tang C, Poloyac SM. A Modeling-Based Approach to Estimate Fentanyl Pharmacokinetics in Obese Critically Ill Children*. Pediatric Critical Care Medicine 2019;20(12):1208–1209. [CrossRef][PubMed]
25. Van Driest SL, Marshall MD, Hachey B, Beck C, Crum K, Owen J, et al. Pragmatic pharmacology: population pharmacokinetic analysis of fentanyl using remnant samples from children after cardiac surgery. Br J Clin Pharmacol 2016;81(6):1165-74. [CrossRef][PubMed]
26. Koren G, Crean P, Klein J, Goresky G, Villamater J, MacLeod SM. Sequestration of fentanyl by the cardiopulmonary bypass (CPBP). European Journal of Clinical Pharmacology 1984;27(1):51–56. [CrossRef][PubMed]
27. Heith CS, Hansen LA, Bakken RM, Ritter SL, Long BR, Hume JR, et al. Effects of an *Ex Vivo* Pediatric Extracorporeal Membrane Oxygenation Circuit on the Sequestration of Mycophenolate Mofetil, Tacrolimus, Hydromorphone, and Fentanyl. J Pediatr Pharmacol Ther 2019;24(4):290-295. [CrossRef][PubMed]
28. Han T, Harmatz JS, Greenblatt DJ, Martyn JAJ. Fentanyl Clearance and Volume of Distribution Are Increased in Patients With Major Burns. The Journal of Clinical Pharmacology 2007;47(6):674–80. [CrossRef][PubMed]
29. Blanchet B, Jullien V, Vinsonneau C, Tod M. Influence of Burns on Pharmacokinetics and Pharmacodynamics of Drugs Used in the Care of Burn Patients. Clinical Pharmacokinetics 2008;47(10):635–54. [CrossRef][PubMed]

**Pregledni rad** **UDC: 615.212.015:616-053.2**
**doi: 10.5633/amm.2023.0108**

# FARMAKOKINETIKA INTRAVENSKE PRIMENE FENTANILA KOD DECE

*Jelena Lilić[1], Vesna Marjanović[1,2], Ivana Budić[1,2], Ivana Mitić[1], Maja Zečević[3], Gorana Nedin-Ranković[4]*

[1] Univerzitetski klinički centar Niš, Klinika za anesteziju i intenzivnu terapiju, Niš, Srbija
[2] Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija
[3] Univerzitetski klinički centar Niš, Klinika za dečiju hirurgiju, dečiju ortopediju i traumatologiju, Niš, Srbija
[4] Univerzitet u Nišu, Medicinski fakultet, Katedra za farmakologiju sa toksikologijom, Niš, Srbija

*Kontakt:* Jelena Lilić
Bulevar dr Zorana Đinđića 48, 18000 Niš, Srbija
E-mail: jjeca8451@gmail.com

Fentanil se obično koristi intrahospitalno za postizanje sedacije i analgezije kod dece. Cilj ovog pregleda jeste razjašnjenje farmakokinetičke aspekte intravenske upotrebe fentanila kod dece.

Generalno, farmakokinetika leka je promenjena kod dece na svim nivoima, ali postoji značajna varijabilnost i između dece različitog uzrasta. Nakon intravenske primene leka, izbegavaju se poteškoće u vezi sa oralnim unosom i gastrointestinalnom apsorpcijom. Promene u distribuciji leka, metabolizmu i eliminaciji su posledica razlika u zapremini ekstracelularnog i ukupnog telesnog vodenog odeljka, perfuziji organa, acido-baznoj ravnoteži, permeabilnosti membrane i funkciji srca, jetre i bubrega. Ipak, najveći uticaj pripisuje se veličini tela.

Deca su najugroženija populacija, pa je zbog toga od izuzetnog značaja da se fentanil dozira bezbedno, ali i efikasno. Uobičajena strategija doziranja zasnovana na težini možda nije uvek optimalna, zbog brojnih kovarijata farmakokinetike fentanila. U određenom kliničkom okruženju, pored skrivenih faktora, kao što su genetika, starost i gestacijsko doba, gojaznost i potencijalne interakcije sa lekovima, prvo se uzimaju u obzir. *Acta Medica Medianae 2023;62(1): 56-61.*

***Ključne reči:*** *fentanil, farmakokinetika, deca*

**Case report**

**UDC: 616.351-006.55**
**doi: 10.5633/amm.2023.0109**

# DYSPLASTIC RECTAL POLYP (LOW GRADE)

*Mladen Kasalović [1,2], Zlatan Elek [1,2], Gojko Igrutinović [1,2], Aleksandar Jakovljević [1,2], Nikola Miljković [1,2], Milica Milentijević [1,2]*

Villous adenoma is a non-cancerous growth in the colon. It develops from the cells that cover the inner surface of the large intestine. These adenomas can develop anywhere along the colon, from the cecum to the rectum. All villous adenomas are associated with an increased risk of developing colon cancer called adenocarcinoma over time. Polyps can be sessile or pedunculated and vary in size. The incidence of polyps ranges from 7−50%; a higher incidence refers to very small polyps (which are usually hyperplastic or adenomas) and are found as an incidental finding at autopsy.

A 72-year-old female patient K. D. presented because of bleeding during defecation and a change of the size of an apple that used to "fall out" from the anus during defecation. She reported to have experienced this change for more than a year and the bleeding from it in the last few weeks. She used suppositories, but there were no changes in the local findings. Further, she performed a colonoscopy, where a pale pink mucosa was seen, with normal findings, except for 3−4 cm, where there was a cauliflower-like change on the stalk, partially covered with fibrin deposits, hyperemic.

According to the data, the combined risk of dysplasia/malignancy is about 83% with a 50% risk of dysplasia and overt malignancy in 33% of cases of giant rectal villous adenomas larger than 8 cm. *Acta Medica Medianae 2023;62(1):62-65.*

***Key words:*** *tubulovillous adenoma, lifestyle, bleeding, cancer*

[1]Clinical Hospital Center Kosovska Mitrovica, Serbia
[2]Faculty of Medicine University of Prishtina-Kosovska Mitrovica, Serbia

*Contact:* Mladen Kasalović,
Anri Dinana br. 10
38220 – Kosovska Mitrovica
mladen.kasalovic@med.pr.ac.rs,

## Introduction

By intestinal polyp we mean any tissue change that grows from the wall of the intestine and spreads into the lumen. Most polyps do not cause any symptoms except for mild bleeding which is usually hidden. Malignant transformation is the most worrisome; most cancers grow from previously benign adenomatous polyps. The diagnosis is made by endoscopy.

Polyps can be sessile or pedunculated and vary in size. The incidence of polyps ranges from 7% to 50%; a higher incidence refers to very small polyps (which are usually hyperplastic or adenomas) and are found as an incidental finding at autopsy. The rectum and sigmoid colon are the most common localization of polyps and they are often multiple. The frequency decreases towards the cecum. Multiple polyps can occur as part of familial adenomatous polyposis. About 25% of colon cancer patients also have adenomatous polyps.

**Adenomatous (neoplastic) polyps** are histologically classified into tubular adenomas, tubulovillous adenomas (viloglandular polyps) or villous adenomas. The possibility of malignant transformation in an adenomatous polyp at the time of diagnosis depends on the size, histological type and degree of dysplasia; the risk of malignant transformation of a tubular adenoma with a diameter of 1.5 cm is 2%, compared to a 35% risk of a villous adenoma with a diameter of 3 cm.

**Non-adenomatous (non-neoplastic) polyps** include hyperplastic polyps, hamartomas, juvenile polyps, pseudopolyps, lipomas, and other rare tumors. **Peutz-Jeghers syndrome** is an autosomal dominant disorder with multiple hamartomatous polyps in the stomach, small intestine, and colon. Symptoms are dark pigmentation of the skin and mucous membranes, especially in the area of the lips and gums. Juvenile polyps occur in childhood. Treatment is only necessary in case of uncontrolled bleeding or intussusception. Inflamed polyps and pseudopolyps occur in chronic ulcerative colitis and Crohn's disease of the colon. Multiple juvenile polyps (but not sporadic) carry an increased risk

of cancer. The specific number of polyps for which there is an increased risk is not known.

**Case report**

A 72-year-old female patient K. D. presented because of bleeding during defecation and a change of the size of an apple that used to "fall out" from the anus during defecation. She reported to have experienced this change for more than a year and the bleeding from it in the last few weeks. She used suppositories, but there were no changes in the local findings. She performed a colonoscopy, where a pale pink mucosa was seen, with normal findings, except for 3–4 cm, where there was a cauliflower-like change on the stalk, partially covered with fibrin deposits, hyperemic.

In the objective findings, hemorrhoidal nodules were evident in the anal region, without signs of inflammation and bleeding. In addition to hemorrhoids, a raspberry-like change was observed that protrudes from the anus, light red in color, which was reponable back into the lumen.

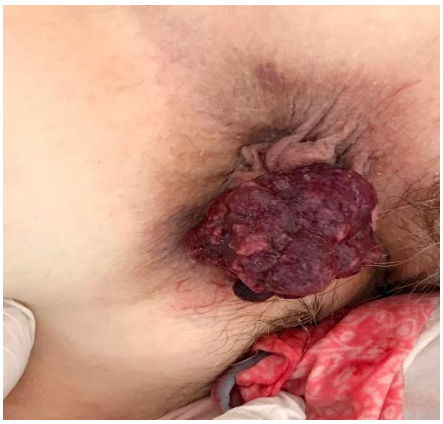


**Figure 1**. Prolapsed adenoma

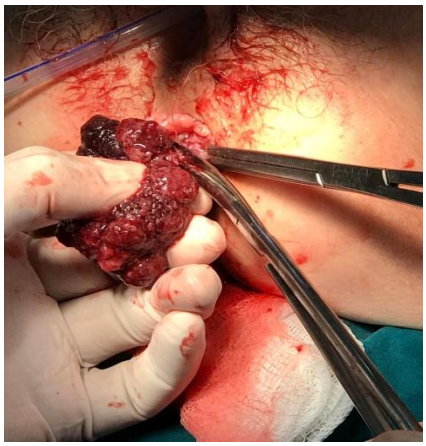


**Figure 2.** Identification of the adenoma stalk

The perianal region findings were normal.

In the surgery department where the patient was admitted, adequate preoperative preparation was done, which consisted of basic laboratory and biochemical analyzes (WBC: 8.29; RBC: 4.48; HGB: 104.8; HCT: 0.33; MCV: 74, 2; PLT: 335.6; albumin: 34; protein: 62.2; CRP: 2.7), X-ray of lungs and heart (normal findings), ECG (normal findings), the internist and anesthesiologist were consulted. After adequate preoperative preparation, the patient underwent operative treatment under conditions of local anesthesia and analgosedation. The patient was placed in the gynecological position.

Surgery (transanal excision) is prescribed if the formation has a villous, adenomatous structure and is removed from the anus up to 10 cm. After dilatation of the anus, a raspberry-like, adenomyomatous change was identified, which was attached to the anal canal on the stalk. The change was mobile.

After identification of the peduncle, pean is placed and the change is excised completely. At the excision site, a suture is made with a pair of stitches. Make a correct hemostasis.

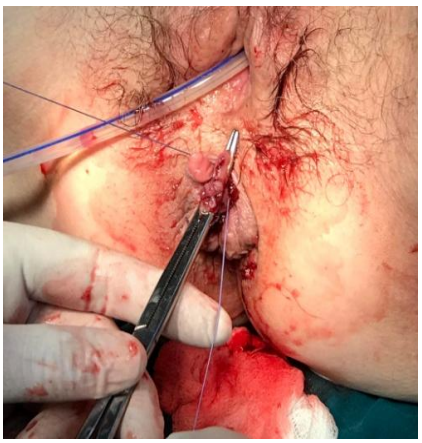


**Figure 3.** Excision site suture

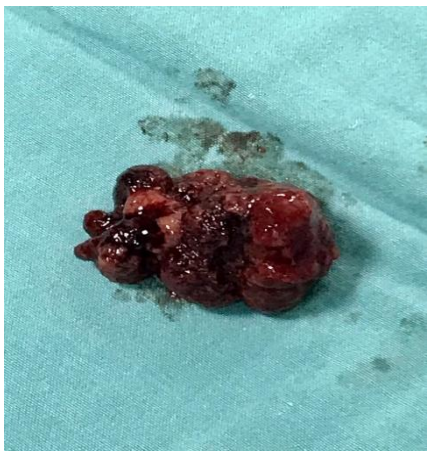


**Figure 4.** Extirpated adenoma in its entirety

The preparation was sent for pathohistological verification. After two weeks, the pathologist's report was received with the diagnosis: *Adenoma tubulovilosum in malignant alteration*.

## Discussion

Transanal minimally invasive surgery has emerged in recent years as a viable alternative to traditional radical resection for both benign and malignant rectal lesions (1). Severe colorectal polyps are lesions that present a challenge to traditional endoscopic polypectomy (2). Serrated polyps have been recognized in the last decade as important premalignant lesions that account for between 15% and 30% of colorectal carcinomas (3). Rectal lesions containing dysplasia or early neoplasia confined to the mucosa are usually treated by a minimally invasive transanal approach (4). Colorectal polyps are an important but uncommon cause of rectal bleeding (5). Polyps are often found throughout the large intestine, and a colonoscopy is therefore a useful method, especially in patients with occasional rectal bleeding. Indications for transanal polyp excision are: impossibility of endoscopic polyp excision, contraindications for general anesthesia due to existing comorbidities, polyp localization up to 10 cm from the anocutaneous line. Contraindications for transanal polyp excision are: multiple polyps, bleeding and the polyp localization more than 10 cm from the anocutaneous line. By statistical analysis, the malignant potential of adenomas is related to their size, growth pattern and degree of epithelial atypia (6). Some high-risk patients receive insufficient monitoring, and lower-risk subjects receive excessive monitoring.

There are two main trends in the surgical treatment of precancerous conditions and early stages of rectal cancer: radical rectal resection and local transanal excision of the affected zone (7). Several lifestyle factors, primarily smoking and alcohol, are associated with the risk of colorectal polyps (8). We believe that the risk of colorectal polyps could be reduced by lifestyle changes. Most colon cancers develop from adenomas, and the life history of this sequence, although variable, probably lasts an average of 10 to 15 years (6). According to the data, the combined risk of dysplasia/malignancy is about 83% with a 50% risk of dysplasia and overt malignancy in 33% of cases of giant rectal villous adenomas larger than 8 cm (9).

## Conclusion

Distinguishing adenoma from submucosal invasion remains a common challenge in clinical practice. The ideal treatment approach for any colorectal change should be one that is cost-effective, minimizes the need for follow-up interventions, and ultimately avoids surgery.

## References


1. Qi-Hui FL, Seng CC, Transanal Minimally Invasive Surgery (TAMIS) for Large Rectal Polyps. Ann Surg Oncol 2019;26(5):1428. [CrossRef][PubMed]
2. Pidala MJ, Cusick MV, The Difficult Colorectal Polyp. Surg Clin North Am 2017;97(3):515-527. [CrossRef][PubMed]
3. East JE, Atkin WS, Bateman AC, Clark SK, Dolwani S, Ket SN, et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut 2017;66(7):1181-1196. [CrossRef][PubMed]
4. Yang D, Draganov PV. Removing large rectal polyps: when the whole may be greater than the sum of its parts. Gastrointest Endosc 2018;87(3):872-874. [CrossRef][PubMed]
5. Latt TT, Nicholl R, Domizio P, Walker-Smith JA, Williams CB. Rectal bleeding and polyps. Arch Dis Child 1993;69(1):144-7. [CrossRef][PubMed]
6. Day DW, Morson BC. The adenoma-carcinoma sequence. Major Probl Pathol 1978;10:58-71. [PubMed]
7. Usenko OY, Tyvonchu OS, Bayura MI. Transanal miniinvasive surgery (TAMIS): first experience of application. Klin Khir 2016;(10):5-8. [PubMed]
8. Bailie L, Loughrey MB, Coleman HG. Lifestyle Risk Factors for Serrated Colorectal Polyps: A Systematic Review and Meta-analysis. Gastroenterology 2017;152(1):92-104. [CrossRef][PubMed]
9. Bains L, Lal P, Vindal A, Singh M. Giant villous adenoma of rectum-what is the malignant potential and what is the optimal treatment? A case and review of literature. World J Surg Oncol 2019;17(1):109. [CrossRef][PubMed]

**Prikaz bolesnika**

**UDC: 616.351-006.55**
**doi: 10.5633/amm.2023.0109**

# DISPLASTIČNI REKTALNI POLIP NISKOG STEPANA

*Mladen Kasalović [1,2], Zlatan Elek[1,2], Gojko Igrutinović [1,2], Aleksandar Jakovljević[1,2], Nikola Miljković[1,2], Milica Milentijević[1,2]*

[1]Kliničko-bolnički centar, Kosovska Mitrovica, Srbija
[2] Univerzitet u Prištini sa privremenim sedištem u Kosovskoj Mitrovici, Medicinski fakultet, Kosovska Mitrovica, Srbija

Kontakt: Mladen Kasalović,
Anri Dinana br. 10
38220 – Kosovska Mitrovica
mladen.kasalovic@med.pr.ac.rs,

Vilozni adenom je nekancerozna izraslina u debelom crevu. Razvija se iz ćelija koje prekrivaju unutrašnju površinu debelog creva. Ovi adenomi mogu se razviti bilo gde duž debelog creva, od cekuma do rektuma. Svi vilozni adenomi povezani su sa povećanim rizikom od razvoja vrste raka debelog creva, tzv.adenokarcinoma tokom vremena. Polipi mogu biti sesilni ili na peteljci, te variraju veličinom. Incidencija polipa iznosi 7% – 50%; veća incidencija odnosi se na vrlo male polipe (koji su obično hiperplastični ili adenomi), te se nađu kao slučajan nalaz na obdukciji.

Pacijent K. D. starosti 72 godine, ženskog pola, dolazi zbog krvarenja pri defekaciji, kao i zbog promene koja „ispada" iz anusa pri defekaciji, veličine jabuke. Za ovu promenu zna više od godinu dana. U poslednjih nekoliko nedelja promena krvari. Pacijentkinja je koristila čepiće, ali nije došlo do promena u lokalnom nalazu. Uradila je kolonoskopiju, gde je viđena sluznica bledoružičaste boje, urednog nalaza, osim na 3 cm – 4 cm, gde se uočava karfiolasta promena na peteljci, delom prekrivena fibrinskim naslagama, hiperemična.

Prema podacima, kombinovani rizik od displazije/maligniteta je oko 83%, sa 50% rizikom od displazije i otvorenog maligniteta u 33% slučajeva džinovskih rektalnih viloznih adenoma većih od 8 cm. *Acta Medica Medianae 2023;62(1): 62-65.*

***Ključne reči:*** *tubulovilozni adenom, način života, krvarenje, karcinom*

**Case report**

**UDC: 616.12-089.819**
**doi: 10.5633/amm.2023.0110**

# REVASCULARISATION STRATEGY IN THE CRITICAL LEFT MAIN CORONARY ARTERY DISEASE ASSOCIATED WITH ACUTE CORONARY SYNDROME AND CHRONIC TOTAL OCCLUSION OF RIGHT CORONARY ARTERY

*Bojan Maričić[1], Zoran Perišić[1,2], Tomislav Kostić[1,2], Svetlana Apostolović[1,2], Sonja Šalinger[1,2], Nenad Božinović[1]

Critical left main stenosis combined with chronic total occlusion of the right coronary artery and cardiogenic shock in acute myocardial infarction has been the most challenging case for an interventional cardiologist. Emergency revascularization, CABG or PCI is mandatory. A 46-year-old man presented with non-ST-elevation myocardial infarction and cardiogenic shock. Coronary angiography revealed chronic total occlusion in the middle portion of RCA and severe bifurcation stenosis of the distal left main (LM). LM bifurcation stenosis includes stenosis of the distal LM 80%, ostial stenosis left anterior descending artery (LAD) 80%, ostial stenosis, left circumflex artery (LCX) 90%. A decision was made to perform a two-step procedure, the first one immediately to solve the lesion of the left main, and the PCI CTO RCA in another act. Considering coronary anatomy, we decided to do the "TAP" (T and protrusion) technique for LM. RCA recanalisation was performed six months later. *Acta Medica Medianae 2023;62(1):66-70.*

***Key words:*** *left main coronary artery, acute coronary syndrome, surgery, percutaneous intervention, chronic total occlusion*

[1]Clinic for cardiovascular diseases, University Clinical Center of Niš,
[2]Faculty of Medicine, University of Niš

*Contact:* Bojan Maričić, 8/32 Cara Dušana St., Niš,
email: bokimaricic@gmail.com,
tel. 0692918755

## Introduction

Critical left main coronary artery (LMCA) stenosis in an acute coronary (ACS) setting is associated with increased morbidity and mortality.

Critical left main (LM) stenosis combined with chronic total occlusion of the right coronary artery (RCA) and cardiogenic shock in acute myocardial infarction (AMI) has been the most challenging case for interventional cardiologists and heart team. There was no clear consensus on unprotected LMCA lesions associated with acute myocardial infarction with a culprit lesion of LMCA (1–4).

## Case presentation

A 46-year-old man presented with non-ST-elevation myocardial infarction (NSTEMI) and cardiogenic shock. His systolic blood pressure was around 90 mmHg even though vasoactive agent use and his heart rate was around 100 to 110/min.

Electrocardiography showed diffuse ST-segment depression in precordial and standard leads and ST elevation in AVR lead. His coronary risk factors include hypertension, hyperlipidemia, and smoking.

Coronary angiography revealed chronic total occlusion in the middle portion of RCA and severe bifurcation stenosis of the distal left main (LM). LM bifurcation stenosis include stenosis of the distal LM 80%, ostial stenosis left anterior descending artery (LAD) 80%, ostial stenosis left circumflex artery (LCX) 90% (Figure 1).

His SYNTAX score (synergy between percutaneous coronary intervention with TAXUS and cardiac surgery) was 21.

The patient and his family refused emergency coronary artery bypass grafting (CABG). Based on this, a decision was made to make a two-step procedure, the first one immediately to solve the lesion of the left main, and the PCI CTO RCA in another act.

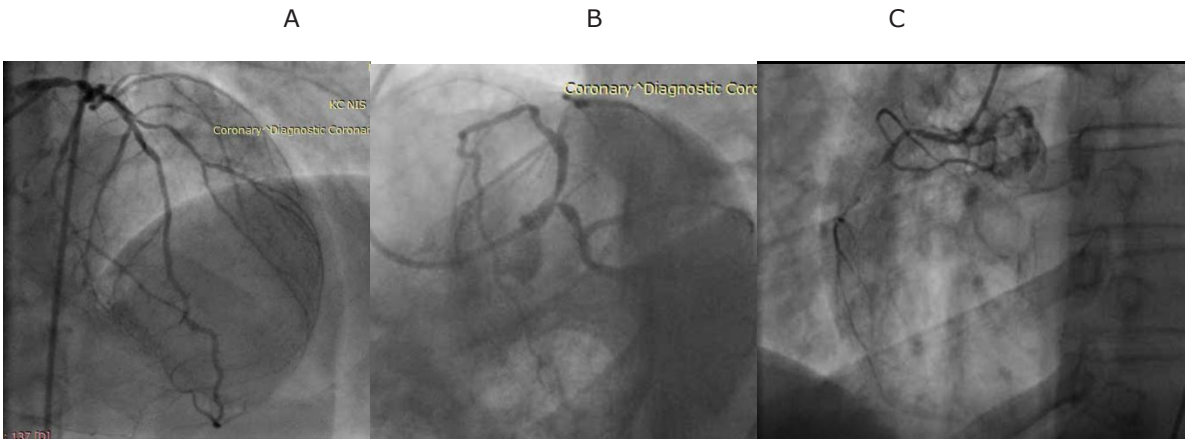



**Figure 1.** A (significant stenosis distal LM). B (distal LM bifurcation stenosis). C (chronic total occlusion RCA)

Due to the significant narrowing of the ostium LCx and its large caliber, it was decided to do a two-stent technique. Considering the favorable angle of separation, we decided to do the "TAP "(T and protrusion) technique.

Coronary intervention was performed via right transfemoral (TF) approach.

A 7-French (Fr.) Extra back-up (EBU) 3.75 guiding catheter (Terumo, Tokyo, Japan) was used for engaging the left main ostium. After advancing a 0.014 Sion blue wire (Asahi, Tokyo, Japan) to the distal LAD and another Sion blue wire to the distal LCx, predilatation was performed using NC Sprinter 2.5x15 mm (Medtronic, Minneapolis, MN) up to 16 atm for ostial LCx and NC Sprinter 2.75x15 mm up to 16 atm for ostial LAD. Drug-eluting stents (DES) (Promus Premier 3.5x16 mm) were deployed from the ostial LM to the proximal LAD (Figure 2 A). Due to occlusive dissection of the LAD on distal stent insertion, another stent (Promus Premier 3.0x16 mm) was implanted with adequate overlapping. Satisfactory result was obtained without residual narrowing and dissection of LM and LAD. Re-wiring was performed and strut opening with a small balloon Sapphire 1.5x10 mm up to 16 atm. Drug-eluting stent Promus Premier 3.0x18 mm was deployed in the LCx with minimal protrusion in the LM (Figure 2 B). "Kissing balloon" was performed with two NC Sprinter Legend 3.0x15 mm balloons (Figure 2 C), and finally POT (proximal optimisation) with NC Sprinter Legend 4.0x12 mm up to 20 atm.

Satisfactory result was obtained without residual narrowing and dissection (Figure 2).

Next intervention was performed six months later via bifemoral (TF) approach for recanalisation CTO RCA. A 7-French Extra back-up (EBU) 3.75 guiding catheter (Terumo, Tokyo, Japan) was used for engaging the left main ostium, and Judkins right (JR) guiding catheter for right coronary artery.

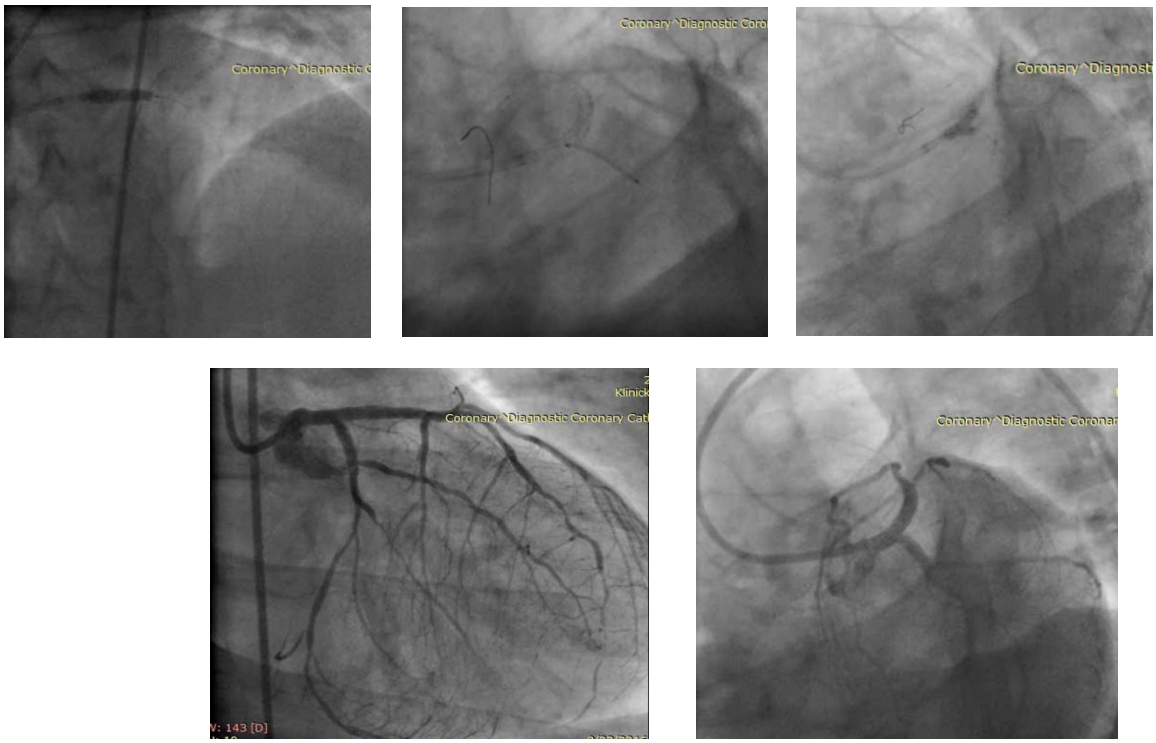
First, an antegrade approach was tried. The wires used were Fielder XT-a (Asahi, Japan), Progress 140 (Abbott Vascular) and Gaia second (Asahi, Japan), but it was unsuccessful. All of these wires went subintimally and it was impossible to make re-entry into the lumen (Figure 3 A). After that, it was decided to try retrograde approach. For passing through the septal collaterals, Sion black wire (Asahi, Japan) supported with Finecross microcatheter (Terumo, Japan) was used. The wire and microcatheter easily passed through the septal channels and entered into the right coronary artery (Figure 3 B).

After that, Sion black wire was exchanged for stiffer wires, Pilot 200 (Abbott Vascular) and Gaia second (Asahi, Japan). It was attempted to cross "lumen-to-lumen" but it was unsuccessful, wires went subintimally. At the occlusion site, the "R-CART" (reverse controlled antegrade and retrograde subintimal tracking) technique was performed. And finally, the retrograde wire Pilot 200 (Abbott Vascular) entered into the lumen and antegrade guiding catheter (Figure 3 C). The procedure was converted to an antegrade procedure using the "Rendezvous" technique with two microcatheters (antegrade and retrograde) (Figure 3 D). Predilatation was performed using balloons Sapphire 1.5x10 mm and Sprinter Legend 2.0x15 mm.

Four drug-eluting stents (DES) were deployed from the proximal to the distal segment right coronary artery with adequate overlapping.

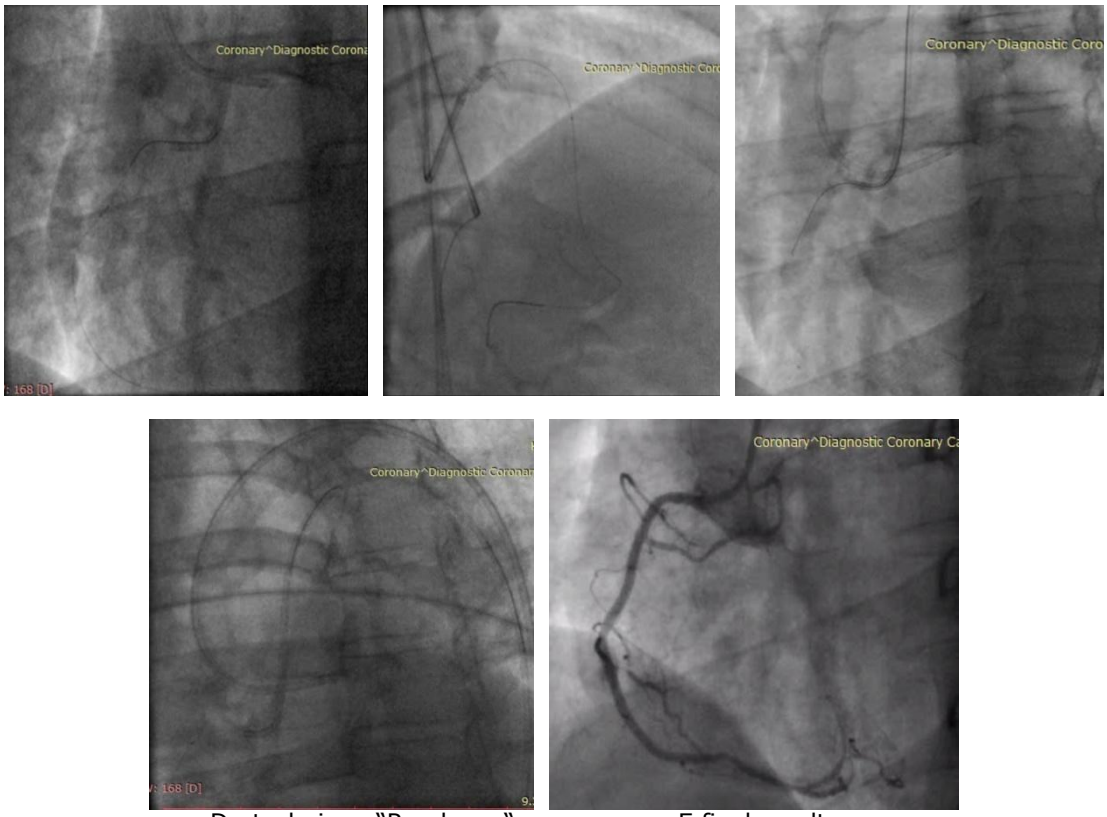
Satisfactory result was obtained without residual narrowing and dissection (Figure 3).

A B C



D final result–caudal E final result-spyder view

**Figure 2.** A(stenta implatation LM-LAD B stent implatataion LM-Cx ( TAP) Ckissing balloon



D technique "Randevou" E final result

**Figure 3.**Aantegrade attemp wire crossingBretrograde crossing wireC retrograde wire in antegrade catheter

## Discussion

Left main coronary artery (LMCA) disease is associated with increased morbidity and mortality.

Optimal treatment for unprotected LMCA, PCI or CABG has been debated for several decades.

Results of large randomized trials NOBEL and EXEL relate to patients in chronic coronary syndrome.

NOBEL (The Nordic-Baltic-British left main revascularization study) published their results in December 2016 in The Lancet and EXCEL (Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease) published their results in The New England Journal of Medicine. In NOBLE, the primary endpoint of major adverse cardiac and cerebrovascular events (MACCE) was 29% for PCI versus 19% for CABG, even though the all-cause mortality was similar (6). In Excel, the conclusion is that the strategy of PCI for LM, including bifurcation lesions of syntax scores <32, was non-inferior to CABG (5).

European guidelines on myocardial revascularization in chronic setting give a class I recommendation for the patients with low SYNTAX score (0–22), class IIa recommendation for the subgroup of patients with intermediate anatomical complexity (SYNTAX score 23–32) (7).

For PCI unprotected LMCA in acute coronary setting, there are no large randomized trials and optimal revascularization strategy is not obvious.

In the case of hemodynamic stability, treatment approach could be either PCI or surgery

in parallel with guidelines for stable patients (2).

## Conclusion

Emergency revascularization of patients with acute myocardial infarction, especially hemodynamically unstable ones, is very important. Therefore, percutaneous intervention of unprotected LMCA lesions can be performed with good results in selected patients.

With the developments in stent design, medical therapy and PCI techniques over the past decade in some of the trials showed that PCI was non-inferior to CABG surgery in the long-term benefits.

## References


1. .Gagnor A, Tomassini F, Romagnoli E, Infantino V, Rosa Brusin MC, Maria C, et al. Percutaneous left maincoronary disease treatment without on-site surgery back-up in patients with acute coronary syndromes: immediateand 2-year outcomes. Catheter Cardiovasc Interv 2012; 79(6): 979–87. [CrossRef] [PubMed]
2. Lee MS, Sillano D, Latib A, Chieffo A, Zoccai GB, Bhatia R, et al. Multicenter international registry of unprotected leftmain coronary artery percutaneous coronary interventionwith drug-eluting stents in patients with myocardialinfarction. Catheter Cardiovasc Interv 2009; 73(1): 15–21. [CrossRef] [PubMed]
3. Claver E, Curós A, López-Ayerbe J, Serra J, Mauri J,Fernández-Nofrerias E, et al. Clinical predictors of leftmain coronary artery disease in high-risk patients with afirst episode of non-ST-segment elevation acute coronarysyndrome [Article in Spanish]. Rev Esp Cardiol 2006; 59(8): 794–800. [PubMed]
4. Lee MS, Bokhoor P, Park SJ, Kim YH, Stone GW, SheibanI, et al. Unprotected left main coronary disease and ST-segment elevation myocardial infarction: a contemporaryreview and argument for percutaneous coronaryintervention. JACC CardiovascInterv 2010; 3(8): 791–5. [CrossRef] [PubMed]
5. Stone GW, Sabik JF, Serruys PW, Simonton CA, Genereux P, Puskas J, et al; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016; 375: 2223–2235. [CrossRef] [PubMed]
6. Makikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, et al, NOBLE Study Investigators. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. Lancet 2016; 388: 2743–2752. [CrossRef] [PubMed]
7. Franz-Josef Neumann, Miguel Sousa-Uva et al. 2018 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2019 Jan 7; 40(2): 87-165. [CrossRef] [PubMed]

**Prikaz bolesnika**

**UDC: 616.12-089.819**
**doi: 10.5633/amm.2023.0110**

# STRATEGIJA REVASKULARIZACIJE BOLESNIKA SA KRITIČNIM SUŽENJEM GLAVNOG STABLA LEVE KORONARNE ARTERIJE U AKUTNOM KORONARNOM SINDROMU UDRUŽENIM SA HRONIČNOM TOTALNOM OKLUZIJOM DESNE KORONARNE ARTERIJE

**Bojan Maričić[1], Zoran Perišić[1,2], Tomislav Kostić[1,2], Svetlana Apostolović[1,2], Sonja Šalinger[1,2] , Nenad Božinović[1]*

[1]Univerzitetski klinički centar Niš, Klinika kardiovaskularne bolesti, Niš, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija

Kontakt osoba: Bojan Maričić, Cara Dušana 8/32, Niš,
email: bokimaricic@gmail.com,
tel. 0692918755

Kritična stenoza glavnog stabla leve koronarne arterije u akutnom infarktu miokarda, praćena kardiogenim šokom, uz hroničnu totalnu okluziju desne koronarne arterije, predstavlja najkompleksniju situaciju za interventnog kardiologa. Urgentna revaskularizacija, hirurška ili perkutana, neophodna je. U našem slučaju, bolesnik muškog pola star 46 godina prezentovan je sa slikom infarkta miokarda bez ST elevacije, praćenog kardiogenim šokom. Hitnom koronarografijom uočena je kritična bifurkaciona stenoza distalnog glavnog stabla leve koronarne arterije i hroničnu totalnu okluziju desne koronarne arterije. Odluka je bila da se uradi intervencija iz dva dela, hitna intervencija na glavnom stablu leve koronarne arterije, a potom za šest meseci rekanalizacija desne koronarne arterije. Na osnovu koronarne anatomije, odluka je bila da se uradi TAP (T and protrusion) tehnika za glavno stablo leve koronarne arterije. Rekanalizacija desne koronarne arterije urađena je nakon šest meseci retrogradnim pristupom preko leve koronarne arterije. *Acta Medica Medianae 2023;62(1): 66-70.*

***Ključne reči:*** *glavno stablo leve koronarne arterije, akutni koronarni sindrom, hirurgija, perkutane koronarne intervencije, hronične totalne okluzije*

**Case report** **UDC: 616.314.3-007-089.23**
**doi: 10.5633/amm.2023.0111**

# ORTHODONTIC-SURGICAL THERAPY OF THE IMPACTED CENTRAL MAXILLARY INCISOR: A CASE REPORT

*Vladimir Mitić[1]*, Kosta Todorović[2], Aleksandar Mitić[3]*

The aim of this study was to clearly determine the possibility of treatment of impacted central incisor liberation in a 9-year-old girl, and then to bring the tooth to its natural place in the dentition in the shortest possible time interval. The paper presents the liberation of the impacted central incisor in a 9-year-old girl. Prior to the intervention, a detailed examination (CBCT) and analysis of all parameters were performed in order to determine the possibility of successful therapy of the impacted tooth. The orthodontic treatment plan included three steps—creation of space, exposure of crown, and forced eruption. After the surgical intervention of releasing the impacted central incisor, a button with a modified direct bonding method was placed in the same act, with a twisted wire by an orthodontist, and after removing the floss, the tooth was pulled with a fixed orthodontic appliance (SWA technique). Follow-ups were done every two weeks until the appearance of teeth in the mouth.The modified method of direct bonding of the button for the surface of the impacted tooth proved to be easier, compared to the conventional method. A quality diagnosis with an adequate multidisciplinary therapy gives a satisfactory result in the optimal time.A multidisciplinary diagnosis and therapy are becoming more and more present in dentistry, and the order of therapy should be taken into account. *Acta Medica Medianae 2023;62(1):71-78.*

***Key words:*** *tooth impaction, closed flap, direct bonding, CBCT*

[1] University of Niš, Faculty of Medicine, Department of Jaw Orthopedics, Niš, Serbia
[2] University of Niš, Faculty of Medicine, Department of Oral Surgery, Niš, Serbia
[3] University of Niš, Faculty of Medicine, Department of Dental Diseases and Endodontics, Niš, Serbia

*Contact:* Dr Vladimir Mitić
7/14 Romanijska St., 18000 Niš
018 229794, 0641138353
mident@mts.rs

## Introduction

One of the most important reasons why patients come for orthodontic therapy is dissatisfaction with their appearance, primarily frontal teeth in the upper jaw. In addition to aesthetics, orthodontists are aware of the fact that these teeth in an adequate relationship with the lower teeth of the same region represent anterior guides, and their importance in addition to the aesthetic moment is invaluable in functional and physiological terms (1). A significant problem in the multidisciplinary sense related to the aesthetics but also the functionality of the orofacial region of our patients are dilatations of the central maxillary incisors, whose prevalence ranges from 0.06% to 0.2% (2).

The period of early mixed dentition of 7–9 years is the time when the symmetrical eruption of central maxillary incisors is expected and when orthodontists are included in synergy with oral surgeons on the beginning of liberation therapy of such impacted teeth, whose planning and therapy can be relatively long and complex (3–5). The treatment of such challenging cases is often accompanied by complications such as ankylosis of the teeth, external resorption of tooth roots and the possibility of unwanted resorption of adjacent teeth (3, 6), primarily the maxillary lateral incisor on the impaction side, which leads to extra caution when extracting these teeth using fixed orthodontic appliances and applying force to the dilated tooth.

Dilacerations occur after a trauma in the area of deciduous teeth, where the bud of a permanent developing tooth is damaged due to the close proximity of a deciduous tooth that came in contact with it. The degree of the damage to a permanent central incisor depends on the developmental phase of a tooth, as well as on the type and direction of a trauma (6) on which the formation of the angle between the crown and the started growth of the root of the central maxillary incisor will depend. The angle formed between the two structures (crown and root of the dilated

tooth) will decide on the type of therapy. If the mentioned angle of the dilated central incisor was not formed, the orthodontic treatment should be started as soon as possible to avoid secondary problems (7). Orthodontic-surgical liberation can be done at a later age with biomechanical knowledge in order to choose the optimal system of forces for the application of an appropriate traction (8, 9).

The aim of treatment of the impacted tooth in this case was a proper alignment in the dental arch, in a stable position with obtaining the highest quality gingival tissue around the cement enamel border of the tooth.

**Case presentation**

The patient was a 9-year old girl in excellent physical health who came to the Department of Jaw Orthopedics at the Clinic of Dental Medicine in Niš. The patient intraoral examination showed late mixed dentition. Intraoral examination revealed Class I molar relationship with an overbite of 3 mm and an overjet of 2 mm. The upper central left crown of the incisor was fractured to 1⁄3 its original size. The periodontal health was good, with acceptably good oral hygiene. Facial proportions were normal. Her parents mentioned a traumatic episode at the age of five. A panoramic radiograph showed the presence of all the permanent teeth buds and impacted central incisor on the right side of the upper jaw in the horizontal labial position, where it was not possible to determine the relationship and possible existence of the crown and root of the impacted tooth, but its high position and at right angles crowns, relative to the direction of tooth eruption, could be observed.The left central incisor was fractured in the area of the incisal third (Figure 1), and had to be restoratively upgraded in order to have an optimal vision of the incisal plane to which we would have to lower the right maxillary central incisor during its traction. It was not possible to obtain more information regarding morphology and exact dimensions and positions of the impacted upper central incisor based on orthopantomography and occlusal image of the upper jaw, so a three-dimensional image of this region was performed on a CBCT device (Sirona, Orthophos SL 3D, Germany).

Orthopantomography as well as occlusal images play a key role in diagnosis, therapy planning and type of therapy, as well as in the prognosis of very complex and complex cases in which two-dimensional images are not able to accurately locate certain and above details (Figure 2a). The previous two-dimensional images have replaced new technologies for imaging the orofacial region, where in such cases CBCT is the method of choice in making an adequate diagnosis, prognosis and final treatment plan. The superiority of the CBCT technique for imaging impacted teeth was presented in our case, which greatly facilitated the consultations of orthodontists and surgeons, and dispelled unknowns and possible doubts that existed during the analysis of both the patient and two-dimensional images. (Figure 3). Also, CBCT images provided the orthodontist with a complete analysis of how and in what way to approach orthodontic therapy after surgery.

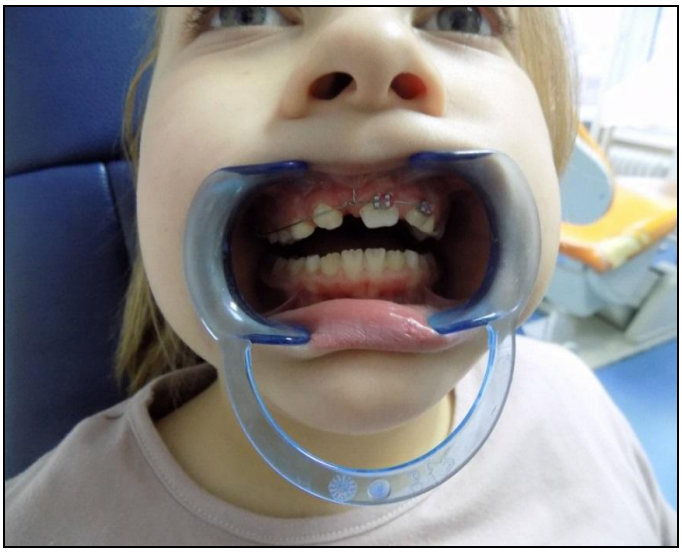


**Figure 1.** Fixed device with twisted wire installed after surgical interventions

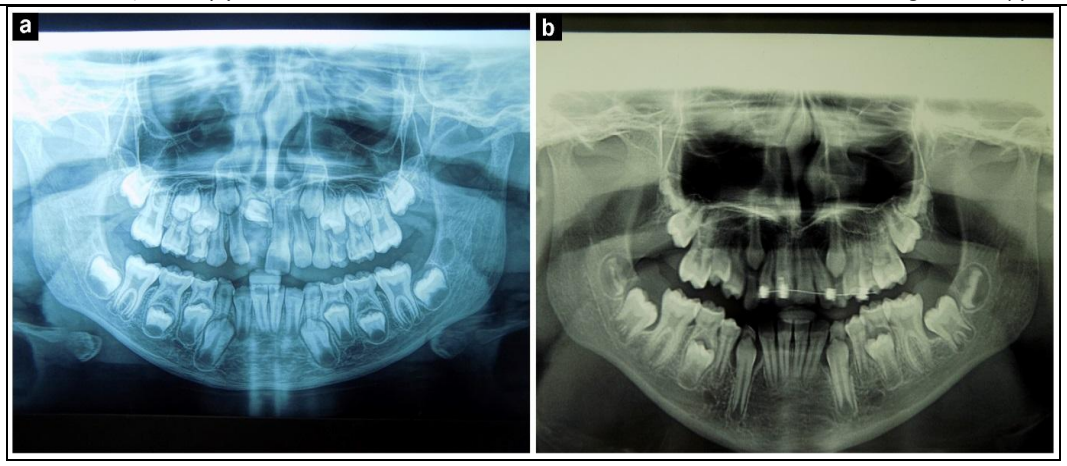



**Figure 2.** Orthopantomographic image of a girl with the impacted central maxillary incisor on the right side (a-before and b-after therapy)

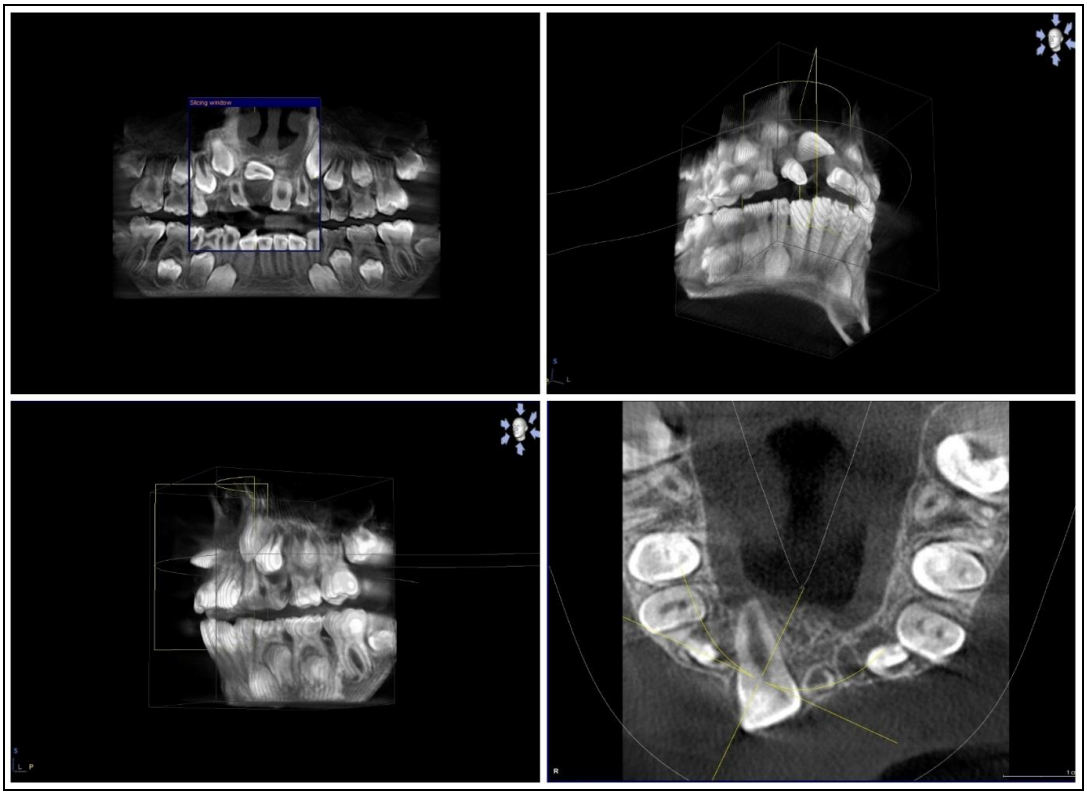


**Figure 3.** Pretreatment CBCT image of a child with the impacted maxillary right central incisor in different positions of the impacted tooth

**Treatment objectives**

The goal of the therapy was to extrude the tooth by applying appropriate pulling forces to the elements of fixed orthodontic appliances on the dilated tooth without an excessive effect which could jeopardize the integrity of the not yet fully formed root of the dilated tooth. Tooth extrusion was followed by straightening the dilated tooth from horizontal to vertical position, taking into account the surrounding bone and gingival architecture in order to meet all functional parameters in addition to the functional result, which posed an additional challenge to surgery.

The approach was multidisciplinary involving a combined surgical-orthodontic treatment.

**Treatment options**

The following are three possible treatment options:

1. Creation of space for impacted tooth, surgical crown exposure and liberation of impacted tooth orthodontically;
2. Extraction of the impacted central incisor and temporary restoration with removable orthodontic appliance, followed by a permanent restoration of the left central incisor;

3. Extraction of the impacted central incisor and closure of the space, converting the lateral incisor into the central incisor with orthodontic fixed appliances with subsequent prosthetic restoration after the growth ceases.

The prognosis of dilacerated tooth liberation depends primarily on: 1.the position and direction of the impacted tooth; 2. the degree of formation of the impacted root; 3. the degree of dilaceration (if a larger angle is formed between the crown and the root of the dilacerated tooth); 4. the size of the space for storing the impacted tooth in the dentition (10−14).

**Treatment progress**

After acquainting the parents with the diagnosis, treatment plan and uncertainty of the orthodontic-surgical liberalization of the dilated tooth, who understood and orally and in writing agreed with the explanations from the orthodontist and the surgeon, the therapy began.

The treatment plan was to place a button with twisted wire in an adequate place on the tooth after surgical liberation of the dilacerated tooth, to apply optimal force to orthodontic appliances when pulling the impacted tooth, to create previously a reduced space for placing the dilacerated tooth in the dentition,taking care not to disturb the integrity of the surrounding tissue, taking into account the shorter and thinnerroot of the lateral incisor on the side of the dilacerated tooth in order to avoid resorption of the root of the same during liberation and traction of the impacted central incisor.

The challenge of this case was to correctly position the brackets onthree frontal teeth vertically, and after the surgery to apply optimal traction that would not put too much strain on the lateral incisor on the side of the dilacerated tooth. First, metal orthodontic brackets with inch slot .022"(Mini sprint, Forestadent, Germany) were placed on the central incisor on the left side, lateral incisors and tubes on the molars, a .014" NiTi arch (G & H Wire Co., Indiana, USA) with an open spring between the central incisor on the left and the lateral incisor on the right. An additional problem was the vertical positioning of the bracket on the central incisor on the left side due to the earlier fracture of the crown of that tooth, where on such a shorter crown of the tooth, the positioning of the bracket had to be bonded rather more gingivally than using the established way of positioning. Care was taken to align the position on the lateral incisors with the positioning of the bracket on the central incisor, in order to avoid excessive supraposition. After verifying the position of the dilacerated central incisor on the right side of the upper jaw with CBCT, as well as determining the non-existent angle between the crown and its root, surgical lifting of the mucoperiosteal trapezius lobe was performed according to Novak-Potter, from the canine region on the right side. After the lobe was lifted, the bone above the labially placed crown of the impacted canine was removed. Round steel drill bits with constant cooling by a physiodispenser were used. After exposure the crown of the tooth from excess bone and hemostasis, already prepared orthodontic button (World Class Technology Corporation, USA) with sterile braided wire (Forestanit® Super weich, Forestadent, Germany) 0.5 mm in diameter was placed on the labial surface of the tooth. Conditioning of the labial surface of the tooth was done with 37% orthophosphoric acid in the gel (Orthodontic Bonding System, Acid Etch, Dentaurum, Germany) for 20 seconds. The acid in the gel was then removed with a moist cotton roll and washed with saline. After drying the tooth surface, the orthodontic button was placed using Transbond XT adhesive material (Transbond XT, 3M Unitek, USA). Due to the very difficult and inaccessible position of the dilacerated central incisor, and due to the proximity of surrounding soft tissue and the presence of blood and oral fluids, the conditioned tooth surface was left dry and without primer, while the orthodontist had constant visual control over the working field and so disabled mixing with saliva that could be concealed if the primer was applied to a part of the conditioned enamel. An adhesive was placed over the primer (Transbond XT Primer, 3M Unitek, USA) on the button base, a primer brush was applied over the adhesive material, and its penetration into the lattice base of the button base was performed with light pressure. In this way, a sufficient amount of thin adhesive was provided on the surface of the button base and at the same time, the excess adhesive was removed during the placement with a sharp scaler, thus avoiding additional button movement. Just before placement the button, we pointed the light source (LED light) on the work unit to the side to avoid premature polymerization of the adhesive. After placing the button with twisted wire, the surface of the impacted tooth was polymerized for 20 seconds with a light-emitting diode lamp Woodpecker Dental Curing Light (LED B. Curing Light, Guangxi, China) with a light intensity of 1200−1400 mW/cm2, optical wavelength 420−480 nm; voltage of 3.7 V; 1500 mAh and with a minimum distance in relation to the set button. After the button was placed, the mucoperiosteal lobe was put back in place and sutured with individual sutures (SMI, AG-Belgium silk usp 3/0) with a round needle (hr-20).In the same operative act, after the fixation of the lobe, a frenectomy of the labial frenulum was performed.

Two months after the operation, and the leveling of the front teeth, the patient was placed in a .016"Ni-Ti round archwire (G&H Wire Co., Indiana, USA). On recent wire, Ni–Ti open coil

(American Orthodontic, Sheboygan, Wisconsin, USA) was used to provide proper space. The same Ni–Ti open coil was maintained to keep proper space. The twisted wire was twisted slightly around a .016"Ni-Ti arc every seven days, with the aim of achieving a constant light force continuity when lowering the impacted tooth. This type of activation is very simple and fast, so it takes less time spent in a dental chair but requires diligent patient behavior, in the form of regular check-ups. Less manipulation during wire activation will cause less pain and discomfort to patients, but also less chance of ligature wire breakage or even button detachment on the impacted tooth.

**Treatment results**

After the tooth appeared up to half of its crown, the button on the buccal surface was removed and replaced with a bracket for the right central incisor, the .014" Ni-Ti arch was restored and ligation with rubber bands was performed. After 9 months of orthodontic therapy, the dilated central incisor on the right side was brought to the dentition where it took another two months to obtain an adequate incisal plane correlated with the incisal edges of the lateral incisors, and 1/3 of the central incisor on the left side had to be restoratively replaced, which was another challenge (Figure 4). The repositioned incisor had slightly irregular gingival contour. The post-treatment radiograph (Figure 2b) showed no resorption of roots, no alveolar bone loss and no resorption of the root of lateral incisor on the right side who suffered the greatest force of orthodontic traction during the liberation of the dilated central incisor.

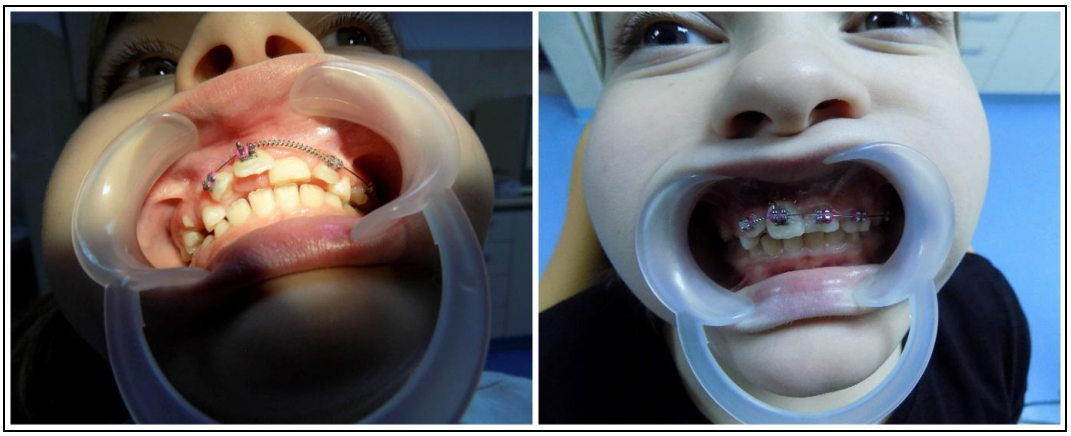


**Figure 4.** Intraoral photograph after 9 months of surgical therapy

**Discussion**

Since dilacerated central incisors are usually above the mucogingival border, the use of a closed eruption technique can provide adequately better gingival contours when the incisor is leveled (11–13). Studies have shown that smaller recessions provide better bone support and superior periodontal parameters by the closed eruption method (14, 15).

Early therapy is of key importance because it enables more adequate development and better morphology of the root tip of the dilacerated tooth, which reduces the possibility of losing alveolar bone on the labial side (16). Most orthodontists believe that dilaceration of the central incisors is a consequence of trauma, but Stewart (17) in his study, which included 41 cases of dilacerated incisors, found that trauma accounted for only 9 cases (22%) and concluded that the cause of dilacerated teeth is the ectopic position of their germs.

Although there are a large number of etiological factors, it is believed that the occurrence of dilacerated central incisors is not fully explained (18–20). As the crowns of maxillary dilacerated incisors are located labially and often near the floor of the nasal cavity, the most common technique used is the closed eruption technique because it is difficult to extract such impacted incisors through the middle ridge using only the elements of the button.

This position of the dilacerated tooth was also in the case of our patient, where the crown of the tooth was positioned horizontally. Factors that are important in deciding on the type of surgical approach to dilacerated incisors depend on the amount of keratinized gingiva that surrounds the tooth crown, the location of the incisal edge and its relationship with the mucogingival joint (21).

It is recommended that the technique of so-called "open window" can lead to an increase in the length of the clinical crown of the tooth as well as to a recognizable scar on the gingiva (22), which is physiologically and aesthetically unacceptable.

A significant increase in the thickness of the alveolar bone occurs in the area of the labial cervical third of the root of the central incisor. These changes may be influenced by incisor position and inclination, orthodontic technique and force applied, and bone remodeling capacity during the retraction (23, 24).

Based on the initial analysis of the position of the dilacerated tooth, the priorities of orthodontic therapy were: extrusion of the impacted tooth, straightening and bringing the tooth into the dental arch. This would establish an adequate function and optimal aesthetics of the growing patient, while preserving the integrity of the periodontium and the surrounding gingival architecture. Orthodontic-surgical treatment of dilacerated maxillary incisors is generally successful but long lasting (25–27). As the phase of orthodontic-surgical liberation of dilacerated incisors begins in mixed dentition, patients very often need the second phase of comprehensive orthodontic therapy. The slow and low but continuous orthodontic traction resulted in good periodontal and periapical health of the tooth. This traction can stimulate root development as well as alveolar bone remodeling (28, 29), thus creating good conditions for normal development of the surrounding gingival tissue, and so avoiding possible later periodontal interventions to improve aesthetics in the frontal region. Effective torque control is the key to a successful therapy of dilacerated teeth, but also very often a challenge when using more conventional metal orthodontic brackets, especially for teeth with shorter and thinner roots, such as lateral incisors (22). Special attention was paid to this moment in order to avoid overloading that the root of the lateral incisor on the side of the dilacerated tooth could suffer. After bringing the dilacerated tooth into the dentition and equalizing and obtaining the appropriate incisal plane as well as the relationship with the surrounding gingivo-dental parameters, the inclination of the front teeth was performed with .019 × .025" stainless steel wire.

Surgical-orthodontic therapy of dilacerated maxillary incisors requires a longer period of time, which can last up to over a year, depending on a number of factors. Assessing the patient's age, crown height, degree of impaired incisor root dilatation as well as crown length can help the orthodontist to better predict the duration of therapy during consultations with patients and parents (30−32). The orthodontic liberation of the impacted central incisor in our case lasted 9, and its placement in the dental arch lasted 11 months.

In this case, the success of the surgical reposition of the horizontally placed permanent central incisor will depend on the degree of tooth root formation. The early phase of root formation would have a far better prognosis for the surgical intervention of a horizontally placed maxillary permanent central incisor with incompletely developed root part, a fact that guided the authors of this paper.

## Conclusion

This work showed that good diagnostics supported by CBCT scanner, adequate multi-disciplinary approach, quality therapy with modified application of orthodontic button placement on impacted tooth, gives satisfactory result in an appropriate time period.

## References


1. Huber KL, Suri L, Taneja P. Eruption disturbances of the maxillary incisors: a literature review 1: J Clin Pediatr Dent 2008; 32(3): 221-30. [CrossRef] [PubMed]
2. Grover PS, Lorton L. The incidence of unerupted permanent teeth and related clinical cases. Oral Surg Oral Med Oral Pathol 1985; 59: 420-5. [CrossRef] [PubMed]
3. Singh GP, Sharma VP. Eruption of an impacted maxillary central incisor with an unusual dilaceration. J Clin Orthod 2006; 40: 353-6. [PubMed]
4. Vermette ME, Kokich VG, Kennedy DB. Uncovering labially impacted teeth: Apically positioned flap and closed-eruption techniques. Angle Orthod 1995; 65: 23-32. [CrossRef] [PubMed]
5. Miloglu O, Cakici F, Caglayan F, Yilmaz AB, Demirkaya F. The prevalence of root dilacerations in a Turkish population. Med Oral Patol Oral Cir Bucal 2010; 15: e441-4. [CrossRef] [PubMed]
6. Brin I, Zilberman Y, Azaz B. The unerupted maxillary central incisor: review of its etiology and treatment. ASDC J Dent Child 1982; 49(5): 352-6. [PubMed]

7. Elefteriadis JN, Athanasiou AE. Evaluation of impacted canines by means of computerized tomography. Int J Adult Orthodon Orthognath Surg 1996; 11(3): 257-64. [PubMed]
8. Lu P, Chew MT. Orthodontic-surgicalmanagement of an unusual dilacerated maxillary incisor. J Orthod Sci 2018; 7:24. [CrossRef] [PubMed]
9. Tanaka E,Hasegawa T, Hanaoka K, Yoneno K, Matsumoto E, Dalla-Bona D et al. Severe crowding and a dilacerated maxillary central incisor in an adolescent. Angle Orthod 2006; 76: 510-8. [CrossRef] [PubMed]
10. Noorollahian S, Shirban F. Chair time saving method for treatment of an impacted maxillary central incisor with 15-month follow-up. Dent Res J 2018; 15: 150-4. [CrossRef] [PubMed]
11. Lin YTJ. Treatment of an impacted dilacerated maxillary central incisor. Am J Orthod Dentofacial Orthop 1999; 115: 406–9. [CrossRef] [PubMed]
12. Tanaka E, Watanabe M, Nagaoka K, Yamaguchi K, Tanne K. Orthodontic traction of an impacted maxillary central incisor. J Clin Orthod 2001; 35: 375–8. [PubMed]
13. Pinho T, Neves M, Alves C. Impacted maxillary central incisor: surgical exposure and orthodontic treatment. Am J Orthod Dento-facial Orthop 2011; 140: 256-65. [CrossRef] [PubMed]
14. Becker A, Chaushu G, Chaushu S. Analysis of failure in the treatment of impacted maxillary canines. Am J Orthod Dentofacial Orthop 2010; 137: 743-54. [CrossRef] [PubMed]
15. Chaushu S, Dykstein N, Ben-Bassat Y, Becker A. Periodontal status of impacted maxillary incisors uncovered by 2 different surgical techniques. J Oral Maxillofac Surg 2009; 67: 120-4. [CrossRef] [PubMed]
16. Sun H, Hu R, Ren M, Lin Y, Wang X, Sun C, Wang Y. The treatment timing of labial inversely impacted maxillary central incisors: A prospective study. Angle Orthod 2016; 86(5): 768-74. [CrossRef] [PubMed]
17. Stewart DJ. Dilacerate unerupted maxillary central incisors. Br Dent J 1978; 145: 229-33. [CrossRef] [PubMed]
18. Topouzelis N, Tsaousoglou P, Pisoka V, Zouloumis L. Dilaceration of maxillary central incisor: a literature review. Dent Traumatol 2010; 26(5): 427-33. [CrossRef] [PubMed]
19. Wei YJ, Lin YC, Kaung SS, Yang SF, Lee SY, Lai YL. Esthetic periodontal surgery for impacted dilacerated maxillary central incisors. Am J Orthod Dentofacial Orthop 2012; 142: 546-51. [CrossRef] [PubMed]
20. Vermette ME, Kokich VG, Kennedy DB. Uncovering labially impacted teeth: Apically positioned flap and closed-eruption techniques. Angle Orthod 1995; 65: 23-32. [CrossRef] [PubMed]
21. Jiang Q, Yang R, Mei L, Ma Q, Wu T, Li H.A novel approach of torque control for maxillary displaced incisors. Am J Orthod Dentofacial Orthop 2019; 155(6): 860-70. [CrossRef] [PubMed]
22. Lyu J, Lin Y, Lin H, Zhu P, Xu Y New clues for early management of maxillary impacted central incisors based on 3-dimensional reconstructed models. Am J Orthod Dentofacial Orthop 2018; 154(3): 390-6. [CrossRef] [PubMed]
23. Domingo-Clérigues M, Montiel-Company JM, Almerich-Silla JM, García-Sanz V, Paredes-Gallardo V, Bellot-Arcís C. Changes in the alveolar bone thickness of maxillary incisors after orthodontic treatment involving extractions - A systematic review and meta-analysis. J ClinExp Dent 2019; 11(1): e76-e84. [CrossRef] [PubMed]
24. Chaushu S, Becker T, Becker A. Impacted central incisors: Factors affecting prognosis and treatment duration. Am J Orthod Dentofacial Orthop 2015; 147: 355-62. [CrossRef] [PubMed]
25. Ho KH, Liao YF. Predictors of surgical-orthodontic treatment duration of unilateral impacted maxillary central incisors. Orthod Craniofac Res 2011; 14: 175-80. [CrossRef] [PubMed]
26. Farronato G, Giannini L, Galbiati G, Maspero CA. 5-year longitudinal study of survival rate and periodontal parameter changes at sites of dilacerated maxillary central incisors. Prog Orthod 2014; 15: 3-8. [CrossRef] [PubMed]
27. Cheng C, Li X, Liu H. Evaluation of the orthodontic treatment outcome in patients with impacted maxillary central incisor in the mixed dentition. Zhonghua Kou Qiang Yi XueZaZhi 2016; 51(5): 263-8. [CrossRef] [PubMed]
28. Nallanchakrava S, Mettu S, Reddy NG, *et al*. Multidisciplinary Approach for the Management of Dilacerated Permanent Maxillary Incisor: A Case Report. Int J Clin Pediatr Dent 2020; 13(6): 725-8. [CrossRef] [PubMed]
29. Khera AK, Rohilla A, Tandon P, Singh GP. Orthodontic management of impacted central incisor: A clinical challenge. J Indian Orthod Soc 2017; 51: 46-50. [CrossRef]
30. Bhikoo C, Xu J, Sun H, Jin C, Jiang H, Hu R. Factors affecting treatment duration of labial inversely impacted maxillary central incisors. Am J Orthod Dentofacial Orthop 2018; 153(5): 708-15. [CrossRef] [PubMed]
31. Felicita AS. Orthodontic management of a dilacerated central incisor and partially impacted canine with unilateral extraction - A case report Saudi Dent J2017; 29( 4): 185-93. [CrossRef] [PubMed]
32. Singh H, Kapoor P, Sharma P, Dudeja P, Maurya RK, Thakkar S. Interdisciplinary management of an impacted dilacerated maxillary central incisor. Dental Press J Orthod 2018; 23(3): 37-46. [CrossRef] [PubMed]

**Prikaz bolesnika**

**UDC: 616.314.3-007-089.23**
**doi: 10.5633/amm.2023.0111**

# ORTODONTSKO-HIRURŠKA TERAPIJA IMPAKTIRANOG, CENTRALNOG, MAKSILARNOG SEKUTIĆA – PRIKAZ SLUČAJA

*Vladimir Mitić[1]*, Kosta Todorović[2], Aleksandar Mitić[3]*

[1]Univerzitet u Nišu, Medicinski fakultet, Katedra za ortopediju vilica i zuba, Niš, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet, Katedra za oralnu hirurgiju, Niš, Srbija
[3]Univerzitet u Nišu, Medicinski fakultet, Katedra za bolesti zuba i endodonciju, Niš, Srbija

Kontakt: Dr Vladimir Mitić
Romanijska 7/14, 18000 Niš
018 229794, 0641138353
midentmts.rs

Cilj ovog rada bio je da se precizno utvrdi mogućnost terapije liberacije impaktiranog centralnog sekutića kod devojčice starosti devet godina, a zatim da se u što kraćem vremenskom intervalu zub dovede na svoje prirodno mesto u zubnom nizu. Pre intervencije pristupilo se detaljnom pregledu (CBCT) i analizi svih parametara, kako bi se utvrdila mogućnost uspešne terapije impaktiranog zuba. Ortodontski plan terapije sastojao se od tri koraka – kreiranje prostora, ekspozicija krunice zuba i forsirana erupcija. Nakon izvršene hirurške intervencije oslobađanja impaktiranog centralnog sekutića, u istom aktu postavljeno je dugme modifikovanom direktnom metodom bondiranja sa upredenom žicom od strane ortodonta, te se nakon skidanja konaca pristupilo vuči ovakvog zuba, pomoću fiksnog ortodontskog aparata (SWA tehnika). Kontrole su rađene na dve nedelje do pojave zuba. Nakon uspešnog izvlačenja impaktiranog zuba i njegovog postavljanja u zubni niz, pristupilo se restauraciji susednog centralnog sekutića sa leve strane, kako bi se dobila adekvatna veličina istog, ali i incizalna ravan, koja bi zadovoljavala sve funkcionalne i estetske parametre vezane za ovo doba deteta. Modifikovana metoda direktnog bondiranja dugmeta za površinu impaktiranog zuba pokazala se kao olakšana metoda, u odnosu na konvencionalnu metodu. Kvalitetna dijagnoza uz adekvatnu multidisciplinarnu terapiju daje zadovoljavajući rezultat u optimalnom vremenu. *Acta Medica Medianae 2023;62(1): 71-78.*

***Ključne reči:*** *: impakcija zuba, hirurgija, ortodoncija, CBCT*

**Case report** **UDC: 616.718-001.5:616.748-001.3-06]:616-089**
**doi: 10.5633/amm.2023.0112**

# SURGICAL TREATMENT OF PIPKIN IV COMMINUTIVE FRACTURE ASSOCIATED WITH HAEMATOMA, SIGNIFICANT SOFT TISSUE DAMAGE, AND DEEP INFECTION – A CASE REPORT

*Igor Merganovski[1,2], Slavco Stojmenski[1,2], Spase Antevski[1,2], Andreja Gavrilovski[1,2]*

Femoral head fractures associated with acetabular fractures are uncommon injuries usually resulting from high-energy mechanisms. This paper is aimed to present a case with successful treatment of Pipkin IV, a comminutive fracture of the head of the femur associated with hematoma, soft tissue damage, and deep infection.

Patient D.M. 1976 was injured from some concrete blocks. The patient was a polytraumatized patient with a severe traumatic shock and Pipkin IV dislocated and comminutive fracture of the left femoral head, comminutive fracture of the left acetabulum, and big hematoma of the left femoral region with soft tissue damage of this region. There was a fracture of the pubic and ischium bone on the right side of the pelvis. He was admitted to the Intensive care unit as an urgent case.

First, we performed an open reduction and internal fixation of the left acetabulum with plate and screws. The patient after that got a serious deep infection of the hematoma in the left femoral region so we had to treat this infection for two months. We had to wait for the next three months without any symptom or sign of the infection (CRP levels were normal) and after that, we performed the application of subtotal prosthesis after removal of all bone fragments of the left femoral head.

The patient had no signs of infection after the second operation and we referred him to receive intensive physiotherapy during the next three months. He could walk without any support three months after the second operation and after continuous physiotherapy and in that time, the range of movements of his left leg was only slightly limited.

We performed x-ray control a year after the operation and the patient developed the signs of ectopic ossification, but the range of motion remained only minimally limited. The Harris Hip Score in that time was 81.

The main treatment should always be an immediate anatomic reduction of the fragments with minimal soft tissue injury and fixation with ORIF in all other Pipkin fractures, but in cases with Pipkin IV fractures associated with previously extensive soft tissue damage and deep infection we recommend waiting for the second operation for at least three months after disappearing of all symptoms and signs of the infection. *Acta Medica Medianae 2023;62(1):79-84.*

***Key words:*** *Pipkin fracture-dislocation, soft-tissue, hematoma, complications*

[1]University Clinic for Traumatology, Orthopaedic Diseases, Anaesthesia, Reanimation, Intensive Care and Emergency Centre, Skopje, Republic of North Macedonia,
[2]St Cyril and Methodius University of Skopje, Medical Faculty, Skopje, Republic of North Macedonia

*Contact:* Igor Merdzanoski
Adresa: Majka Tereza 17, 1000 – Skopje, Makedonija
Telefon: +389 75238191
e-mail: igormerganoski@hotmail.com

## Introduction

These types of fractures are fractures of the femoral head associated with hip dislocation and fracture of the acetabulum. They are extremely rare and are associated with poor functional outcomes.

Keely and Lipscomb reported that the incidence of the Pipkin fractures is two cases per one million patients per year, but the incidence of Pipkin IV fracture is much rarer than the previous. There are also very controversial treatment strategies for this type of fracture. In Pipkin II and III fractures, there is really one of few orthopedic emergencies but in Pipkin IV fractures there is no need for an emergency but there is a need to achieve good functional outcomes. Essentially, Pipkin IV fractures can be treated surgically by ORIF of the acetabular fracture and fixation or excision of the femoral head fragments and application of subtotal or total hip prosthesis.

**Case presentation:**

Patient D.M. 1976 was injured from some concrete blocks. The patient was polytraumatized with a severe traumatic shock and Pipkin IV dislocated and comminutive fracture of the left femoral head, comminutive fracture of the left acetabulum, and big hematoma of the left femoral region with soft tissue damage of this region. There was a fracture of pubic and ischium bone on the right side of the pelvis. He was admitted to the Intensive care unit as an emergency case (Figure 1).

This type of fracture has a very high percentage of postoperative aseptic necrosis of the femoral head and because of that we decided to perform a total hip prosthesis with screw fixation of the acetabular part and to solve the problem with one operation, but the acetabular surface was so comminutive and there was no place for fixing the acetabular cup and there was also big hematoma with soft tissue damage of all left femoral region. Because of that, we decided to make the Kocher Langebeck approach and to proceed in two steps: first to fix acetabulum with plate and screws with checking the acetabular inner surface and removing the pieces of the femoral head and after that to perform the second operation with removal of the remaining particles of comminutive fractured femoral head and to applicate a subtotal prosthesis. We did not use a total hip prosthesis because of the risk of infection.

First, we performed an open reduction and internal fixation of the left acetabulum with plate and screws from the Kocher Langebeck approach (Figure 2). We intended to remove the fragments from the femoral head and to perform Muller subtotal prosthesis in a second step, but the patient got an intensive deep infection of the hematoma in the left femoral region so we had to treat this infection.

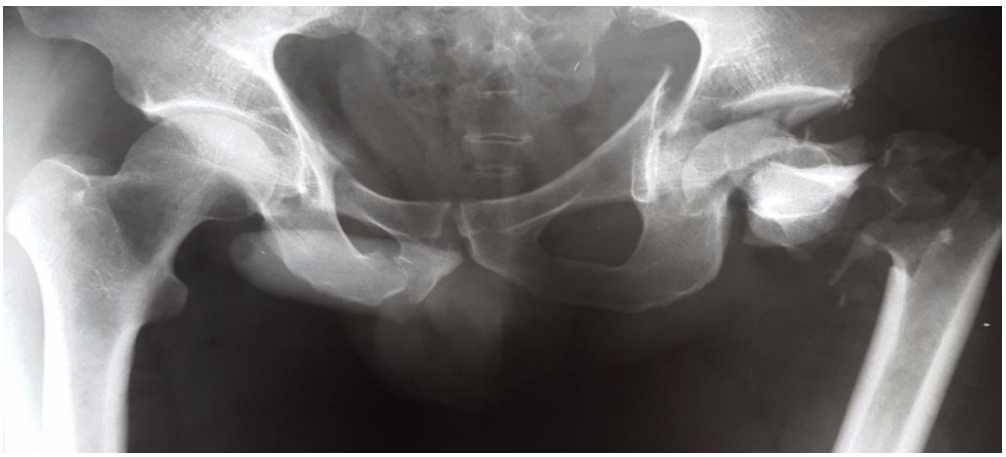


**Figure 1:** X-ray on the admission of the patient

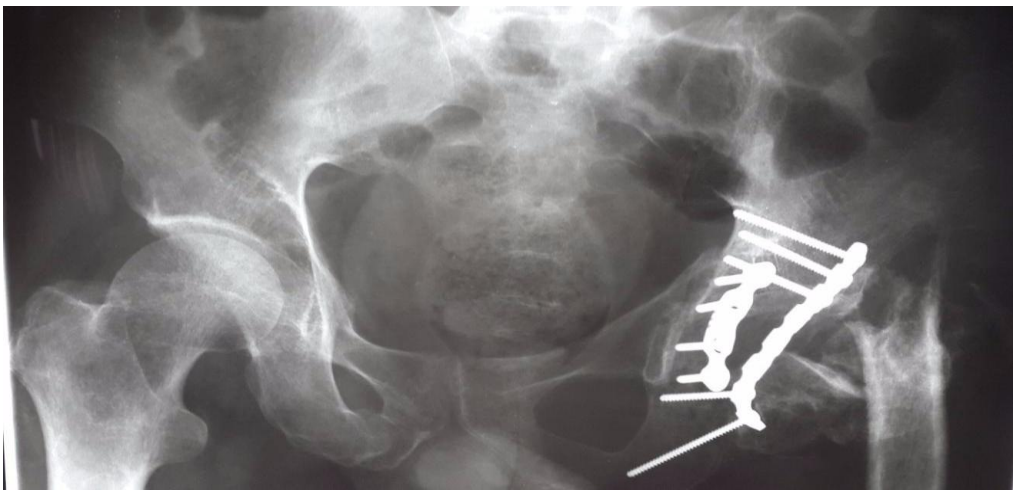


**Figure 2**: X-ray after the first operation

We isolated Pseudomonas aeruginosa et Klebsiella pneumoniae and had to use two antibiotics according to antibiogram: Linezolid S 2x1 and Garamycin S 2x120 during ten days in two repeated times. Local treatment of the infection was performed at the time of two months with every day special silver dressings and patches combined with local application of antibiotics according to antibiogram. When there was no more secretion produced (fistula) at the place of the operation we stopped with the local treatment, but we continued with systemic antibiotic application several days after that.

We had to wait for the next three months without any symptom or sign of the infection (the levels of CRP were normal) and after that, we performed the application of subtotal prosthesis after removal of all bone fragments of the left femoral head (Figure 3).

The patient had no signs of the infection after the second operation and we referred him to receive intensive physiotherapy for a period of three months. He could walk without support three months after the second operation and continuous physiotherapy during three months, and at that time his left leg movement range was only slightly limited (Figure 4).

We perform RTG control a year after the operation and the patient develops signs of ectopic ossification but the range of motion remained minimally limited. The Harris Hip Score at that time was 81. (Figure5).

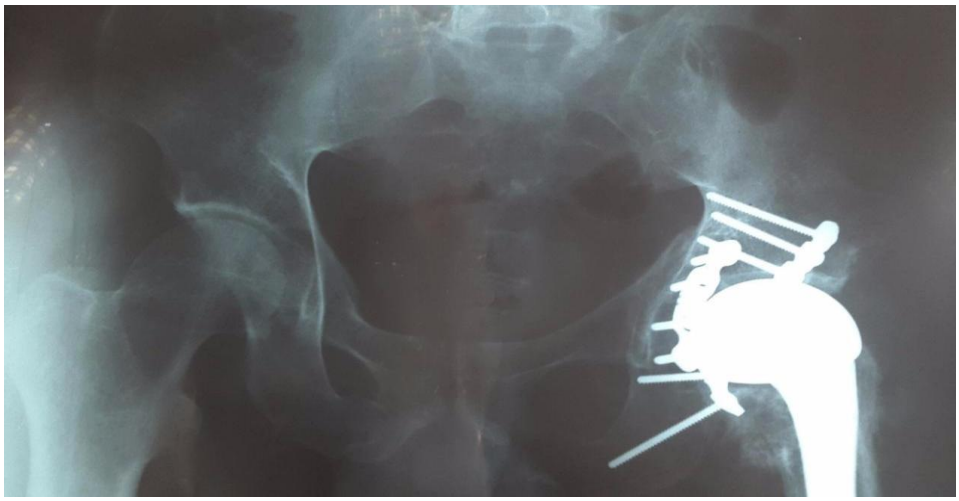


**Figure 3:** X-ray after the second operation

**Figure 4:** Picture with the patient, functional tests after 3 months of intensive physiotherapy

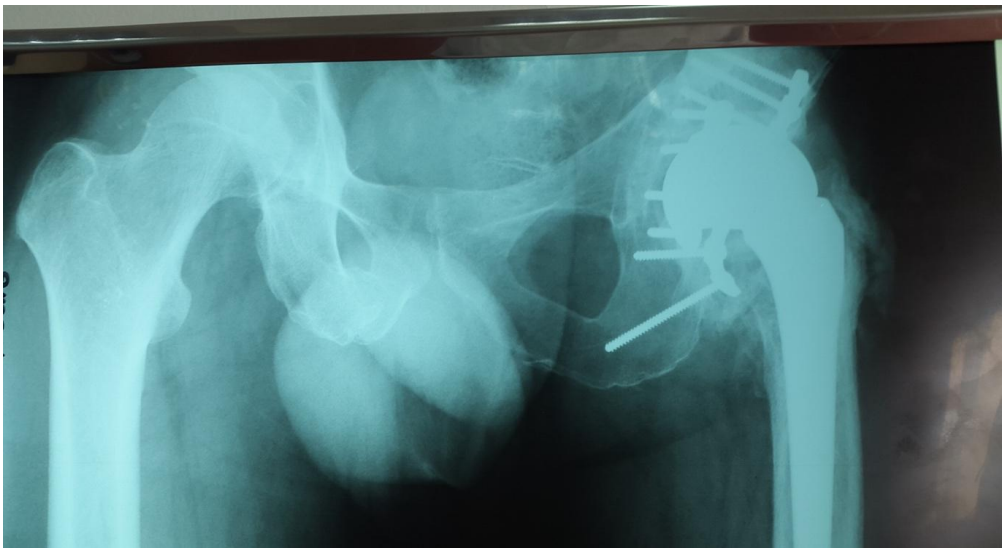


**Figure 5:** X-ray control one year after the first operation

## Discussion

In this case of Pipkin IV fracture, we think that the time elapsed between traumatic dislocation of the hip joint and the reduction is not a key element for a good outcome because we do not hope that the reconstruction of the femoral head is possible and that the femoral head will survive. It is recommended to perform a CT scan with 3D reconstruction so that a more accurate evaluation of the fracture pattern and the comminution can be achieved. This is also helpful in deciding which treatment to pursue. We assume that anatomic reconstruction and fixation of acetabular fracture through posterior Kocher – Langebeck approach and excision of femoral head intra-articular bodies as a first operation and removal of some femoral headpieces and application of subtotal bipolar prosthesis if there is no infection can be a recommended method of treatment for this type of fracture.

In this case, we could not achieve any optimal reconstruction of the femoral head and we thus decided not to fix the femoral head. In the meantime, we had a serious infection near the femoral head so we had to wait for the definitive application of the prosthesis for more than 5 months.

We did not want to perform THR because we were afraid of the tips of the screws used to fix the plates on the acetabular posterior wall. One of the options was to remove the plates and screws from the posterior wall of the acetabulum and after that to perform THR. However, we were able to achieve ideal reconstruction of the acetabular surface without any defect of the wall and during the second operation, five months after the first one, we checked if the acetabular dome was without any defects and that helped us to decide to perform only subtotal prosthesis. Further, in the circumstances where the tissue near the fracture was not with normal characteristics and we were not sure whether there was an infection or not, we decided to proceed without removal of osteosynthesis of the acetabular wall and with the use of minimal implants – subtotal hip prosthesis.

## Conclusion

Femoral head fractures associated with acetabular fractures are uncommon injuries usually resulting from high-energy mechanisms. Outcomes of Pipkin type IV fractures have been historically poor, with high rates of osteonecrosis, post-traumatic arthritis, and heterotopic ossification.

The main treatment aim should always be anatomic reduction of the fragments with minimal soft tissue injury and fixation with ORIF in all other Pipkin fractures, but in the cases with Pipkin IV fractures associated with previously extensive soft tissue damage and deep infection, we believe that this approach has to be changed.

We can recommend this system of treatment in patients with Pipkin IV fracture combined with big soft tissue damage, large hematoma, and infection, and we recommend waiting for the second operation for a minimum of three months after disappearance of all symptoms and signs of the infection.

## References


1. Stannard JP, Harris HW, Volgas DA, Alonso JE. Functional outcome of patients with femoral head fractures associated with hip dislocations. Clin Orthop Relat Res 2000; 377: 44-56. [CrossRef] [PubMed]
2. 2. Kelly PJ, Lipscomb PR. Primary vitallium-mold arthroplasty for posterior dislocation of the hip with fracture of the femoral head. J Bone Joint Surg 1958; 40: 675-80. [PubMed]
3. 3. Moed BR, Maxey JW. Evaluation of fractures of the femoral head using the CT-directed pelvic oblique radiograph. Clin Orthop Relat Res 1993; 296: 161-167. [PubMed]
4. 4. Henle P, Kloen P, Siebenrock KA. Femoral head injuries which treatment strategy can be recommended? Injury 1993; 38: 478-488. [CrossRef] [PubMed]
5. 5. Kloen P, Siebenrock KA, Raaymakers ELFB, Marti RK, Ganz R, et al. Femoral head fractures revisited. European Journal of Trauma 2002; 4: 221-223. [CrossRef]
6. 6. Pipkin G. Treatment of Grade IV fracture-dislocation of the hip. J Bone Joint Surg Am 1957; 39: 1027-1042. [PubMed]
7. 7. Ugino FK, Righetti CM, Pinheiro Lédio Alves D, Guimarães RP, Honda EK, et al. Evaluation of the reliability of the modified Merle d'Aubigné and Postel Method. Acta Ortop Bras 2012; 20: 213-217. [CrossRef] [PubMed]
8. 8. Epstein HC. Traumatic dislocations of the hip. Clin Orthop Relat Res 1973; 116-142. [CrossRef] [PubMed]
9. 9. McMurtry IA, Quaile A. Closed reduction of the traumatically dislocated hipa new technique. Injury 2001; 32: 162-164. [CrossRef] [PubMed]
10. Lederer S, Tauber M, Karpik S, Bogner R, Auffarth A, et al. Fractures of the femoral head. A multicenter study. Unfallchirurg 2007; 110: 513-520. [CrossRef] [PubMed]
11. Park KS, Lee KB, Na BR, Yoon TR. Clinical and radiographic outcomes of femoral head fractures excision vs. fixation of fragment in Pipkin type I what is the optimal choice for femoral head fracture? J Orthop Sci 2015; 20: 702-707. [CrossRef] [PubMed]
12. Lin D, Lian K, Chen Z, Wang L, Hao J, et al. Emergent surgical reduction and fixation for Pipkin type I femoral fractures. Orthopedics 2013; 36: 778-782. [CrossRef] [PubMed]
13. Chen ZW, Lin B, Zhai WL, Guo ZM, Liang Z, et al. Conservative versus surgical management of Pipkin type I fractures associated with posterior dislocation of the hip randomized controlled trial. Int Orthop 2011; 35: 1077-1081. [CrossRef] [PubMed]
14. Epstein HC, Wiss DA, Cozen L. Posterior fracture dislocation of the hip with fractures of the femoral head. Clin Orthop Relat Res 1985; 201: 9-17. [PubMed]
15. Butler JE. Pipkin Type-II fractures of the femoral head. J Bone Joint Surg Am 1981; 6: 1292-1296. [PubMed]
16. Chakraborti S, Miller IM. Dislocation of the hip associated with fracture of the femoral head. Injury 1975; 7: 134-142. [CrossRef] [PubMed]
17. Helms JR, Nowotarski PJ. Posterior wall acetabulum fracture–dislocation with subsequent ipsilateral Pipkin IV fracture–dislocation. How many hits can a hip take? Trauma Case Reports 2015; 1: 65-72. [CrossRef] [PubMed]

**Prikaz bolesnika** **UDC: 616.718-001.5:616.748-001.3-06]:616-089**
**doi: 10.5633/amm.2023.0112**

# TRETMAN PIPKIN TIP IV FRAKTURE-LUKSACIJE UDRUŽENE ZA HEMATOMOM, ZNAČAJNOM MEKOTKIVNOM POVREDOM I DUBOKOM INFEKCIJOM – PRIKAZ SLUCAJA

*Igor Merganovski[1,2], Slavco Stojmenski[1,2], Spase Antevski[1,2], Andreja Gavrilovski[1,2]*

[1]Univerzitetska klinika za traumatologiju,
ortopedske bolesti, anesteziju, reanimaciju i urgentni centar, Skoplje,
Republika Severna Makedonija
[2]Univerzitet "Sveti Ćirilo i Metodije" u Skoplju,
Medicinski fakultet, Skoplje, Republika Severna Makedonija

Kontakt: Igor Merdzanoski
Adresa: Majka Tereza 17, 1000 – Skopje, Makedonija
Telefon: +389 75238191
e-mail: igormerganoski@hotmail.com

Frakture glave femura povezane sa frakturama acetabuluma predstavljaju nesvakidašnje povrede koje su rezultat visokoenergetskog mehanizma. Ovaj rad ima za cilj da prezentuje uspešan operativni tretman Pipkin tip IV frakture, kominutivne frakture glave femura povezane sa hematomom, povredom mekih tkiva i dubokom infekcijom.

Bolesnik D.M. rođen 1976 godine povređen je betonskim blokovima. Bolesnik je politraumatizovan sa traumatskim šokom i Pipkin IV dislociranom i kominutivnom frakturom leve femoralne glave, uz kominutivnu frakturu acetabuluma i sa velikim hematomom leve femoralne regije, kao i sa mekotkivnim oštečenjem. Bolesnik je imao frakturu pubične i išijadične kosti sa desne strane karlice. Bio je odmah primljen u jedinicu intenzivne nege, kao hitan slučaj.

Prvo, izveli smo otvorenu repoziciju i unutrašnju fiksaciju levog acetabuluma sa pločom i šrafovima. Onda je bolesnik dobio ozbiljnu infekciju hematoma leve femoralne regije, zbog čega smo morali da tretiramo infekciju u naredna dva meseca. Bili smo primorani da čekamo tri meseca, kako bi utvrdili da nema bilo kakvih znakova infekcije (nivoa CRP u normali) i onda smo postavili subtotalnu protezu, nakon što smo izvadili fragmente glave femura.

Bolesnik nije imao nikakve znakove infekcije nakon drugog operativnog tretmana i odlučili smo da je vreme da započne intenzivnu fizikalnu terapiju u trajanju od tri meseca. Mogao se kretati bez bilo kakvih pomagala nakon tri meseca od završenog operativnog tretmana i završene fizikalne terapije, uz mala ograničenja u pokretima.

Uradili smo radiološku kontrolu godinu dana nakon operacije, koja je pokazala ektopičnu osifikaciju, ali bez bilo kakvih zabrinjavajućih ograničenja u pokretima. Harris hip score u tom periodu bio je 81.

Glavni tretman uvek bi trebao biti usmeren ka momentalnoj anatomskoj redukciji fragmenata sa minimalnim oštećenjem mekih tkiva i fiksaciji uz ORIF u slučajevima svih ostalih tipova Pipkin fraktura, ali u slučajevima Pipkin IV frakture povezane sa prethodno masivnim ostećenjem mekih tkiva i dubokom infekcijom mi preporučujemo da se sačeka druga po redu opertivna intervencija, bar tri meseca od prestanka simptoma infekcije. *Acta Medica Medianae 2023;62(1): 79-84.*

***Ključne reči:*** *Pipkin fraktura-luksacija, hematom, meka tkiva, komplikacije*

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Ideja o postavljanju jedinstvenih kriterijuma za objavljivanje radova u časopisima za biomedicinske nauke iskristalisana je 1978. godine u Vankuveru. Ovi kriterijumi za rukopise, uključujući pravila za pisanje bibliografije, prvi put su objavljeni 1979. godine. Vankuverska grupa je vremenom prerasla u Međunarodni komitet urednika medicinskih časopisa — International Committee of Medical Journal Editors (ICMJE). Trenutno je na snazi peta revizija kriterijuma za objavljivanje radova u biomedicinskim časopisima, doneta 1997. godine.

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Reference se obeležavaju arapskim brojevima u zagradama, pri čemu se reference obele-žavaju brojevima onim redosledom kojim se pojavljuju u tekstu. Reference citirane jedino u tabelama ili legen-di moraju se obeležiti brojem u skladu sa redosledom pojavljivanja u tekstu.

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Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood–leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996;73:1006-12.

*2. Organizacija kao autor*

The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996;164:282-4.

*3. Članak bez poznatih autora*

Cancer in South Africa (editorial). S Afr Med J 1994;84:15.

*4. Volumen sa suplementom*

Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994; 102 Suppl 1:275-82.

*5. Broj sa suplementom*

Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. Semin Oncol 1996;23(1 Suppl 2):89-97.

*6. Volumen sa više delova*

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

*7. Broj sa više delova*

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

*8. Časopisi sa brojem bez volumena*

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

*9. Časopisi bez volumena i broja*

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

*10. Reference u obliku apstrakta ili prethodnih saopštenja*

Enzensberger W, Fischer PA. Metronome in Parkinson's disease (letter) Lancet 1996;347:1337.

Clement J, De Bock R. Hematological complica–tions of hantavirus nephropathy (HVN) (abstract). Kidney Int 1992; 42:1285.

**Udžbenici i monografije**

*11. Monografija*

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

*12. Autori kao urednici*

Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

*13. Organizacija kao autor i izdavač*

Institute of Medicine (US). Looking at the future of the Medicaid program. Washington: The Institute; 1992.

*14. Poglavlje u knjizi*

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

*15. Conference proceedings*

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

*16. Conference paper*

Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors.

MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

*17. Istraživački ili tehnički izveštaji*

**Službeni izveštaji (Issued by funding / sponsoring agency):**

Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept. of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860.

**Sponzorisani izveštaji (Issued by performing agency)**

Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research.

*18. Magistarske i doktorske disertacije*

Kaplan SJ. Post-hospital home health care: the elderly's access and utilization [dissertation]. St. Louis (MO): Washington Univ.; 1995.

**Druge vrste publikovanog materijala**

**Neobjavljeni materijal**

*19. U štampi (In press)*

Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med. In press 1996.

**Elektronski zapisi**

*20. Internet članak u elektronskom formatu*

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar "cited 1996 Jun 5"; 1(1)(24 screens). Available from: URL: http://www.cdc.gov/ncidod/EID/eid.htm

*21. Monografija u elektronskom formatu*

CDI, clinical dermatology illustrated (monograph on CD-ROM). Reeves JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego: CMEA; 1995.

*22. Kompjuterski podaci*

Hemodynamics III: the ups and downs of hemodynamics (computer program). Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

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