YU ISSN 0042-8450

ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

Часопис лекара и фармацеута Војске Србије

Military Medical and Pharmaceutical Journal of Serbia

Vojnosanitetski pregled

Vojnosanit Pregl 2024; March Vol. 81 (No. 3): pp. 129–192.

Vojnosanitetski Pregled 2024 March Vol. 81 (No. 3): pp. 129–192.

Military Medical Academy

Vol. 81, No. 3, 2024

VOJNOSANITETSKI PREGLED

The first issue of *Vojnosanitetski pregled* was published in September 1944
The Journal continues the tradition of Vojno-sanitetski glasnik which was published between 1930 and 1941

PUBLISHER
Ministry of Defence of the Republic of Serbia, University of Defence, Belgrade, Serbia

ISSN 0042-8450
eISSN 2406-0720

Editorial Office: University of Defence, Faculty of Medicine of the Military Medical Academy, Center for Medical Scientific Information, Crnotravska 17, 11 040 Belgrade, Serbia. E-mail: **vsp@vma.mod.gov.rs**

Papers published in the Vojnosanitetski pregled are indexed in: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, SCOPUS, Excerpta Medica (EMBASE), Google Scholar, EBSCO, Biomedicina Serbica, Serbian Citation Index (SCIndex), DOAJ. Contents are published in Giornale di Medicine Militare and Revista de Medicina Militara. Reviews of original papers and abstracts of contents are published in International Review of the Armed Forces Medical Services.

The Journal is published monthly. Subscription: Giro Account No. 840-19540845-28, refer to number 122742313338117. To subscribe from abroad phone to +381 11 3608 997. Subscription prices per year: individuals 5,000.00 RSD, institutions 10,000.00 RSD, and foreign subscribers 150 €.

Printed by: Vojna štamparija, Beograd, Resavska 40b

Vol. 81, br. 3, 2024

VOJNOSANITETSKI PREGLED

Prvi broj *Vojnosanitetskog pregleda* izašao je septembra meseca 1944. godine
Časopis nastavlja tradiciju *Vojno-sanitetskog glasnika*, koji je izlazio od 1930. do 1941. godine

IZDAVAČ
Ministarstvo odbrane Republike Srbije, Univerzitet odbrane, Beograd, Srbija

ISSN 0042-8450
eISSN 2406-0720
Open Access
(CC BY-SA)

Adresa redakcije: Univerzitet odbrane, Medicinski fakultet Vojnomedicinske akademije, Centar za medicinske naučne informacije, Crnotravska 17, 11 040 Beograd, Srbija. Informacije o pretplati (tel.): +381 11 3608 997. E-mail (redakcija): **vsp@vma.mod.gov.rs**

Radove objavljene u „Vojnosanitetskom pregledu“ indeksiraju: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, SCOPUS, Excerpta Medica (EMBASE), Google Scholar, EBSCO, Biomedicina Serbica, Srpski citatni indeks (SCIndeks), DOAJ. Sadržaje objavljuju Giornale di Medicine Militare i Revista de Medicina Militara. Prikaze originalnih radova i izvoda iz sadržaja objavljuje International Review of the Armed Forces Medical Services.

Časopis izlazi dvanaest puta godišnje. Pretplate: Žiro račun br. 840-19540845-28, poziv na broj 122742313338117. Za pretplatu iz inostranstva obratiti se službi pretplate na tel. +381 11 3608 997. Godišnja pretplata: 5 000 dinara za građane Srbije, 10 000 dinara za ustanove iz Srbije i 150 € za pretplatnike iz inostranstva. Kopiju uplatnice dostaviti na gornju adresu.

Štampa: Vojna štamparija, Beograd, Resavska 40b

CONTENTS / SADRŽAJ

CASE REPORTS / KAZUISTIKA

Military Medical Academy

In March of this year, the Military Medical Academy, the highest professional, scientific, and educational institution of the medical service of the Serbian Armed Forces, celebrated its 180th anniversary (see Editorial, pp. 133-135).

U martu ove godine Vojnomedicinska akademija, najviša stručna, naučna i obrazovna institucija sanitetske službe Vojske Srbije, proslavila je 180 godina postojanja (vidi Uvodnik, str. 133-135).

E D I T O R I A L

UDC: 355.721:061.5
DOI: https://doi.org/10.2298/VSP2403133V

The first 180 years

Prvih 180 godina

Miroslav Vukosavljević

Military Medical Academy, Clinic for Ophthalmology, Belgrade, Serbia; University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia

The jubilee of the Military Medical Academy (MMA) and its existence for 180 years in the service of its people, its army, and the country was marked on March 4, 2024, with a ceremonial academy in the presence of high-ranking officials.

On the occasion of this jubilee, which hardly anyone in the country and beyond has the opportunity to celebrate, it is difficult to summarize even just a decade behind us, let alone, by all standards, the binding history and tradition that the MMA inherits.

This year, on the eve of the birthday, each of which has so far deserved powerful words, we had a demanding task in front of us – to adequately present and mark the integrity of the MMA's existence. This institution is a symbol of the origin and development of the medical corps of Serbia and a solid foundation of not only military medicine but also Serbian medicine in general. The professional, educational, and scientific research work of generations of the best military and civilian doctors and nurses employed has been maintained and improved for decades, thus ensuring the continuity of trust of all patients and people in successful treatment, education, and quality care.

Archives of the Media Center "Odbrana" – the old building of the Military Medical Academy

Archives of the Media Center "Odbrana" – the new building of the Military Medical Academy

Precisely for these reasons, it is difficult and ungrateful to expect comprehensiveness during one event because numerous papers have been written about the MMA, and its value has grown and strengthened every day since. In addition to recalling the most important moments from the previous 180 years, a great effort was made during the ceremony to introduce numerous dignitaries to the continuity of progress and development of this first military healthcare institution, which developed from the Central Military Hospital of the Principality of Serbia in 1844 to today's "temple of health and education", to the pride of our country and beyond its borders.

Not long ago, I finished reading Thomas Carlyle's book "On Heroes". He advocated the theory that history was created only by great personalities, and great personalities who remain remembered can only be heroes. For me, it is very real and true, it is all those who built this house, as well as those who work in it now. I am asking you, right at the be

Correspondence to: Miroslav Vukosavljević, Military Medical Academy, Clinic for Ophthalmology, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: vuki032@yahoo.com

ginning, to find your heroes, who will be a true inspiration for some future success.

When we list all the decisions we have made to this day, it is perhaps best to start from the beginning, and a new beginning is what is at the end!

The jubilee has a special weight for me, a weight that is 18 decades old. You will admit that it is an imposing figure that dominates in its sustainability. The MMA was created with the idea of eternity, and the starting point of success is desire. All employees at the MMA have the desire to make everyday life more beautiful, it is part of our calling, and with true passion, we approach projects that continue to grow in scope even after these 180 years.

Intensive care unit

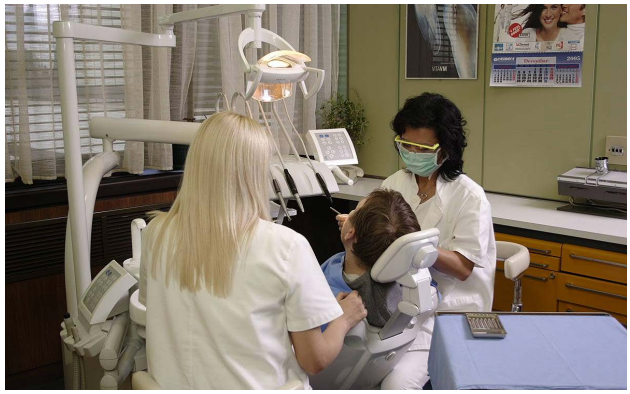
Hyperbaric chamber

When I became the head of this house seven years ago, I knew that there would be challenges and life changes, but I was even more aware of the fact that if the spirit was fearless, the head would be held high. Such spirit and enthusiasm have not left me even to this day. As long as there is creativity, imagination, and courage to make something happen or try something that has not been done before, I am the first in line to participate.

They say that a person goes through several stages in their life and working life. We are now clearly at a stage where proving ourselves is no longer on the agenda. I want us to make the team around us grow together with the program we will make in the best of faith. We waited to show and prove to the world how vital we are in all life's changes, challenges, years, hopes, and joys. We managed to return to the crown of surgery – transplantation, after a successful fight with the coronavirus pandemic. It is a permanent task not only for us but also for the entire country.

Scanner

The MMA is not just a name – it is an expression of identity, inspiration, and originality. Health is the most essential protagonist, and health means the existence of our only life. Openness, understanding, and cooperation can and must be bridges that connect, not walls that separate. Looking through this prism, our perspective becomes different. That is why the MMA is a world and a home for everyone who strives for excellence. A privilege you deserve. We have never been the ones who kept quiet and hid our faces behind our fists and walls. We have always been the ones who move things and stand on the right side of everything. Surrendering, anytime and to anyone, was never our option.



Stomatology

Health care service

The MMA is proud of all its generations of employees, successes, and brave endeavors in the diagnosis and treatment of the most serious diseases of its patients, always ready to progress and work more and better, transfer knowledge, learn, and always be in the company of the best.

Expecting that the younger generations, who are growing up in our ranks, will continue to proudly preserve the valuable heritage and build new values, we only have to remember all the successes in which we, together with our predecessors, have participated. Furthermore, we expect only the best results in future work because the MMA deserves it and has been proving it for 180 years.

Let the celebrating sounds of the MMA's 180 years be the codes of rebirth and new age. Until the next jubilee, cheers.

ORIGINAL ARTICLES

UDC: 616.94-06::616.831-037
DOI: https://doi.org/10.2298/VSP230911004Z

Prognostic values of tumor necrosis factor-alpha, monocyte chemoattractant protein-1, and neuron-specific enolase in patients with sepsis-associated encephalopathy

Prognostička vrednost faktora nekroze tumora alfa, monocitnog hemoatraktantnog proteina-1 i neuron-specifične enolaze kod bolesnika sa encefalopatijom izazvanom sepsom

Bingnan Zhu, Fengqi Liu, Zhongnan Jia, Zhidong Chen, Luyin Wang

The First People's Hospital of Huzhou, Department of Intensive Care Unit, Huzhou, Zhejiang Province, China

Abstract

Background/Aim. Sepsis-associated encephalopathy (SAE) is a severe complication of sepsis, characterized by brain dysfunction and associated with a poor prognosis. SAE has a complex pathogenesis, and its severity is in close association with the levels of various serum factors. The aim of the study was to investigate the correlation of tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, and neuron-specific enolase (NSE) levels with the severity of SAE and to analyze the prognostic values of the three parameters. **Methods**. This prospective study enrolled 126 patients treated for SAE from June 2020 to June 2022. The levels of TNF-α, MCP-1, and NSE were measured, and the severity of SAE was evaluated using the Sequential Organ Failure Assessment (SOFA) score. Based on the SOFA score, the patients were assigned to two groups: a group with a bad prognosis and a group with a good prognosis. The correlations of TNF-α, MCP-1, and NSE levels with the severity of SAE were analyzed, and their prognostic values were evaluated during a 28-day follow-up. **Results**. The mean levels of TNF-α, MCP-1, and NSE and the SOFA score of the 126 patients with SAE were 6.52 ± 1.48 pg/mL, 62.53 ± 18.49 pg/mL, 8.61 ± 2.17 ng/mL, and 10.24 ± 2.86 points, respectively. Pearson's analysis demonstrated significant correlations between TNF-α, MCP-1, and NSE levels and the SOFA score of patients with SAE ($r > 0$, $p < 0.05$). Of the 126 patients, 61 (48.4%) had a poor prognosis, while 65 (51.6%) had a good prognosis. Increased serum TNF-α, MCP-1, and NSE levels were risk factors for the poor prognosis of patients with SAE [odds ratio (OR) > 1, $p < 0.05$]. The areas under the receiver operating characteristic (ROC) curves of serum TNF-α, MCP-1, and NSE levels were all > 0.7, suggesting high predictive values of these parameters. **Conclusion**. Serum TNF-α, MCP-1, and NSE levels are closely correlated with the severity of SAE and may work as valuable predictors of treatment outcome.

Key words:
correlation of data; monocyte chemoattractant protein-1; prognosis; risk factors; sepsis associated encephalopathy; tumor necrosis factor-alpha; neuron-specific enolase.

Apstrakt

Uvod/Cilj. Encefalopatija izazvana sepsom (EIS) je teška komplikacija sepse, koju karakteriše disfunkcija mozga, a povezana je sa lošom prognozom. Patogeneza EIS je složena, a težina njene manifestacijhe je u bliskoj korelaciji sa nivoima različitih faktora u serumu. Cilj rada bio je da se ispita korelacija nivoa faktora nekroze tumora (*tumor necrosis factor*-TNF)-α, monocitnog hemoatraktantnog proteina (*monocyte chemoattractant protein*-MCP)-1 i neuron-specifične enolaze (NSE) sa težinom EIS i analizira prognostička vrednost ova tri parametra. **Metode.** Ovom prospektivnom studijom obuhvaćena su 126 bolesnika sa EIS, lečena u periodu od juna 2020. do juna 2022. godine. Određivani su nivoi TNF-α, MCP-1 i NSE, a težina EIS procenjena je korišćenjem skora procene sekvencijalnog popuštanja organa (*Sequential Organ Failure Assessment* – SOFA). Na osnovu SOFA skora, bolesnici su podeljeni u dve grupe – grupu sa lošom prognozom i grupu sa dobrom prognozom. Analizirane su korelacije nivoa TNF-α, MCP-1 i NSE sa težinom EIS, a njihove prognostičke vrednosti procenjivane su tokom 28-dnevnog praćenja. **Rezultati.** Prosečni nivoi TNF-α, MCP-1, NSE i SOFA skora kod 126 bolesnika sa EIS bili su 6,52 ± 1,48 pg/mL, 62,53 ± 18,49 pg/mL, 8,61 ± 2,17 ng/mL i 10,24 ± 2,86 poena, redom. Pirsonova analiza pokazala je značajne korelacije između nivoa TNF-α, MCP-1 i

Correspondence to: Bingnan Zhu, The First People's Hospital of Huzhou, Department of Intensive Care Unit, 313 000 Huzhou, Zhejiang Province, China. E-mail: zhubnfphh@uic-edu.cn

NSE i SOFA skora bolesnika sa EIS ($r > 0$, $p < 0,05$). Od 126 bolesnika, njih 61 (48,4%) imalo je lošu prognozu, dok je njih 65 (51,6%) imalo dobru prognozu. Faktori rizika za lošu prognozu kod bolesnika sa EIS bili su povišeni nivoi TNF-α, MCP-1 i NSE u serumu [*odds ratio* (OR) > 1, $p < 0,05$]. Površine ispod *receiver operating characteristic* (ROC) krive za TNF-α, MCP-1 i NSE u serumu bile su > 0,7, što ukazuje na visoke prognostičke vrednosti tih parametara. **Zaključak.** Nivoi TNF-α, MCP-1 i NSE usko su povezani sa težinom EIS i mogu biti vredni prediktori ishoda lečenja.

Ključne reči:
podaci, korelacija; monocitni hemoatraktantni protein-1; prognoza; faktori rizika; encefalopatija izazvana sepsom; faktor nekroze tumora – alfa; neuron-specifična enolaza.

Introduction

Sepsis-associated encephalopathy (SAE) is a severe complication of sepsis, characterized by brain dysfunction and associated with a poor prognosis [1]. As a critical disease, SAE can cause sudden and severe chills, high fever, a series of uncomfortable symptoms in the central nervous system, secondary epilepsy, as well as respiratory, circulatory, and renal failure [2, 3]. The treatment of SAE is difficult, so the hospitalization stay is prolonged, and the mortality rate of septic patients is elevated [4]. Moreover, SAE has a complex pathogenesis, and its severity is closely related to the levels of various serum factors [5]. Therefore, it is of guiding significance to identify relevant serum markers for early evaluation of the severity and prognosis of SAE for clinical treatment.

Tumor necrosis factor (TNF)-α is a well-established pro-inflammatory cytokine with a pivotal role in the pathogenesis of sepsis and the inflammatory response of SAE. TNF-α can stimulate the generation of inflammatory transmitters and affect the release of inflammatory cells, making it a useful indicator for evaluating the severity of SAE [6]. Georgescu et al. [7] reported that TNF-α can be used as a predictor of sepsis susceptibility and progression. Monocyte chemoattractant protein (MCP)-1 is a chemotactic cytokine closely related to brain tissue injury, which can exert a chemotactic effect on T lymphocytes, cause neutrophil aggregation, and increase inflammatory mediators, thus worsening brain tissue injury [8]. Chen et al. [9] reported that MCP-1 was a potential marker for patients with sepsis. Neuron-specific enolase (NSE), a biomarker of brain injury, is frequently used in the clinical diagnosis of hypoxic-ischemic encephalopathy and brain injury. Shaik et al. [10] found that NSE was a marker of neuronal damage in patients with epileptic seizures. Thus, NSE may also be associated with SAE [11].

Having all this in perspective, the aim of this study was to investigate the association between TNF-α, MCP-1, and NSE levels and the severity of SAE. Additionally, the predictive value of the three indicators was analyzed in order to provide references for the evaluation of SAE severity and prognosis of disease outcomes.

Methods

A prospective study was conducted on 126 patients with SAE from June 2020 to June 2022, including 69 males and 57 females aged 56–73 years, with an average ± standard deviation (SD) age of 65.3 ± 4.6 years. The body mass index (BMI) was 19–30 kg/m^2, and the average ± SD value was 25.9 ± 2.4 kg/m^2.

The inclusion criteria were as follows: (1) patients who met the relevant diagnostic criteria for SAE (serious infections, such as abdominal infection and sepsis, as well as abnormal symptoms of the central nervous system, such as disturbance of consciousness and decreased orientation) [12], (2) duration of symptoms from onset to admission ≤ 48 hrs, and (3) patients with signed informed consent form. The exclusion criteria involved: (1) cerebrovascular accidents, (2) metabolic encephalopathy, (3) intracranial organic lesions, (4) central nervous system infection, (5) patients who died within 24 hrs after admission, (6) patients who used high-dose hormone drugs in the past one month, (7) acquired immunodeficiency syndrome-AIDS, viral hepatitis, or other severe infectious diseases, (8) hematological diseases or malignancies, and (9) those who gave up treatment halfway and discharged themselves from the hospital.

On admission, 4 mL of venous blood was drawn from each patient and centrifuged at 3,500 rpm for 10 min to separate serum. Then, the levels of serum TNF-α and MCP-1 were measured by enzyme-linked immunosorbent assay, and the NSE level was measured using an automated chemiluminescence immunoassay analyzer (Beckman Coulter, UniCel DxI 800 Access). The severity of the disease was assessed using the Sequential Organ Failure Assessment (SOFA) [13] scoring system for six organ systems/functions (coagulation, respiratory system, cardiovascular system, liver function, renal function, and central nervous system). With 0–4 points for each of the six functions, the total score range was 0–24 points, and a higher score indicated a more severe organ failure and higher severity of disease.

The prognosis for all patients was observed during a 28-day follow-up period. The patients who survived after 28 days were enrolled in the good prognosis group, while those who died within 28 days were classified in the poor prognosis group. The prognosis was poor in 61 (48.4%) patients and good in 65 (51.6%) patients.

The following indicators were compared between the good prognosis group and the poor prognosis group: gender (male, female), age, BMI, diabetes mellitus (DM) (Yes or No; fasting blood glucose ≥ 7.0 mmol/L or 2 hrs postprandial blood glucose ≥ 11.1 mmol/L was considered DM), hypertension (Yes or No; defined as diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg measured for three consecutive times on different days), hyperuricemia (Yes or No; defined as blood uric acid > 480 μmol/L in males or > 380 μmol/L in females), coagulation disorders [Yes or No; defined as prolonged thrombin time (reference range – RR: 9.2–11.9 s), activated partial thromboplastin time (RR: 24.1–32.3 s), coagulation time (bleeding time RR: 1–4 min, clotting time

RR: 3–5 min); decreased fibrinogen (RR: 2.2–5.2 g/L), platelets (RR: 130–400 × 10^9/L)], malnutrition (Yes or No; defined as albumin level < 35 g/L), drinking history (Yes or No; defined as average daily alcohol consumption > 20 g in females or > 40 g in males for more than one month, or drinking more than once a month for more than six months), smoking history [Yes or No; defined as a smoking index (number of cigarettes per day × years of smoking) ≥ 200], blood analysis [white blood cell (WBC) count RR: 4.5–11.0 × 10^9/L, hemoglobin RR: 12–18 g/dL, and platelet count], procalcitonin (normal value < 0.1 μg/L), C-reactive protein-CRP (normal value < 1 mg/dL), and serum TNF-α (RR: 0–8.1 pg/mL), MCP-1 (RR: 11–88 pg/mL), and NSE (RR: 0–12.5 ng/mL) levels.

Statistical analysis

Statistical analysis was conducted using SPSS 23.0 software. The continuous data were presented as mean ± SD and analyzed by the *t*-test. The discrete data were shown as numbers (percentages) and compared by the χ^2 test. Pearson's correlation analysis was performed between the levels of TNF-α, MCP-1, and NSE and the SOFA score. Logistic regression analysis was employed to determine the effects of serum TNF-α, MCP-1, and NSE levels on the prognosis of patients with SAE. The predictive values of serum TNF-α, MCP-1, and NSE levels for prognosis were analyzed using receiver operating characteristic (ROC) curves, and the $p < 0.05$ was considered statistically significant.

Results

The mean ± SD SOFA score for all 126 patients with SAE was 10.24 ± 2.86 points. The results of Pearson's correlation analysis showed that the serum levels of TNF-α, MCP-1, and NSE were positively correlated with the SOFA score of patients with SAE ($r = 0.453$, 0.446, and 0.559, respectively; $p < 0.001$).

The levels of WBC count, procalcitonin, CRP, TNF-α, MCP-1, and NSE were higher in the poor prognosis group than those in the good prognosis group ($p < 0.05$). There were no significant differences in gender, age, BMI, DM, hypertension, hyperuricemia, coagulation disorders, malnutrition, drinking history, smoking history, hemoglobin level, and platelet count between the two groups ($p > 0.05$) (Table 1).

Table 1

Clinical data of sepsis-associated encephalopathy patients in good and poor prognosis group

Parameter	Poor prognosis group (n = 61)	Good prognosis group (n = 65)	Statistical value	*p*-value
Gender				
male (n = 69)	35 (57.38)	34 (52.31)	$\chi^2 = 0.326$	0.568
female (n = 57)	26 (42.62)	31 (47.69)		
Age (years)	65.47 ± 4.36	65.18 ± 4.21	$t = 0.432$	0.666
Body mass index (kg/m^2)	26.02 ± 2.28	25.77 ± 2.39	$t = 0.600$	0.550
Diabetes mellitus				
yes (n = 15)	8 (13.11)	7 (10.77)	$\chi^2 = 0.165$	0.685
no (n = 111)	53 (86.89)	58 (89.23)		
Hypertension				
yes (n = 46)	24 (39.34)	22 (33.85)	$\chi^2 = 0.410$	0.522
no (n = 80)	37 (60.66)	43 (66.15)		
Hyperuricemia				
yes (n = 56)	29 (47.54)	27 (41.54)	$\chi^2 = 0.459$	0.498
no (n = 70)	32 (52.46)	38 (58.46)		
Coagulation disorders				
yes (n = 35)	18 (29.51)	17 (26.15)	$\chi^2 = 0.177$	0.674
no (n = 91)	43 (70.49)	48 (73.85)		
Malnutrition				
yes (n = 52)	28 (45.90)	24 (36.92)	$\chi^2 = 1.047$	0.306
no (n = 74)	33 (54.10)	41 (63.08)		
Drinking history				
yes (n = 38)	18 (29.51)	20 (30.77)	$\chi^2 = 0.024$	0.877
no (n = 88)	43 (70.49)	45 (69.23)		
Smoking history				
yes (n=39)	17 (27.87)	22 (33.85)	$\chi^2 = 0.526$	0.468
no (n=87)	44 (72.13)	43 (66.15)		
White blood cells count (×10^9/L)	15.36 ± 3.64	14.12 ± 3.58	$t = 2.083$	0.039
Hemoglobin (g/L)	116.53 ± 12.95	115.84 ± 11.36	$t = 0.318$	0.751
Platelet count (×10^9/L)	208.62 ± 43.25	211.76 ± 42.57	$t = 0.411$	0.682
Procalcitonin (pg/mL)	32.58 ± 6.54	29.75 ± 6.18	$t = 2.497$	0.014
C-reactive protein (mg/dL)	22.18 ± 4.36	20.09 ± 4.52	$t = 2.639$	0.009
TNF-α (pg/mL)	7.22 ± 1.26	5.86 ± 1.32	$t = 5.908$	< 0.001
MCP-1(pg/mL)	71.04 ± 16.37	54.54 ± 15.96	$t = 5.728$	< 0.001
NSE(ng/mL)	9.35 ± 1.96	7.92 ± 1.82	$t = 4.247$	< 0.001

TNF– tumor necrosis factor; MCP – monocyte chemoattractant protein; NSE – neuron-specific enolase.
All values are expressed as numbers (percentages) or mean ± standard deviation.

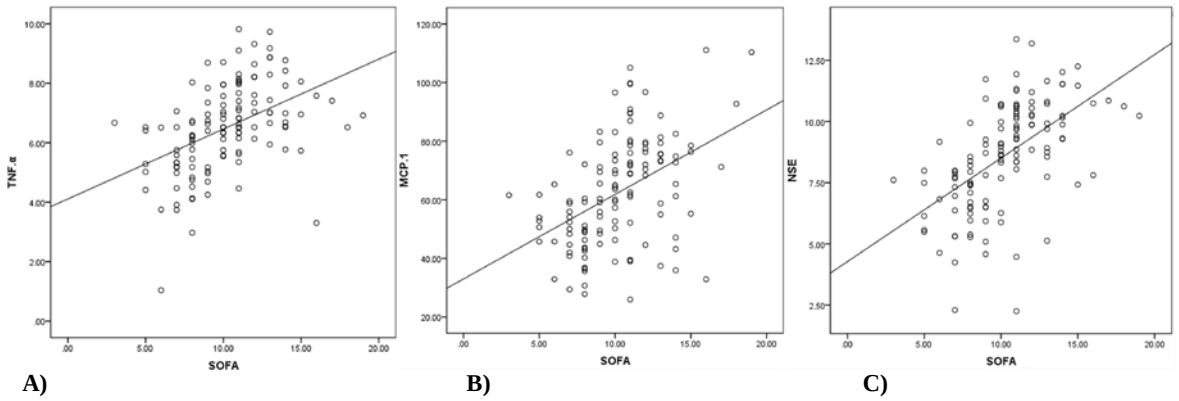
In the 126 patients with SAE, the range of levels of TNF-α was 3.32–10.45 pg/mL, with a mean of 6.52 ± 1.48 pg/mL. The range of MCP-1 levels was 16.42–102.26 pg/mL, with a mean of 62.53 ± 18.49 pg/mL. The range of NSE levels was 4.71–14.30 ng/mL, with a mean of 8.61 ± 2.17 ng/mL. The distribution of the levels according to the severity of SAE is shown in Figure 1.

Effects of serum TNF-α, MCP-1, and NSE levels on the prognosis of patients with SAE

Logistic regression analysis was performed with the levels of TNF-α, MCP-1, and NSE as independent variables (all continuous variables) and the prognosis for patients with SAE as a dependent variable (1 = poor prognosis, 0 = good prognosis). The results showed that the levels of serum TNF-α, MCP-1, and NSE could be considered risk factors for the poor prognosis of patients with SAE (OR > 1, $p < 0.05$) (Table 2 and Figure 2).

Predictive values of serum TNF-α, MCP-1, and NSE levels for the prognosis of patients with SAE

ROC curves were plotted with the levels of TNF-α, MCP-1, and NSE as test variables and the prognosis of patients with SAE as a state variable (1 = poor prognosis, 0 = good prognosis). It was found that the areas under the curves of serum TNF-α, MCP-1, and NSE levels for pre-



A) **B)** **C)**

Fig. 1 – Distribution of TNF-α (A), MCP-1 (B), and NSE (C) levels according to the severity of sepsis-associated encephalopathy (SOFA score).
SOFA – Sequential Organ Failure Assessment. For other abbreviations, see Table 1.

Table 2

TNF-α, MCP-1, and NSE serum levels as risk factors in disease outcome prognosis

Parameter	β	SE	χ^2*	*p*-value	OR	95% CI
TNF-α	0.698	0.198	12.387	< 0.001	2.010	1.363–2.966
MCP-1	0.064	0.016	16.004	< 0.001	1.066	1.033–1.101
NSE	0.442	0.135	10.737	0.001	1.556	1.195–2.028

β – maximum likelihood of estimation coefficient; SE – standard error; OR – odds ratio; CI – confidence interval. For other abbreviations, see Table 1.
***Wald Chi-square distribution.**

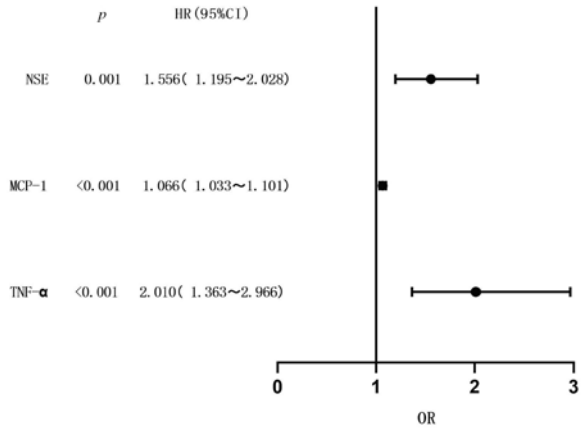


Fig. 2 – A forest plot of multivariate logistic regression analysis for TNF-α, MCP-1, and NSE levels.
HR – hazard ratio. For other abbreviations, see Tables 1 and 2.

Table 3

TNF-α, MCP-1, and NSE serum levels as predictive factors for disease outcome prognosis

Parameter	AUC	SE	*p*-value	95% CI	Cut-off value	Sensitivity	Specificity	Youden index
TNF-α (pg/mL)	0.770	0.042	< 0.001	0.688–0.852	6.48	0.787	0.677	0.464
MCP-1 (pg/mL)	0.761	0.043	< 0.001	0.676–0.845	66.81	0.754	0.754	0.508
NSE (ng/mL)	0.704	0.046	< 0.001	0.614–0.795	8.38	0.705	0.615	0.320
Combined detection	0.809	0.039	< 0.001	0.732–0.886	-	0.836	0.631	0.467

AUC – Area Under the Receiver Operating Characteristic Curve. For other abbreviations, see Tables 1 and 2.

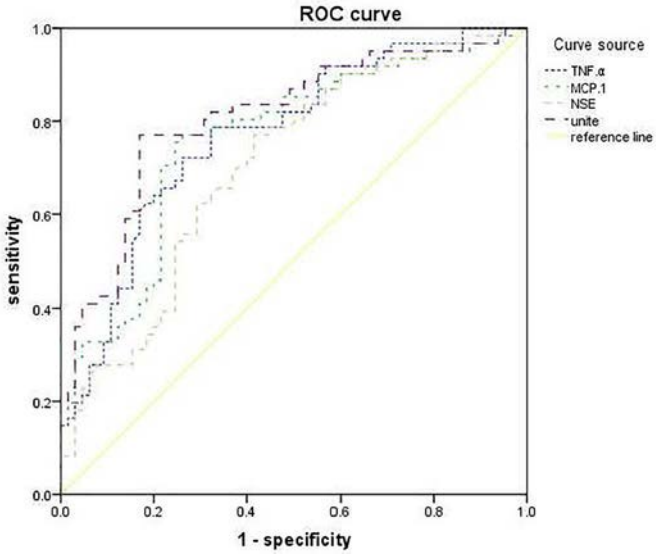


Fig. 3 – Receiver Operating Characteristic (ROC) curves of serum TNF-α, MCP-1, and NSE levels as predictive factors of outcome for patients with SAE. For abbreviations, see Table 1.

dicting the poor prognosis of patients with SAE were all > 0.7, suggesting certain predictive value and the predictive value of combined detection of these three indicators was higher (Table 3 and Figure 3).

Discussion

The underlying pathological mechanism of SAE remains elusive, which may be related to direct nerve injury, oxidative stress injury, inflammatory reaction, etc. [14]. At any stage of sepsis, SAE can occur, and patients mainly present with changes in consciousness, arousal, behavior, and cognition, and deep coma in severe cases [15]. Despite advances in clinical awareness of SAE and treatment methods, the mortality rate of SAE remains high [16]. In this study, 61 out of 126 patients with SAE had a poor prognosis, accounting for 48.4% of the total number of patients, suggesting a high rate of poor prognosis. Therefore, it is of great significance to explore the related indicators of the severity and prognosis of SAE for early evaluation of disease severity and prognostic prediction [17].

At present, many routine detection indicators are available for SAE, including WBC count, procalcitonin, and CRP, which can reflect the inflammatory status of patients to a certain extent [18]. However, the levels of these indicators can also increase to varying degrees in patients with simple sepsis, resulting in low specificity in evaluating SAE. Therefore, there is still a need to explore other detection indicators. Patients with SAE are in a severe stress state that can stimulate the activation of a large number of monocytes, macrophages, neutrophils, etc., and the release of a variety of inflammatory cytokines, including TNF-α [19]. TNF-α is a polypeptide cytokine with various biological activities, including involvement in many pathological and physiological processes, such as inflammatory response and immune defense [20]. In this study, the results of Pearson's correlation analysis showed a positive correlation between the serum TNF-α level and the SOFA score of patients with SAE, indicating that the higher the serum TNF-α level, the more severe the disease. The serum TNF-α level was higher in the poor prognosis group than the levels in the good prognosis group. Moreover, logistic regression analysis revealed that the serum TNF-α level was a risk factor for poor prognosis of patients with SAE. The possible reason is that TNF-α can directly mediate the development of inflammatory response and induce the release of other cytokines, such as interleukin-8 and interleukin-6, leading to a cytokine cascade and the formation of a complex regulatory network. This cascade can initiate systemic inflammatory response syndrome, causing severe inflammatory responses in multiple important organs and inducing multiple organ failure, which in turn worsens the patient's condition and negatively affects prognosis [21, 22].

MCP-1, also known as monocyte chemotactic activating factor and monocyte activating factor, plays an important role in the occurrence and development of hypoxic-ischemic brain injury [23]. In this study, the serum MCP-1 level was positively correlated with the SOFA score of patients with SAE, and it was significantly higher in the poor prognosis group than in the good prognosis group. Furthermore, the serum MCP-1 level is closely associated with the disease severity and prognosis, being consistent with previous literature [24]. MCP-1, mainly produced by monocytes, participates in the migration of neutrophils, natural killer cells, memory T cells, and monocytes. It recruits these cells to inflammatory lesions, aggravating the inflammatory response and leading to inflammatory injury of multiple organs and tissues, thereby worsening the condition of disease and the prognosis [25, 26].

NSE, secreted by neuroendocrine cells, is a protease widely present in human nerve tissues, which can nourish nerves and participate in nerve energy metabolism. In the case of cranial nerve injury, NSE can diffuse into intercellular space and cerebrospinal fluid [27]. NSE is a biochemical marker for brain diseases such as cerebral infarction and brain injury, and an increased serum NSE level usually indicates the worsening of neurological function [28, 29]. In this study, the serum NSE level was significantly correlated with the severity of SAE and could seriously impact the prognosis of patients. In patients with SAE, the systemic inflammatory response can lead to blood-brain barrier damage, making NSE enter the bloodstream from the central nervous system. That leads to abnormal energy metabolism in brain tissues due to NSE deficiency, thus triggering neuronal apoptosis, perivascular edema, central pontine myelinolysis, astrocyte terminal swelling, and multiple necrotic white matter lesions, which can worsen the prognosis of patients [30, 31]. Furthermore, the ROC curves were plotted in this study, and it was found that the area under the ROC curve of serum TNF-α, MCP-1, and NSE levels for predicting the poor prognosis of patients with SAE was > 0.7 for all three biochemical markers, suggesting certain predictive value. The predictive value of the combined detection of these three indicators was higher. Therefore, in the future, close attention should be paid to the serum TNF-α, MCP-1, and NSE levels in patients with sepsis; patients with abnormal levels of the three indicators should be given brain tissue-protecting and cerebral metabolism-improving treatment to prevent the occurrence of SAE or reduce the severity of disease, thereby ameliorating the prognosis of disease outcome in patients.

Conclusion

TNF-α, MCP-1, and NSE levels are closely associated with the severity of SAE and can be used to predict the prognosis of the sepsis outcome. It is necessary to closely monitor the changes in the above three indicators in patients for early evaluation of severity, thereby providing references for the development of timely, adequate therapeutic regimens.

Funding

This study was financially supported by the Zhejiang Provincial Medical and Health Science and Technology Plan Project (No. 2021KY1094) and the Public Welfare General Project of Huzhou Science and Technology Bureau (No. 2021GYB49).

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. *Chen J, Shi X, Diao M, Jin G, Zhu Y, Hu W,* et al. A retrospective study of sepsis-associated encephalopathy: epidemiology, clinical features and adverse outcomes. BMC Emerg Med 2020; 20(1): 77.
2. *Xiong Y, Yang J, Tong H, Zhu C, Pang Y.* HMGB1 augments cognitive impairment in sepsis-associated encephalopathy by binding to MD-2 and promoting NLRP3-induced neuroinflammation. Psychogeriatrics 2022; 22(2): 167–79.
3. *Wang H, Wang H, Song Y, Liu C, Qian X, Zhang D,* et al. Overexpression of Foxc1 ameliorates sepsis-associated encephalopathy by inhibiting microglial migration and neuroinflammation through the IκBα/NF-κB pathway. Mol Med Rep 2022; 25(3): 107.
4. *Feng Q, Ai YH, Gong H, Wu L, Ai ML, Deng SY,* et al. Characterization of sepsis and sepsis-associated encephalopathy. J Intensive Care Med 2019; 34(11–12): 938–45.
5. *Hu J, Xie S, Li W, Zhang L.* Diagnostic and prognostic value of serum S100B in sepsis-associated encephalopathy: A systematic review and meta-analysis. Front Immunol 2023; 14: 1102126.
6. *Hugo Montes A, Valle-Garay E, Martin G, Collazos J, Alvarez V, Meana A,* et al. The *TNF-a (-238 G/A)* polymorphism could protect against development of severe sepsis. Innate Immun 2021; 27(5): 409–20.
7. *Georgescu AM, Banescu C, Azamfirei R, Hutanu A, Moldovan V, Badea I, et al.* Evaluation of TNF-α genetic polymorphisms as predictors for sepsis susceptibility and progression. BMC Infect Dis 2020; 20(1): 221.
8. *Zhang Y, Huang T, Jiang L, Gao J, Yu D, Ge Y,* et al. MCP-induced protein 1 attenuates sepsis-induced acute lung injury by modulating macrophage polarization via the JNK/c-Myc pathway. Int Immunopharmacol 2019; 75: 105741.
9. *Chen Z, Li C, Yu J.* Monocyte chemoattractant protein-1 as a potential marker for patients with sepsis: systematic review and meta-analysis. Front Med (Lausanne) 2023; 10: 1217784.
10. *Shaik AJ, Reddy K, Mohammed N, Tandra SR, Kandadai RM, Kss SB.* Neuron specific enolase as a marker of seizure related neuronal injury. Neurochem Int 2019; 131: 104509.
11. *Quispe-Cornejo AA, McDUFF S, Crippa IA, Vincent JL, Creteur J, Taccone FS.* Neuron-specific enolase levels are not related to cerebral autoregulation in septic patients. Minerva Anestesiol 2021; 87(2): 238–9.
12. *Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS,* et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 775–87.

13. *Iyer D, Hunt L, Frost SA, Aneman A.* Daily intra-abdominal pressure, Sequential Organ Failure Score and fluid balance predict duration of mechanical ventilation. Acta Anaesthesiol Scand 2018; 62(10): 1421–7.
14. *Guo W, Li Y, Li Q.* Relationship between miR-29a levels in the peripheral blood and sepsis-related encephalopathy. Am J Transl Res 2021; 13(7): 7715–22.
15. *Chung HY, Wickel J, Brunkhorst FM, Geis C.* Sepsis-Associated Encephalopathy: From Delirium to Dementia? J Clin Med 2020; 9(3): 703.
16. *Becker AE, Teixeira SR, Lunig NA, Mondal A, Fitzgerald JC, Topjian AA,* et al. Sepsis-Related Brain MRI Abnormalities Are Associated With Mortality and Poor Neurological Outcome in Pediatric Sepsis. Pediatr Neurol 2022; 128: 1–8.
17. *Mazeraud A, Righy C, Bouchereau E, Benghanem S, Bozza FA, Sharshar T.* Septic-Associated Encephalopathy: a Comprehensive Review. Neurotherapeutics 2020; 17(2): 392–403.
18. *Tang C, Zhou W, Chen X, Wang F, Men W, Liu J,* et al. Research Progress of Biomarkers of Sepsis-Associated Encephalopathy. Intensive Care Res 2023; 3: 69–76.
19. *Gu M, Mei XL, Zhao YN.* Sepsis and Cerebral Dysfunction: BBB Damage, Neuroinflammation, Oxidative Stress, Apoptosis and Autophagy as Key Mediators and the Potential Therapeutic Approaches. Neurotox Res 2021; 39(2): 489–503.
20. *Lendak DF, Mihajlović DM, Novakov-Mikić AS, Mitić IM, Boban JM, Brkić SV.* The role of TNF-α superfamily members in immunopathogenesis of sepsis. Cytokine 2018; 111: 125–30.
21. *Wang H, Guo S, Wan C, Yang T, Zeng N, Wu Y,* et al. Tumor necrosis factor-α -308 G/A polymorphism and risk of sepsis, septic shock, and mortality: an updated meta-analysis. Oncotarget 2017; 8(55): 94910–9.
22. *Lee J, Son W, Hong J, Song Y, Yang CS, Kim YH.* Downregulation of TNF-α via macrophage-targeted RNAi system for the treatment of acute inflammatory sepsis. J Control Release 2021; 336: 344–53.
23. *Liu R, Liao XY, Tang JC, Pan MX, Chen SF, Lu PX,* et al. BpV(pic) confers neuroprotection by inhibiting M1 microglial polarization and MCP-1 expression in rat traumatic brain injury. Mol Immunol 2019; 112: 30–9.
24. *Wang Y, Liu Q, Liu T, Zheng Q, Xu X, Liu X,* et al. Early plasma monocyte chemoattractant protein 1 predicts the development of sepsis in trauma patients: A prospective observational study. Medicine (Baltimore) 2018; 97(14): e0356.
25. *Ebihara T, Matsumoto H, Matsubara T, Matsuura H, Hirose T, Shimizu K,* et al. Adipocytokine Profile Reveals Resistin Forming a Prognostic-Related Cytokine Network in the Acute Phase of Sepsis. Shock 2021; 56(5): 718–26.
26. *He J, Chen Y, Lin Y, Zhang W, Cai Y, Chen F,* et al. Association study of MCP-1 promoter polymorphisms with the susceptibility and progression of sepsis. PLoS One 2017; 12(5): e0176781.
27. *Lu W, Jiang C, Wang Z, Chen Y, Bai R, Yan G,* et al. Lactic acid, neuron-specific enolase, and blood-brain barrier index after a severe traumatic brain injury: a prospective study. Br J Neurosurg 2020; 1–5.
28. *Echeverría-Palacio CM, Agut T, Arnaez J, Valls A, Reyne M, Garcia-Alix A.* Neuron-Specific Enolase in Cerebrospinal Fluid Predicts Brain Injury After Sudden Unexpected Postnatal Collapse. Pediatr Neurol 2019; 101: 71–7.
29. *Bagnato S, Andriolo M, Boccagni C, Lucca LF, De Tanti A, Pistarini C,* et al. Reduced Neuron-Specific Enolase Levels in Chronic Severe Traumatic Brain Injury. J Neurotrauma 2020; 37(2): 423–7.
30. *Ehler J, Saller T, Wittstock M, Rommer PS, Chappell D, Zwissler B,* et al. Diagnostic value of NT-proCNP compared to NSE and S100B in cerebrospinal fluid and plasma of patients with sepsis-associated encephalopathy. Neurosci Lett 2019; 692: 167–73.
31. *Anderson BJ, Reilly JP, Shashaty MGS, Palakshappa JA, Wysoczanski A, Dunn TG,* et al. Admission plasma levels of the neuronal injury marker neuron-specific enolase are associated with mortality and delirium in sepsis. J Crit Care 2016; 36: 18–23.

Received on September 11, 2023
Revised on October 15, 2023
Revised on December 9, 2023
Accepted on December 19, 2023
Online First January 2024

ORIGINAL ARTICLE

UDC: 616.831-005.1-06-037
DOI: https://doi.org/10.2298/VSP230927009Z

The predictive value of the CONUT score combined with the A^2DS^2 scale for post-ischemic stroke infection

Vrednost skora CONUT u kombinaciji sa skalom A^2DS^2 za predikciju infekcije posle ishemijskog moždanog udara

Yongqing Zhang, Wei Zhang, Yiwu Zhou

Sichuan University, West China Hospital, Department of Emergency Medicine, Emergency Medical Laboratory, Chengdu, Sichuan, China

Abstract

Background/Aim. Stroke-associated infection is the most common and most serious complication of ischemic stroke (IS), which is the most important cause of death and disability in humans. The aim of the study was to determine the predictive value of nutrition risk score – Controlling Nutritional Status (CONUT) combined with Age, Atrial Fibrillation, Dysphagia, Sex, Stroke Severity (A^2DS^2) scale for post-IS infection (PISI) in IS patients. **Methods.** This retrospective study analyzed the clinical data of 333 IS patients admitted to the Emergency Department of West China Hospital of Sichuan University from December 2017 to April 2019. Patients were divided into the No-PISI group (244 cases) and the PISI group (89 cases) based on whether they had a PISI. Multivariate logistic regression analysis was used to identify independent risk factors for PISI. Receiver operating characteristic (ROC) curve analysis was used to evaluate the accuracy of different variables in predicting the outcome. **Results.** Multivariable logistic regression analysis showed that the CONUT score [odds ratio (OR) = 1.321, 95% confidence interval (CI): 1.040–1.677, $p < 0.05$] and age (OR = 1.026, 95%CI: 1.004–1.048, $p < 0.05$) were independent influencing factors for PISI. With the increase of the CONUT score, the proportion of PISI increased. Area under the ROC curve for predicting PISI was 0.651, 0.696, and 0.725 for CONUT, A^2DS^2, and CONUT plus A^2DS^2, respectively. **Conclusion.** Combining the CONUT score and A^2DS^2 scale enhances their predictability of PISI, thereby serving as a valuable tool for early risk assessment and clinical intervention.

Key words:
age factors; infections; nutritional status; prognosis; risk factors; stroke.

Apstrakt

Uvod/Cilj. Infekcija povezana sa moždanim udarom je najčešća i najozbiljnija komplikacija ishemijskog moždanog udara (IMU), koji je najvažniji uzrok smrti i invalidnosti kod ljudi. Cilj rada bio je da se utvrdi vrednost skora nutritivnog rizika – kombinacije skora *Controlling Nutritional Status* (CONUT) i skale *Age, Atrial Fibrillation, Dysphagia, Sex, Stroke Severity* (A^2DS^2) za predikciju infekcije posle IMU (IPIMU) kod bolesnika sa IMU. **Metode.** Ovom retrospektivnom studijom analizirani su podaci 333 bolesnika sa IMU, primljenih na Odeljenje hitne pomoći Zapadnokineske bolnice Univerziteta Sičuan od decembra 2017. do aprila 2019. godine. Bolesnici su bili podeljeni na osnovu toga da li su imali ili ne IPIMU u dve grupe: grupu bez-IPIMU (244 bolesnika) i grupu IPIMU (89 bolesnika). Za identifikaciju nezavisnih faktora rizika od IPIMU, korišćena je multivarijantna logistička regresiona analiza. Za procenu tačnosti različitih varijabli u predviđanju ishoda, korišćena je analiza *receiver operating characteristic* (ROC) krive. **Rezultati.** Multivarijantna logistička regresiona analiza pokazala je da su skor CONUT [*odds ratio* (OR) = 1,321, 95% interval poverenja (IP): 1,040–1,677, $p < 0,05$] i životno doba (OR=1,026, 95% IP: 1,004–1,048, $p < 0,05$) bili nezavisni faktori koji su uticali na IPIMU. Sa porastom CONUT skora, proporcija IPIMU se povećavala. Površina ispod ROC krive za predikciju IPIMU iznosila je 0,651, 0,696 i 0,725 za CONUT skor, A^2DS^2 skalu i CONUT skor sa A^2DS^2 skalom, redom. **Zaključak.** Kombinovanje skora CONUT i skale A^2DS^2 povećava njihovu prediktabilnost IPIMU, i služi kao dragoceno sredstvo za ranu procenu rizika i kliničko delovanje.

Ključne reči:
životno doba, faktor; infekcija; nutritivni status; prognoza; faktori rizika; moždani udar.

Correspondence to: Yiwu Zhou, Sichuan University, West China Hospital, Department of Emergency Medicine, Emergency Medical Laboratory, No.37 Guoxue Road, Chengdu, Sichuan 610041, China. E-mail: 456zyw@163.com

Introduction

Stroke is a neurologic dysfunction caused by acute focal injury of the central nervous system due to vascular reasons. It currently ranks second among global human causes of death and is the leading cause in China [1, 2]. Ischemic stroke (IS) is the most important cause of human death and disability, with stroke-associated infection (SAI) being the most common and most serious complication, occurring at a rate of 23%–65% [3]. Research has shown that post-stroke infection (PSI) is an important factor that affects the recovery and mortality of stroke patients; hence, early diagnosis is crucial [4]. Pneumonia and urinary tract infections are common after IS. They are difficult to control clinically and often lead to rapid deterioration or even death of patients, thus seriously affecting early control and functional recovery of stroke patients, bringing a heavy economic burden to families and society [5]. It has become a major clinical problem that urgently needs to be solved in the field of cerebrovascular disease.

Currently, there have been studies on the Age, Atrial Fibrillation, Dysphagia, Sex, Stroke Severity (A^2DS^2) scale for predicting PSI, but the sensitivity and specificity of the prediction are unsatisfactory [6, 7]. Therefore, there is a lack of accurate early predictive indicators and effective prevention and treatment strategies for PSI, such as prophylactic antibiotics, prevention of aspiration, and management of the respiratory tract. These measures have been proven to be ineffective in reducing the incidence of PSI and improving the clinical prognosis of PSI patients. Therefore, exploring early specific warning diagnostic factors for PSI can achieve early clinical intervention and treatment and reduce the mortality and disability caused by stroke.

Malnutrition-related diseases are the most common challenge in healthcare, whether in developed or developing countries. The relationship between nutritional status and prognosis of cardiovascular disease patients has increasingly gained interest among scholars. The Controlling Nutritional Status (CONUT) score, proposed by Ignacio et al. [8] in 2005, is a new nutritional assessment system that comprehensively evaluates patients' nutritional and immune status based on serum albumin concentration, total lymphocyte count, and total cholesterol concentration. The CONUT score is the most effective method among various nutritional assessment indicators and can assist in evaluating patients' nutritional status during hospitalization. Previous studies have shown that CONUT is associated with the prognosis of various malignancies [9–11], but there are few reports on its application in predicting infections after IS. Therefore, the aim of the study was to evaluate the predictive value of the CONUT score combined with the A^2DS^2 scale for post-IS infection (PISI) in IS patients.

Methods

Patients

This retrospective observational study included a total of 333 patients (216 males and 117 females) diagnosed with IS and admitted to the Emergency Department of the West China Hospital of Sichuan University between December 2017 and April 2019. The study was approved by the Ethics Committee of West China Hospital of Sichuan University and the Ethics Committee of the Wuhan Red Cross Hospital of Hubei Province (No. 1175, 2021).

The inclusion criteria for the study were age ≥ 18 years, onset time < 12 hrs and the patients had to meet the diagnostic criteria for acute IS in the "Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018" formulated by the Neurology Branch of the Chinese Medical Association in 2018 [12]. The exclusion criteria (one must be met) were as follows: concurrent infectious diseases before admission; recent use of steroids or long-term use of immunosuppressive agents; incomplete clinical data or laboratory data; previous blood system diseases; history of severe trauma or surgery within one month; patients with a history of ischemic or hemorrhagic cerebrovascular disease and residual sequelae; patients who refuse to participate in this study.

Data

General clinical data of the study subjects, such as gender, age, hypertension, diabetes mellitus, heart rate, blood pressure, and body temperature, were collected through follow-up and electronic medical records. Laboratory indicators on admission (within 2 hrs) were collected, and the A^2DS^2 score and the CONUT score were calculated.

After providing institutional review board approval at each institution, written informed consent was obtained from each patient or the patient's legally authorized guardian before conducting study-specific procedures.

Score scales

The A^2DS^2 score scale was proposed by Hofmann et al. [13] and assesses the risk of early-onset pneumonia in patients with acute IS based on age, atrial fibrillation, dysphagia, sex, and stroke severity. The sensitivity and specificity of the Hoffmann scale in China are 69% and 73%, respectively, with a total score of 10 points. Scores of 0–4 indicate low risk, while scores of 5–10 indicate high risk.

Reference for the CONUT score standard was as follows: serum albumin levels of 3.5–4.5 g/dL, 3.0–3.49 g/dL, 2.5–2.9 g/dL, and < 2.5 g/dL are assigned scores of 0, 2, 4, and 6 points, respectively. Serum total cholesterol levels of > 180 mg/dL, 140–180 mg/dL, 100–139 mg/dL, and < 100 mg/dL are assigned scores of 0, 1, 2, and 3 points, respectively. Peripheral blood total lymphocyte counts of > 1,600 $\times 10^3$/mL, 1,200–1,599 $\times 10^3$/mL, 800–1,199 $\times 10^3$/mL, and < 800 $\times 10^3$/mL are assigned scores of 0, 1, 2, and 3 points, respectively. The sum of these three items is the CONUT score. Scores of 0–1 indicate normal nutritional status, scores of 2–4 indicate mild malnutrition, scores of 5–8 indicate moderate malnutrition, and scores of 9–12 indicate severe malnutrition.

Definition of outcomes and grouping

The main indicator observed in this study is PSI, also known as SAI [14]. This refers to an infection that occurs within seven days of stroke onset in patients who did not have any symptoms of infection or were not, at the time of stroke, in the latent period of infection, such as pulmonary or urinary tract infections or fever of unknown origin. Patients were divided into two groups based on whether they had a PISI: No-PISI group, with 244 patients, and the PISI group, with 89 patients. Baseline data and clinical indicators were compared among the two groups of patients. Finally, independent risk factors for PISI were screened through multivariate analysis.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. Normally distributed continuous variables were expressed as mean ± standard deviation, while non-normally distributed continuous variables were expressed as median and interquartile range. Group comparisons were performed using analysis of variance (for normally distributed data) or the Mann-Whitney *U* test (for non-normally distributed data). Categorical variables were expressed as frequency (percentage) and compared using a Chi-square test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the accuracy of different variables in predicting the outcome. Multivariate logistic regression analysis was used to identify independent risk factors for PISI. A p-value < 0.05 was considered statistically significant.

Results

The average age in the No-PISI group was 63 years, while in the PISI group, it was 68. The male proportion in the No-PISI group was 64.8%, while it was 65.2% in the PISI group. The study found that hemoglobin, albumin, and absolute lymphocyte count were significantly higher in the No-PISI group compared with the PISI group (141 g/L vs. 138 g/L, 43.2 g/L vs. 40.6 g/L, 1.66 $\times 10^9$/L vs. 1.26 $\times 10^9$/L, respectively). On the other hand, white blood cell count, total bilirubin, A^2DS^2, and CONUT were significantly higher in the PISI than in the No-PISI group (6.72 $\times 10^9$/L vs. 7.82 $\times 10^9$/L, 12.7 ± 5.85 μmol/L vs. 14.5 ± 7.22 μmol/L, 3.0 ± 2.0 vs. 5.0 ± 2.00, 1.00 vs. 2.00), as shown in Table 1.

After adjusting for potential confounding factors, multifactor logistic regression analysis revealed that the CONUT score and age were independent variables significantly associated with PISI, as shown in Table 2.

The ROC curve analysis showed that the area under the curve (AUC) for predicting PISI was 0.651, 0.696, and 0.725 for CONUT, A^2DS^2, and CONUT plus A^2DS^2, respectively. The combined prediction of CONUT plus A^2DS^2 had a larger

Table 1

Baseline characteristics of included patients with and without post-ischemic stroke infection (PISI)

Characteristic	Group		*p*
	No-PISI (n = 244)	PISI (n = 89)	
Age, years	63.0 (51.0–72.0)	68.0 (59.0–78.0)	0.001
Male gender	158 (64.8)	58 (65.2)	0.997
Body mass index, kg/m²	24.3 ± 3.1	23.1 ± 3.3	0.015
Drinking	70 (28.7)	31 (34.8)	0.345
Smoking	111 (45.5)	41 (46.1)	0.998
Hypertension	150 (61.5)	48 (53.9)	0.265
Diabetes	52 (21.3)	29 (32.6)	0.048
Admission vital signs			
systolic blood pressure, mmHg	85.0 (76.0–97.0)	85.0 (75.0–100)	0.556
diastolic blood pressure, mmHg	78.0 (67.0–87.0)	81.0 (68.0–93.0)	0.294
temperature, ℃	36.5 (36.3–36.6)	36.5 (36.3–36.7)	0.009
heart rate, beats/min	20.0 (19.0–20.0)	20.0 (19.0–20.0)	0.329
Hemoglobin, g/L	141 (129–152)	138 (122–146)	0.015
Albumin, mmol/L	43.2 (40.9–45.2)	40.6 (36.2–43.1)	< 0.001
White blood cell count, $\times 10^9$/L	6.72 (5.68–8.07)	7.82 (6.50–9.84)	< 0.001
Absolute lymphocyte count, $\times 10^9$/L	1.66 (1.25–2.12)	1.26 (0.94–1.75)	< 0.001
Absolute neutrophil count, $\times 10^9$/L	4.31 (3.34–5.79)	5.95 (4.43–7.76)	< 0.001
Low-density lipoprotein, mmol/L	2.42 (1.88–3.04)	2.32 (1.83–2.83)	0.323
High-density lipoprotein, mmol/L	1.21 (0.97–1.43)	1.12 (0.92–1.43)	0.217
Triglycerides, mmol/L	1.76 ± 1.39	1.47 ± 1.06	0.054
Alanine aminotransferase, U/L	25.8 ± 17.8	28.9 ± 38.4	0.473
Aspartate aminotransferase, U/L	21.0 (17.0–27.0)	23.0 (17.5–31.5)	0.060
Creatinine, μmol/L	73.0 (61.0–87.0)	76.0 (62.5–97.0)	0.390
Urea nitrogen, mmol/L	5.10 (4.20–6.40)	5.60 (3.95–6.75)	0.335
Total bilirubin, μmol/L	12.7 ± 5.85	14.5 ± 7.22	0.036
A^2DS^2 scale	3.0 ± 2.0	5.0 ± 2.00	< 0.001
CONUT	1.00 (0.00–2.00)	2.00 (1.00–3.00)	< 0.001

A^2DS^2 – Age, Atrial fibrillation, Dysphagia, Sex, Stroke Severity; CONUT – Controlling Nutritional Status. Values are given as mean ± standard deviation, mean (minimum-maximum), or numbers (percentages).

AUC than CONUT and A^2DS^2 alone (Figure 1). Through the decision curve analysis of CONUT, A^2DS^2, and COUNT plus A^2DS^2, it can be found that the net return rate of all factors is greater than 0 during a certain risk threshold. The results showed that three factors had a certain impact on the outcome of PISI, and COUNT plus A^2DS^2 had the best benefit (Figure 2).

Discussion

Infection is a frequent complication during the early stages of a stroke, with reported rates ranging from 5–65%. However, discrepancies in patient demographics, study methodology, and infection definition may contribute to the wide range of reported rates [15–17]. Early prediction of PISI to

Table 2

Logistic regression analysis of influencing factors of post-ischemic stroke infection

Factor	Univariate			Multifactor		
	OR	95% CI	*p*	OR	95% CI	*p*
CONUT	1.517	1.278–1.799	< 0.001	1.321	1.040–1.677	0.023
Age	1.035	1.015–1.055	0.001	1.026	1.004–1.048	0.018
White blood cell count	1.246	1.120–1.385	< 0.001	0.999	0.996–1.003	0.790
Diabetes mellitus	1.785	1.041–3.059	0.035	0.588	0.319–1.083	0.089
Lymphocyte absolute value	1.353	1.205–1.519	< 0.001	0.740	0.416–1.316	0.305
Aspartate transaminase	1.384	1.241–1.601	< 0.001	1.020	0.999–1.041	0.057

CONUT – Controlling Nutritional Status. OR – odds ratio; CI – confidence interval.

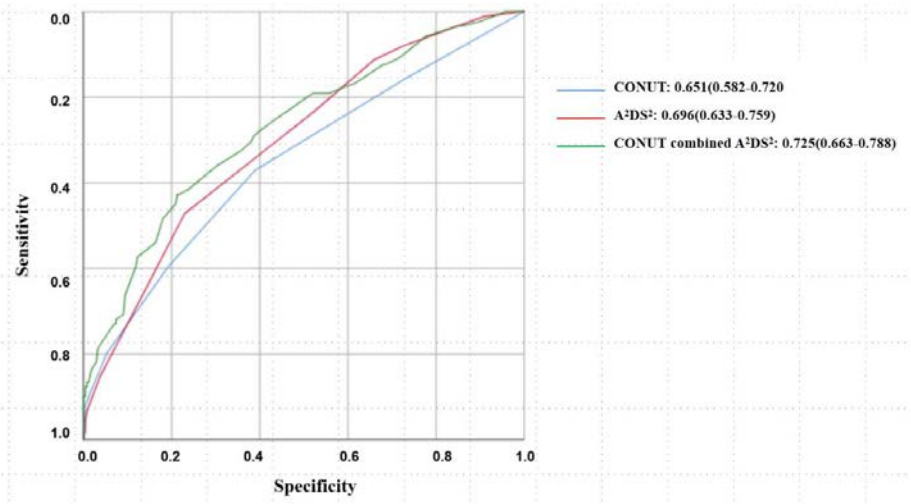


Fig. 1 – The receiver operating characteristic curve of nutritional risk score for post-ischemic stroke infection.
For abbreviations, see Table 1.

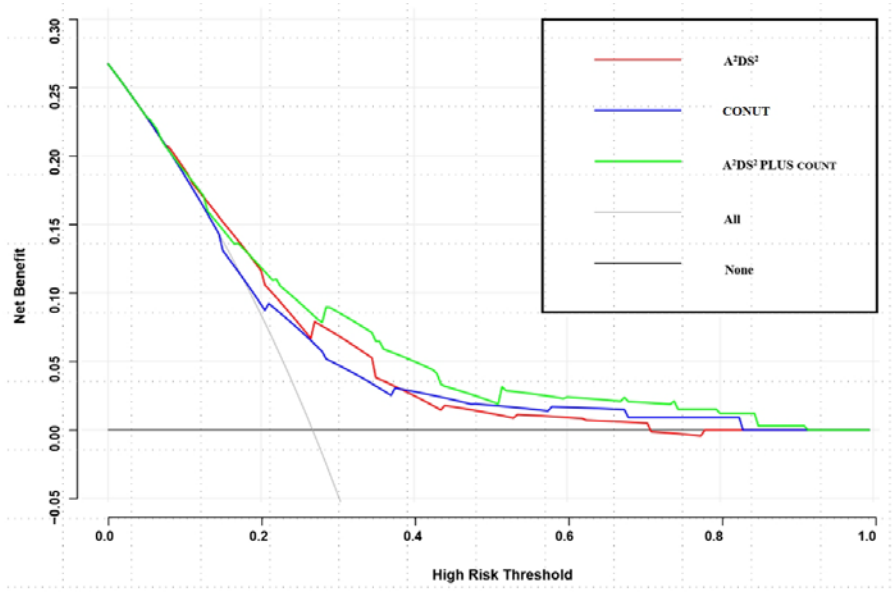


Fig. 2 – Decision curve analysis of nutritional risk score for post-ischemic stroke infection.
For abbreviations, see Table 1.

guide clinical interventions can help reduce disability and mortality rates. The A^2DS^2 scale is one of the most widely used rankings and has been extensively used in the clinic [6]. Multivariate analysis was employed to identify the risk factors and assign scores for the A^2DS^2 scale [7, 18]. Different studies have reported different sensitivities and specificities, which may be related to race, incidence, study methodology, and optimal cut-off for the scale [19–21]. With the improvement of people's living standards, the impact of nutritional balance and supplementation on diseases has increasingly received attention from clinical doctors. Patients' nutritional status has attracted more and more attention in various clinical fields, and studies have shown that early nutritional support can improve the prognosis of stroke patients. The CONUT score is one of the tools for objectively evaluating nutritional status [22]. The score is calculated using three factors: serum albumin levels, white blood cell counts, and body mass index. Compared with the currently recognized subjective global assessment and Full Nutrition Assessment subjective nutritional evaluation tools, the CONUT score has high sensitivity and specificity, is easy to operate and popularize, and is suitable for early screening and dynamic monitoring of population nutrition [23, 24]. There are no studies that combine two scores to predict the occurrence of PISI.

The CONUT score has also been suggested as a tool to predict SAIs [25]. Several studies have investigated the use of the CONUT score in predicting the risk of infections following acute IS. A study investigated the relationship between nutritional scales and prognosis in elderly patients after acute IS [26]. The study included 218 patients and found that a lower CONUT score was significantly associated with an increased risk of pneumonia. The authors concluded that the CONUT score appeared to be more useful than Geriatric Nutritional Risk Index (UNR-GNRI) scores for predicting the prognosis of elderly patients with acute IS at discharge [26]. Our study also found that the CONUT score was more sensitive than the A^2DS^2 score in predicting the incidence of PISI. If the two scores are combined, they can increase the efficiency of predicting PISI. Another study indicated that a high CONUT score was associated with an increased risk of 90-day mortality in patients with pleural infection and can be considered for clinical evaluations in practice [27].

The limitation of the CONUT score is that the optimal cut-off values have not been established. Different studies have used different cut-off values, ranging from 4 to 6, and it is unclear which cut-off value is the most accurate in predicting infections [28, 29]. This lack of standardization makes it challenging for clinicians to use the score consistently across different patient populations [30]. Furthermore, the CONUT score may be less useful in patients with pre-existing conditions that affect their immune or nutritional status [31, 32]. For instance, patients with chronic kidney or liver disease may have abnormal serum albumin levels that do not accurately reflect their overall nutritional status [33, 34]. In these cases, the CONUT score may not provide an accurate prediction of the risk of infection, and clinical decision-making should consider additional factors beyond the CONUT score.

Despite these limitations, the CONUT score has potential as a tool for predicting SAIs. Future research should investigate whether incorporating additional laboratory markers into the score improves its predictive ability. Studies should also compare the accuracy of the CONUT score with other commonly used tools for predicting infections, such as the Glasgow Coma Scale and the National Institutes of Health Stroke Scale. Furthermore, additional research is needed to determine the optimal cut-off values for the CONUT score in different patient populations.

The A^2DS^2 scale is an effective tool for evaluating SAIs, but the CONUT score is also a potential tool for predicting SAIs, especially pneumonia. Combining both scoring tools improves their clinical predictive efficacy. Clinicians should consider additional factors beyond the CONUT score, particularly in patients with pre-existing conditions that affect their immune or nutritional status. Further research is needed to establish the clinical utility of the CONUT score in predicting infections and guiding clinical decision-making in patients with acute stroke.

Limitations of the study

The study had several limitations. First, this study is a retrospective observational study. Second, the sample size was quite small. Third and final, there was a lack of dynamic assessment of the CONUT score during hospitalization.

Conclusion

The study suggests that combining the CONUT score and A^2DS^2 scale enhances their predictability of post-ischemic stroke infection, thereby serving as a valuable tool for early risk assessment and clinical intervention.

Funding

This study was supported by the Funds of Technology Department of Sichuan Province, China (No. 2023YFS0242, 2023YFS0240).

Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *GBD 2017 Mortality Collaborators*. Global, regional, and national age-sex-specific mortality and life expectancy, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392(10159): 1684–735. Erratum in: Lancet 2019; 393(10190): e44.
2. *Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L*, et al. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults. Circulation 2017; 135(8): 759–71.
3. *Bustamante A, Vilar-Bergua A, Guettier S, Sánchez-Poblet J, García-Berrocoso T, Giralt D*, et al. C-reactive protein in the detection of post-stroke infections: systematic review and individual participant data analysis. J Neurochem 2017; 141(2): 305–14.
4. *Sunnerhagen KS, Opheim A, Alt Murphy M*. Onset, time course and prediction of spasticity after stroke or traumatic brain injury. Ann Phys Rehabil Med 2019; 62(6): 431–4.
5. *Westendorp WF, Nederkoorn PJ, Vermeij JD, Dijkgraaf MG, van de Beek D*. Post-stroke infection: a systematic review and meta-analysis. BMC Neurol 2011; 11: 110.
6. *Ni J, Shou W, Wu X, Sun J*. Prediction of stroke-associated pneumonia by the A2DS2, AIS-APS, and ISAN scores: a systematic review and meta-analysis. Expert Rev Respir Med 2021; 15(11): 1461–72.
7. *Zapata-Arriaza E, Moniche F, Blanca PG, Bustamante A, Escudero-Martínez I, Uclés O,* et al. External Validation of the ISAN, A2DS2, and AIS-APS Scores for Predicting Stroke-Associated Pneumonia. J Stroke Cerebrovasc Dis 2018; 27(3): 673–6.
8. *Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A,* et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp 2005; 20(1): 38–45.
9. *Wang PY, Chen XK, Liu Q, Xu L, Zhang RX, Liu XB,* et al. Application of four nutritional risk indexes in perioperative management for esophageal cancer patients. J Cancer Res Clin Oncol 2021; 147(10): 3099–111.
10. *Li W, Li M, Wang T, Ma G, Deng Y, Pu D,* et al. Controlling Nutritional Status (CONUT) score is a prognostic factor in patients with resected breast cancer. Sci Rep 2020; 10(1): 6633.
11. *Yılmaz A, Tekin SB, Bilici M, Yılmaz H*. The Significance of Controlling Nutritional Status (CONUT) Score as a Novel Prognostic Parameter in Small Cell Lung Cancer. Lung 2020; 198(4): 695–704.
12. *Peng B, Wu B*. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. Chin J Neurol 2018; 51(9): 666–82.
13. *Hoffmann S, Malzahn U, Harms H, Koennecke HC, Berger K, Kalic M,* et al. Development of a clinical score (A^2DS^2) to predict pneumonia in acute ischemic stroke. Stroke 2012; 43(10): 2617–23.
14. *Worthmann H, Tryc AB, Dirks M, Schuppner R, Brand K, Klawonn F*, et al. Lipopolysaccharide binding protein, interleukin-10, interleukin-6 and C-reactive protein blood levels in acute ischemic stroke patients with post-stroke infection. J Neuroinflammation 2015; 12: 13.
15. *Hannawi Y, Hannawi B, Rao CP, Suarez JI, Bershad EM*. Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis 2013; 35(5): 430–43.
16. *Fang F, Shu Y, Xiao Z*. Clinical research progress in stroke-associated pneumonia. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2019; 31(11): 1429–34. (Chinese)
17. *Vermeij FH, Scholte op Reimer WJ, de Man P, van Oostenbrugge RJ, Franke CL, de Jong G,* et al. Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the Netherlands Stroke Survey. Cerebrovasc Dis 2009; 27(5): 465–71.
18. *Chen X, Li D, Liu Y, Zhu L, Jia Y, Gao Y*. Nutritional risk screening 2002 scale and subsequent risk of stroke-associated infection in ischemic stroke: The REMISE study. Front Nutr 2022; 9: 895803.
19. *Yang J, Dai Y, Zhang Z, Chen Y*. Value of Combination of the A^2DS^2 Score and IL-6 in Predicting Stroke-Associated Pneumonia. Neuropsychiatr Dis Treat 2020; 16: 2353–9.
20. *Li Y, Zhang Y, Ma L, Niu X, Chang J*. Risk of stroke-associated pneumonia during hospitalization: predictive ability of combined A^2DS^2 score and hyperglycemia. BMC Neurol 2019; 19(1): 298.
21. *Tu TM, Phua SS, Acharyya S, Ng WM, Oh DC*. Predicting Pneumonia in Acute Ischaemic Stroke: Comparison of Five Prediction Scoring Models. Ann Acad Med Singap 2017; 46(6): 237–44.
22. *Yoo SH, Kim JS, Kwon SU, Yun SC, Koh JY, Kang DW*. Undernutrition as a predictor of poor clinical outcomes in acute ischemic stroke patients. Arch Neurol 2008; 65(1): 39–43.
23. *Lee EC, Jeong YG, Jung JH, Moon HI*. Validity of the Controlling Nutritional Status score as a Nutritional Assessment Tool early after stroke. Int J Rehabil Res 2022; 45(1): 58–64.
24. *Crary MA, Humphrey JL, Carnaby-Mann G, Sambandam R, Miller L, Silliman S*. Dysphagia, nutrition, and hydration in ischemic stroke patients at admission and discharge from acute care. Dysphagia 2013; 28(1): 69–76.
25. *Altuntas E, Karadeniz FO, Cetin S, Demir S*. Relationship Between Atrial Fibrillation and Controlling Nutritional Status Score in Acute Ischemic Stroke Patients. J Coll Physicians Surg Pak 2023; 33(2): 165–9.
26. *Akimoto T, Hara M, Morita A, Uehara S, Nakajima H*. Relationship between Nutritional Scales and Prognosis in Elderly Patients after Acute Ischemic Stroke: Comparison of Controlling Nutritional Status Score and Geriatric Nutritional Risk Index. Ann Nutr Metab 2021; 77(2): 116–23.
27. *Oh J, Yu G, Ra SW*. Clinical Implications of the Controlling Nutritional Status Score on Short-term Outcomes in Patients with Pleural Infection. Intern Med 2023; 62(11): 1591–8.
28. *Arero G, Arero AG, Mohammed SH, Vasheghani-Farahani A*. Prognostic Potential of the Controlling Nutritional Status (CONUT) Score in Predicting All-Cause Mortality and Major Adverse Cardiovascular Events in Patients With Coronary Artery Disease: A Meta-Analysis. Front Nutr 2022; 9: 850641.
29. *Aoyama T, Komori K, Nakazano M, Hara K, Tamagawa H, Kazama K,* et al. The Clinical Influence of the CONUT Score on Survival of Patients With Gastric Cancer Receiving Curative Treatment. In Vivo 2022; 36(2): 942–8.
30. *Wang A, He Z, Cong P, Qu Y, Hu T, Cai Y,* et al. Controlling Nutritional Status (CONUT) Score as a New Indicator of Prognosis in Patients With Hilar Cholangiocarcinoma Is Superior to NLR and PNI: A Single-Center Retrospective Study. Front Oncol 2020; 10: 593452.
31. *Baysal M, Bas V, Demirci U, Gulsaran SK, Umit E, Kirkizlar HO,* et al. The Utility of CONUT Score in Diffuse Large B Cell Lymphoma Patients. Niger J Clin Pract 2021; 24(8): 1194–9.
32. *Çağliyan GA, Hacioğlu S, Koluman BU, Ilkkiliç K, Nar R, Başer MN*, et al. Is CONUT score a prognostic index in patients with diffuse large cell lymphoma? Turk J Med Sci 2021; 51(4): 2112–9.

33. *Spoletini G, Ferri F, Mauro A, Mennini G, Bianco G, Cardinale V,* et al. CONUT Score Predicts Early Morbidity After Liver Transplantation: A Collaborative Study. Front Nutr 2021; 8: 793885.
34. *Nishikawa H, Yoh K, Enomoto H, Ishii N, Iwata Y, Takata R,* et al. The Relationship between Controlling Nutritional (CONUT) Score and Clinical Markers among Adults with Hepatitis C Virus Related Liver Cirrhosis. Nutrients 2018; 10(9): 1185.

Received on September 27, 2023
Revised on October 30, 2023
Revised on January 4, 2023
Accepted on January 9, 2024
Online First February, 2024

ORIGINAL ARTICLE

UDC: 616-006-036
DOI: https://doi.org/10.2298/VSP231020002S

Translation, transcultural adaptation, and validation of the Serbian version of the University of Washington Quality of Life (UW-QoL) Questionnaire – a pilot study

Prevod, transkulturalna adaptacija i validacija srpske verzije upitnika *University of Washington Quality of Life* (UW-QoL) *Questionnaire* – pilot studija

Dragana Stanišić*, Dragana Daković†, Ružica Kozomara†, Raša Mladenović*, Sara Mijailović*, Milica Djurdjević*, Dejan Jovanović†, Sanja Vujović*

***University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia; †University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia**

Abstract

Background/Aim. The University of Washington Quality of Life (UW-QoL) questionnaire is one of the most frequently applied instruments for the evaluation of the health-related quality of life of head and neck cancer patients worldwide. The aim of this study was to perform a formal translation of the original version into the Serbian language, assess its psychometric properties, and validate it for use in the Serbian-speaking population. **Methods.** The study was designed as pilot research and conducted between August and October 2023. The internal consistency of the questionnaire was established by calculating Cronbach's alpha coefficient (CA). The intraclass correlation coefficient (ICC) was a measure of temporal stability. The construct validity of the instrument was assessed by correlating its total scores with Oral Health Impact Profile-14 (OHIP-14) and Emotion Regulation Questionnaire results. **Results.** A total of 30 patients (23 males and 7 females) with a mean age of 58.07 ± 13.59 years were enrolled in the research. Mean values of the physical function and social-emotional function subscales were 59.50 ± 12.68 and 55.39 ± 15.26 (the researchers interviewed the participants) and 58.78 ± 12.57 and 57.72 ± 14.91 (the patients completed the questionnaire by themselves). CA value of the Serbian version of the UW-QoL questionnaire was 0.816 (the questionnaire was filled out by the researchers) and 0.802 (the subjects completed it on their own). ICC was 0.797. There was a statistically significant strong correlation between the UW-QoL questionnaire and OHIP-14 total scores. The obtained results showed a weak, non-significant correlation between the UW-QoL questionnaire and the Emotion Regulation Questionnaire. **Conclusion.** Our pilot research showed that the Serbian version of the UW-QoL questionnaire appears as psychometrically valid and reliable as the original English version.

Key words:
head and neck neoplasms; oral health; quality of life; serbia; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Upitnik o kvalitetu života Univerziteta u Vašingtonu (*University of Washington Quality of Life* – UW-QoL) jedan je od najčešće primenjivanih instrumenata za procenu kvaliteta života u vezi sa zdravljem bolesnika sa karcinomom glave i vrata širom sveta. Cilj rada bio je da se izvrši formalni prevod originalne verzije upitnika na srpski jezik, procene njegova psihometrijska svojstva i da se validira za upotrebu u populaciji bolesnika sa srpskog govornog područja. **Metode.** Studija je dizajnirana kao pilot istraživanje i sprovedena je u periodu od avgusta do oktobra 2023. godine. Interna konzistentnost upitnika utvrđena je izračunavanjem Kronbahovog koeficijenta alfa (KK). Unutarklasni koeficijent korelacije (UKK) bio je mera vremenske stabilnosti upitnika. Konstruktivna validnost instrumenta procenjena je korelacijom njegovih ukupnih rezultata sa rezultatima srpske verzije upitnika *Oral Health Impact Profile-14* (OHIP-14) i upitnika emocionalne regulacije. **Rezultati.** U istraživanje je bilo uključeno ukupno 30 bolesnika (23 muškarca i 7 žena) prosečne starosti od 58,07 ± 13,59 godina. Srednje vrednosti fizičke i socijalno-emocionalne skale bile su 59,50 ± 12,68 i 55,39 ± 15,26 (kada su učesnike intervjuisali istraživači) i 58,78 ± 12,57 i 57,72 ± 14,91 (kada su sami bolesnici popunjavali upitnik). Vrednost KK za srpsku verziju upitnika UW-QoL bila je 0,816 (kada su upitnik popunjavali istraživači) i 0,802 (kada su upitnik popunjavali sami ispitanici). Vrednost UKK bila je 0,797. Postojala je statistički značajna jaka korelacija

Correspondence to: Dragana Stanišić, University of Kragujevac, Faculty of Medical Sciences, Svetozara Markovica 69, 34 000 Kragujevac, Serbia. E-mail: stanisic92@yahoo.com

između rezultata upitnika UW-QoL i OHIP-14. Dobijeni rezultati pokazali su slabu korelaciju između upitnika UW-QoL i upitnika emocionalne regulacije. **Zaključak.** Naše pilot istraživanje pokazalo je da je srpska verzija upitnika UW-QoL psihometrijski validna i pouzdana kao i originalna verzija na engleskom jeziku.

Ključne reči:
glava i vrat, neoplazme; usta, zdravlje; kvalitet života; srbija; ankete i upitnici.

Introduction

Head and neck cancer (HNC) is a heterogeneous group of cancers that accounts for more than 550,000 cases and 380,000 deaths annually worldwide [1]. Patients undergoing treatments for HNC are at high risk of developing various devastating problems with a substantial impact on their physical and emotional quality of life (QoL) [2]. Radiotherapy represents one of the most important treatment options for HNC, either as a single modality or combined with surgery and/or chemotherapy [3]. Mucositis, an inflammation of oral and oropharyngeal mucosa, and candidiasis are among the earliest post-radiation complications. Late toxic reactions to radiotherapy include osteoradionecrosis, xerostomia, and subcutaneous fibrosis [4]. Some of the most common symptoms related to HNC are chronic pain, sensory impairment, and difficulties with swallowing, speaking, and breathing [5]. Anxiety, depression, and fatigue are also frequently associated with HNC [6]. It is estimated that the prevalence of depressive symptoms after radiotherapy in HNC patients is between 29% and 42% [6]. In addition, a high level of post-traumatic stress has been noted in HNC survivors [7]. Not only do the patients with HNC face a potentially life-threatening disease, but they also have to deal with the impact of treatment modalities on all aspects of their QoL [2].

Health-related QoL (HRQoL) is a multi-dimensional concept that represents a significant patient-reported outcome in HNC, where overall survival rates are at approximately 50% [8]. Fourteen disease-specific HRQoL instruments have been developed so far for HNC patients, including the European Organization for Research into Treatment of Cancer Quality of Life Questionnaire & Head and Neck Cancer-specific module (EORTC QLQ-C30 & HN35), the Functional Assessment of Cancer Therapy Head and Neck Scale (FACT-HNS), and the University of Washington Quality of Life (UW-QoL) Questionnaire [5]. HNC and its treatment modalities can affect well-being and daily functioning so profoundly that it is of utmost importance to take into account the patient's perspective [9]. Moreover, the HRQoL concept is a very valuable tool in the clinical setting as it might become a beneficial asset to treatment planning [5].

The UW-QoL is a brief, simple-to-complete, self-administered instrument specifically designed for HRQoL evaluation of patients diagnosed with HNC. It consists of 12 single-item domains and three global questions. Additionally, the UW-QoL is divided into two subscales – physical function and social-emotional function [10]. The whole questionnaire is focused on the patient's health and well-being in the past seven days.

To date, there is no validated Serbian version of this questionnaire, so our study aims to formally translate, culturally adapt, and assess the psychometric properties of the UW-QoL instrument in the Serbian population.

Methods

The research was designed as a clinical pilot study and conducted at the Clinic for Dentistry of the Military Medical Academy (MMA), Belgrade, Serbia, between August and October 2023. The study was approved by the Ethics Committee of MMA (No. 59/2023). All of the patients signed the written informed consent prior to participation in the study after being given all the necessary information regarding the research protocol. Thirty patients with the diagnosis of HNC, currently undergoing radiotherapy, who came to a scheduled appointment at the Clinic for Dentistry were enrolled in the research. The inclusion criteria were the following: patients with HNC subjected to radiotherapy, aged 18 years or above. The exclusion criteria were the following: age below 18, mental disorders, and patients who were not willing to participate in the study. All patients were invited to fill in the following set of surveys: UW-QoL, Oral Health Impact Profile (OHIP-14), and Emotion Regulation Questionnaire (ERQ). After attaining socio-demographic characteristics and the aforementioned questionnaires, the patients were swabbed on the *Candida albicans spp*. for future research (the 14th day since the first radiotherapy round).

HRQoL of patients with HNC undergoing radiotherapy was assessed using the Serbian version of the UW-QoL questionnaire, which was formally translated, adapted, and validated in this paper. Translation and cultural adaptation of the UW-QoL instrument were performed following the standard translation/back-translation protocol, according to internationally accepted guidelines [11]. The original version of the instrument was first translated into Serbian by two independent authors of this paper, native in Serbian and fluent in English. After this process was completed, the two translations were combined in a single forward version with minor wording changes. The questionnaire was then back-translated into English by a proficient English speaker, fluent in Serbian, who had not been previously familiar with the original instrument. The back-translation was compared with the original, and the authors of the article agreed on the final Serbian version of the instrument. Characteristics of the original and the Serbian version of the UW-QoL questionnaire are given in the *Appendix*.

Two different modes of questionnaire completion were tested – first, the questionnaires were filled in by the researchers questioning the participants, after which they com-

pleted all the surveys by themselves. In 14 days, study subjects completed the UW-QoL instrument once again so the temporal stability of the questionnaire could be evaluated.

The UW-QoL questionnaire is a self-administered instrument designed specifically for HRQoL evaluation of patients diagnosed with HNC [12]. It contains 12 single-item domains (pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood, and anxiety), assessed by multiple-choice questions scored from 0 (worst QoL) to 100 (best QoL). This questionnaire also includes three global questions [13]. The first one is about participants' HRQoL compared with the period one month before the cancer diagnosis, scored on a 5-point Likert scale (much better, somewhat better, about the same, somewhat worse, much worse). The other two are associated with patients' health-related and overall QoL in the last seven days. In addition, participants were asked to choose the three most significant domains of their HRQoL in the past week. At the end of the UW-QoL instrument, patients may offer open-ended comments about certain issues not covered by the questionnaire [14].

The OHIP-14 is a self-reported 14-item instrument that is divided into seven domains: functional limitation, pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. It is designed to determine the effect of oral health on the overall QoL aspects. Items can be evaluated on a 5-point Likert scale (never = 0, hardly ever = 1, occasionally = 2, fairly often = 3, and very often = 4). The total score is calculated by summing the values of all 14 questions. The higher results indicate a negative impact of oral health on overall health and well-being [15].

ERQ is a scale that consists of 10 questions. It is designed to evaluate individual differences in emotion regulation using two frequent strategies: cognitive reappraisal and emotion suppression. Questions are measured on a 7-point Likert scale (from 1 – strongly disagree to 7 – strongly agree). The cognitive reappraisal includes questions 1, 3, 5, 7, 8, and 10, while items 2, 4, 6, and 9 belong to the emotion suppression subscale. An individual result is obtained for each of the domains. The higher scores represent the more dominant use of that particular emotion regulation strategy [16].

Statistical analysis

Statistical data processing was conducted in the SPSS statistical program, version 22. The response rate, percentage of missing data, and average time for completing the questionnaire were used as measures of the questionnaire's feasibility. The reliability of the instrument was tested in three ways. First, the internal consistency (IC) was determined by calculating Cronbach's alpha coefficient (CA) for the whole questionnaire. IC was deemed satisfactory if the CA was 0.7 or higher [11]. After that, the instrument was divided into two halves by the split-half method, and the Spearman-Brown coefficient was calculated using the "prediction" formula [17]. The temporal stability of the questionnaire was assessed by measuring the intraclass correlation coefficient (ICC). Values of ICC greater than 0.7 indicated satisfactory test-retest reliability [11]. The construct validity of the instrument was established by the correlation of its total scores with the patients' OHIP-14 (convergent validity – the degree to which various assessment tools, theoretically designed to gauge the same underlying construct, indeed produce comparable or closely correlated outcomes) and ERQ (divergent validity – assesses the extent to which measurements of different constructs are distinct and do not correlate strongly with each other) results, implementing Spearman's rank correlation. A p-value < 0.05 was considered a measure of statistical significance for all statistical tests.

Results

The English version of the UW-QoL questionnaire was successfully translated and adapted to the Serbian language without any difficulties regarding linguistic and cultural differences.

Thirty HNC patients with an average age of 58.07 ± 13.59 years were included in this pilot study. Their socio-demographic characteristics are presented in Table 1.

Table 1

Socio-demographic characteristics of the study subjects

Variable	Values
Gender	
male	23 (76.70)
female	7 (23.30)
Employment status	
employed	17 (56.67)
unemployed	1 (3.33)
retired	12 (40.00)
Smoking	
no	14 (46.70)
yes	16 (53.30)
Treatment modality	
surgery and radiotherapy	12 (40.00)
radiotherapy and chemotherapy	2 (6.70)
surgery, radiotherapy, and chemotherapy	16 (53.30)
Candidiasis	
no	12 (40.00)
yes	18 (60.00)

All values are expressed as numbers (percentages).

Mean values of the physical function and social-emotional function subscales were 59.50 ± 12.68 and 55.39 ± 15.26 when the researchers interviewed the participants and 58.78 ± 12.57 and 57.72 ± 14.91 when the patients completed the questionnaire by themselves. Two weeks after the initial testing, the recorded results of the physical function and social-emotional function domains were 51.33 ± 11.48 and 53.42 ± 11.31, respectively. The UW-QoL average domain scores are shown in Table 2.

Table 3 represents which three domain issues were the most significant to the patients in the past seven days. The mean values of the general questions were 39.14, 47.33, and 47.33 when researchers questioned the subjects and 38.33, 50.33, and 50.67 when the participants completed the questionnaire by themselves. After two weeks, the average values of the three general questions were as follows: 39.17, 48.00, and 47.33.

Mean OHIP-14 and ERQ values were 28.20 ± 8.00 and 52.60 ± 6.69 when the investigators interviewed the patients and 28.20 ± 8.29 and 52.63 ± 5.44 when the patients completed the surveys on their own.

The response rate of the questionnaire was 100%, and there were no missing data, so the feasibility of the questionnaire was considered satisfactory. The average time measured for completing the questionnaire was 7.41 min (ranging between 5.46 and 9.27 min) when the researchers were questioning the subjects and 6.25 min (ranging from 3.25 to 9.03 min) when the participants did it on their own, indicating minimal patient burden. In general, patients had no difficulties understanding the questions and felt like the domains of the instrument adequately addressed different aspects of their disease when asked by researchers after the questionnaire completion.

Analysis of IC revealed excellent reliability of the Serbian version of the UW-QoL instrument (CA = 0.816 when the questionnaire was filled by the researchers; CA = 0.802 when the participants did it by themselves). The Spearman-Brown coefficient was calculated after dividing the questionnaire into two parts by the split-half method. The obtained values were 0.722 (researchers interviewed the subjects) and 0.871 (patients completed the questionnaire). Since the Spearman-Brown coefficient remained above 0.7 after implementing the split-half method, the satisfactory reliability of the Serbian version of the UW-QoL instrument was confirmed. ICC, a measure of temporal stability, was 0.797 [95% confidence interval (CI): 0.573–0.903], which demonstrated a satisfactory test-retest reliability of the questionnaire.

Table 2

The UW-QoL questionnaire's average domain scores

Parameter	UW-QoL	
	rated by researchers	rated by patients
Pain	61.67 ± 17.04	65.83 ± 24.11
Appearance	58.33 ± 18.95	56.67 ± 19.62
Activity	55.83 ± 15.65	59.17 ± 16.72
Recreation	54.17 ± 16.19	54.17 ± 16.19
Swallowing	57.33 ± 22.43	56.33 ± 21.09
Chewing	53.33 ± 18.26	53.33 ± 18.26
Speech	68.33 ± 23.94	66.67 ± 20.40
Shoulder	69.67 ± 25.80	71.00 ± 24.69
Taste	55.00 ± 24.60	56.67 ± 22.64
Saliva	64.47 ± 21.93	63.00 ± 24.52
Mood	46.47 ± 24.33	49.17 ± 21.26
Anxiety	47.00 ± 29.79	47.00 ± 27.69

UW-QoL – University of Washington Quality of Life.
All values are expressed as mean ± standard deviation.

Table 3

Domain-importance rating

Parameter	Rated by researchers	Rated by patients	Rank order
Pain	0 (0.00)	0 (0.00)	12
Appearance	6 (20.00)	4 (13.33)	8
Activity	5 (16.67)	4 (13.33)	9
Recreation	2 (6.67)	1 (3.33)	11
Swallowing	17 (56.67)	17 (56.67)	1
Chewing	8 (26.67)	8 (26.67)	5
Speech	5 (16.67)	6 (20.00)	7
Shoulder	4 (13.33)	4 (13.33)	10
Saliva	9 (30.00)	10 (33.33)	4
Taste	6 (20.00)	7 (23.33)	6
Mood	16 (53.33)	16 (53.33)	2
Anxiety	12 (40.00)	13 (43.33)	3

All values are expressed as numbers (percentages).

The correlation of the UW-QoL and OHIP-14 scales (when they were rated by researchers and subjects themselves) was assessed to determine the convergent validity of the Serbian version of the UW-QoL questionnaire. There was a statistically significant strong correlation between the total scores of both subscales of UW-QoL and OHIP-14. The relationship between UW-QoL and ERQ (when the instruments were completed by researchers and participants themselves) was established to test divergent validity. The obtained results showed a weak, non-significant correlation between these two questionnaires.

Spearman's correlation coefficients are shown in the multitrait-multimethod matrix (Table 4).

Table 4

Multitrait-multimethod correlation matrix

Parameter	UW-QoL PF (R)	UW-QoL SEF (R)	UW-QoL PF (P)	UW-QoL SEF (P)	UW-QoL PF retest	UW-QoL SEF retest	OHIP-14 (R)	OHIP-14 (P)	ERQ (R)	ERQ (P)
UW-QoL PF (R)	1	0.632**	0.811**	0.696**	0.233	0.394*	-0.664**	-0.724**	0.068	0.095
UW-QoL SEF (R)	0.632**	1	0.407*	0.923**	0.488**	0.687**	-0.626**	-0.668**	0.094	0.110
UW-QoL PF (P)	0.811**	0.407*	1	0.565**	0.055	0.166	-0.647**	-0.692**	0.141	0.151
UW-QoL SEF (P)	0.696**	0.923**	0.565**	1	0.523**	0.687**	-0.747**	-0.790**	0.022	0.068
UW-QoL PF retest	0. 233	0.488**	0.055	0.523**	1	0.905**	-0.256	-0.228	-0.152	-0.097
UW-QoL SEF retest	0.394*	0.687**	0.166	0.687**	0.905**	1	-0.418*	-0.400*	-0.113	-0.064
OHIP-14 (R)	-0.664**	-0.626**	-0.647**	-0.747**	-0.256	-0.418*	1	0.971**	-0.092	-0.123
OHIP-14 (P)	-0.724**	-0.668**	-0.692**	-0.790**	-0.228	-0.400*	0.971**	1	-0.020	-0.053
ERQ (R)	0.068	0.094	0.141	0.022	-0.152	-0.113	-0.092	-0.020	1	0.953**
ERQ (P)	0.095	0.110	0.151	0.068	-0.097	-0.064	-0.123	-0.053	0.953**	1

UW-QoL – University of Washington Quality of Life; PF – physical function; SEF – social-emotional function; OHIP-14 – Oral Health Impact Profile-14; ERQ – Emotional Regulation Questionnaire; R – rated by researchers; P – rated by patients. * $p < 0.05$; ** $p < 0.001$.

Discussion

HRQoL assessment of HNC patients has evolved into a major necessity in the past two decades as this group of diseases and their treatment modalities significantly affect all aspects of daily lives and functioning [5]. Most HRQoL instruments have been developed in English, so to use them in other languages and cultures, they first need to be formally translated and validated [18].

The main aim of this research was to translate, culturally adapt, and test the psychometric characteristics of the UW-QoL questionnaire.

We measured the time participants needed to complete the Serbian version of the UW-QoL questionnaire to illustrate its ease of use. Considering that the required period is less than 10 min both when researchers interviewed the patients and when they completed it themselves, it can be concluded that the UW-QoL questionnaire is among the most practical instruments for HRQoL evaluation in HNC patients, as confirmed in other studies [5].

Analysis of the questionnaire's IC revealed a good value of the CA, similar to those calculated by Adnane et al. [18] (0.83), Nazar et al. [5] (0.84), and Linardoutsos et al. [19] (0.83). The temporal stability of the questionnaire was also satisfactory, as confirmed in previous articles [18–21]. The results of our pilot research are consistent with those obtained in similar studies, indicating that the Serbian version of the UW-QoL questionnaire is a reliable HRQoL instrument for HNC patients.

To determine convergent validity, we assessed the correlation between UW-QoL and OHIP-14 scores. OHIP-14 is one of the most widespread instruments that measure the impact of oral health problems on general health and well-being [15]. Seeing that various domains of UW-QoL (swallowing, chewing, speech, taste, and saliva) are affected by HNC and its treatment modalities, we found a statistically significant strong correlation between these two questionnaires.

The use of UW-QoL in routine clinical practice might provide numerous benefits as it can help clinicians gain valuable insights into patients' perspectives regarding their health. Given that our research has identified the main impacted domains of the questionnaire (swallowing, mood, and anxiety), treatment strategies should prioritize these aspects.

This present study has some limitations. One of them is a small sample size, which consisted of patients from only one tertiary institution. Our goal is to conduct research that will encompass a large number of participants with various HNC types, cancer stages, and treatment modalities in the future to test UW-QoL properties in those circumstances. Furthermore, we did not compare the UW-QoL to other disease-specific HRQoL instruments for HNC patients, such as EORTC QLQ-C30 & HN35 and FACT-HNS scales, as we wanted to avoid burdening our study subjects with extensive questionnaires. Another limitation of our study is that it focused exclusively on patients who underwent radiation therapy as their treatment approach, and the research was carried out concurrently with radiotherapy. In our forthcoming research, we aim to assess QoL in these patients who received different treatment modalities and also after the completion of their therapy.

Conclusion

Our pilot research showed that the Serbian version of the UW-QoL instrument possesses adequate feasibility, reliability, and validity and appears as psychometrically valid and reliable as the original English version. Thus, a Serbian adaptation of the UW-QoL instrument may be applied as a valuable tool for HRQoL assessment of patients with HNC, not only for research purposes but also in routine practice. Still, novel clinical studies that will include a greater number of patients are necessary to further confirm its psychometric properties in the Serbian population.

Conflict of interest

The authors declare no conflict of interest.

Source of funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. *Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA,* et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2017; 3(4): 524–48.
2. *Sharma Y, Mishra G, Parikh V*. Quality of Life in Head and Neck Cancer Patients. Indian J Otolaryngol Head Neck Surg 2019; 71(Suppl 1): 927–32.
3. *Wan Leung S, Lee TF, Chien CY, Chao PJ, Tsai WL, Fang FM*. Health-related quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. BMC Cancer 2011; 11: 128.
4. *Alfouzan AF*. Radiation therapy in head and neck cancer. Saudi Med J 2021; 42(3): 247–54.
5. *Nazar G, Garmendia ML, Royer M, McDowell JA, Weymuller EA Jr, Yueh B*. Spanish validation of the University of Washington Quality of Life questionnaire for head and neck cancer patients. Otolaryngol Head Neck Surg 2010; 143(6): 801–7, 807. e1–2.
6. *Hammermüller C, Hinz A, Dietz A, Wichmann G, Pirlich M, Berger T,* et al. Depression, anxiety, fatigue, and quality of life in a large sample of patients suffering from head and neck cancer in comparison with the general population. BMC Cancer 2021; 21(1): 94.
7. *Moschopoulou E, Hutchison I, Bhui K, Korszun A*. Post-traumatic stress in head and neck cancer survivors and their partners. Support Care Cancer 2018; 26(9): 3003–11.

8. *Senchak JJ, Fang CY, Bauman JR.* Interventions to improve quality of life (QOL) and/or mood in patients with head and neck cancer (HNC): a review of the evidence. Cancers Head Neck 2019; 4: 2.
9. *Ringash J, Bezjak A.* A structured review of quality of life instruments for head and neck cancer patients. Head Neck 2001; 23(3): 201–13.
10. *Rogers SN, Lowe D, Yueh B, Weymuller EA Jr.* The physical function and social-emotional function subscales of the University of Washington Quality of Life Questionnaire. Arch Otolaryngol Head Neck Surg 2010; 136(4): 352–7.
11. *Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A,* et al. Principles of good practice for the translation and cultural adaptation process for Patient-Reported Outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value Health 2005; 8(2): 94–104.
12. *Rogers SN, Lowe D.* Health-related quality of life after oral cancer treatment: 10-year outcomes. Oral Surg Oral Med Oral Pathol Oral Radiol 2020; 130(2): 144–9.
13. *Vartanian JG, Carvalho AL, Yueh B, Priante AV, de Melo RL, Correia LM,* et al. Long-term quality-of-life evaluation after head and neck cancer treatment in a developing country. Arch Otolaryngol Head Neck Surg 2004; 130(10): 1209–13.
14. *Lee YH, Lai YH, Yueh B, Chu PY, Chen YJ, Chen SC,* et al. Validation of the University of Washington Quality of Life Chinese Version (UWQOL-C) for head and neck cancer patients in Taiwan. J Formos Med Assoc 2017; 116(4): 249–56.
15. *Lekić M, Daković D, Kovačević V, Čutović T, Ilić I, Ilić M.* Testing of the Serbian version of the Oral Health Impact Profile-14 (OHIP-14) questionnaire among professional members of the Serbian Armed Forces. Vojnosanit Pregl 2021; 78(12): 1257–62.
16. *Popov S, Janičić B, Dinić B.* Validation of the Serbian adaptation of the Emotion regulation questionnaire (ERQ). Primenj Psihol 2016; 9(1): 63–81.
17. *Janković SM, Bogavac-Stanojević N, Mikulić I, Izetbegović S, Ilićković I, Krajnović D,* et al. A questionnaire for rating health-related quality of life. Zdr Varst 2021; 60(4): 260–8.
18. *Adnane C, Oubahmane T, Adouly T, Elhani L, Rouadi S, Abada RL,* et al. Cross-cultural and Moroccan Validation of the University of Washington Quality of Life Questionnaire for Patients With Head and Neck Cancer. Ann Otol Rhinol Laryngol 2016; 125(2): 151–9.
19. *Linardoutsos G, Rapidis AD, Lowe D, Bramis I, Rogers SN.* Development of the Greek version of the University of Washington quality of life questionnaire for patients with head and neck cancer. J Craniomaxillofac Surg 2014; 42(5): 601–7.
20. *Vartanian JG, Carvalho AL, Yueh B, Furia CL, Toyota J, McDowell JA,* et al. Brazilian-Portuguese validation of the University of Washington Quality of Life Questionnaire for patients with head and neck cancer. Head Neck 2006; 28(12): 1115–21.
21. *Vujović S, Desnica J, Mijailović S, Milovanović D.* Translation, transcultural adaptation, and validation of the Serbian version of the PSS-QoL questionnaire – a pilot research. Vojnosanit Pregl 2023; 80(6): 493–9.

Received on October 20, 2023
Revised on November 12, 2023
Accepted on December 19, 2023
Online First December 2023

Appendix

The original University of Washington Quality of Life Questionnaire (UW-QoL)

This questionnaire asks about your health and quality of life over the past **seven days**. Please answer all of the questions by checking one box for each question.

1. **Pain.** (Check one box: □)

□ I have no pain.
□ There is mild pain not needing medication.
□ I have moderate pain - requires regular medication (codeine or nonnarcotic).
□ I have severe pain controlled only by narcotics.
□ I have severe pain, not controlled by medication.

2. **Appearance.** (Check one box: □)

□ There is no change in my appearance.
□ The change in my appearance is minor.
□ My appearance bothers me but I remain active.
□ I feel significantly disfigured and limit my activities due to my appearance.
□ I cannot be with people due to my appearance.

3. **Activity.** (Check one box: □)

□ I am as active as I have ever been.
□ There are times when I can't keep up my old pace, but not often.
□ I am often tired and have slowed down my activities although I still get out.
□ I don't go out because I don't have the strength.
□ I am usually in bed or chair and don't leave home.

4. **Recreation.** (Check one box: □)

□ There are no limitations to recreation at home or away from home.
□ There are a few things I can't do but I still get out and enjoy life.
□ There are many times when I wish I could get out more, but I'm not up to it.
□ There are severe limitations to what I can do, mostly I stay at home and watch TV.
□ I can't do anything enjoyable.

5. **Swallowing.** (Check one box: □)

□ I can swallow as well as ever.
□ I cannot swallow certain solid foods.
□ I can only swallow liquid food.
□ I cannot swallow because it "goes down the wrong way" and chokes me.

6. **Chewing.** (Check one box: □)

□ I can chew as well as ever.
□ I can eat soft solids but cannot chew some foods.
□ I cannot even chew soft solids.

7. **Speech.** (Check one box: □)

□ My speech is the same as always.
□ I have difficulty saying some words but I can be understood over the phone.
□ Only my family and friends can understand me.
□ I cannot be understood.

8. Shoulder. (Check one box: □)

□ I have no problem with my shoulder.
□ My shoulder is stiff but it has not affected my activity or strength.
□ Pain or weakness in my shoulder has caused me to change my work.
□ I cannot work due to problems with my shoulder.

9. Taste. (Check one box: □)

□ I can taste food normally.
□ I can taste most foods normally.
□ I can taste some foods.
□ I cannot taste any foods.

10. Saliva. (Check one box: □)

□ My saliva is of normal consistency.
□ I have less saliva than normal, but it is enough.
□ I have too little saliva.
□ I have no saliva.

11. Mood. (Check one box: □)

□ My mood is excellent and unaffected by my cancer.
□ My mood is generally good and only occasionally affected by my cancer.
□ I am neither in a good mood nor depressed about my cancer.
□ I am somewhat depressed about my cancer.
□ I am extremely depressed about my cancer.

12. Anxiety. (Check one box: □)

□ I am not anxious about my cancer.
□ I am a little anxious about my cancer.
□ I am anxious about my cancer.
□ I am very anxious about my cancer.

Which issues have been the most important to you during the past 7 days?
Check □ up to 3 boxes.

□ Pain	□ Swallowing	□ Taste
□ Appearance	□ Chewing	□ Saliva
□ Activity	□ Speech	□ Mood
□ Recreation	□ Shoulder	□ Anxiety

GENERAL QUESTIONS

Compared to the month before you developed cancer, how would you rate your health-related quality of life? (check one box: □)

□ Much better
□ Somewhat better
□ About the same
□ Somewhat worse
□ Much worse

In general, would you say your **health-related quality of life** during the past 7 days has been: (check one box: □)

□ Outstanding
□ Very good
□ Good
□ Fair
□ Poor
□ Very poor

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your **overall quality of life** during the past 7 days. (check one box: □)

□ **Outstanding**
□ **Very good**
□ **Good**
□ **Fair**
□ **Poor**
□ **Very poor**

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).

Serbian version of the University of Washington Quality of Life Questionnaire (UW-QoL)

Upitnik sadrži pitanja o Vašem zdravlju i kvalitetu života u proteklih **sedam dana**. Odgovorite na sva pitanja tako što ćete označiti jedno polje za svako pitanje.

1. **Bol.** (Označite jedno polje: □)

□ Nemam bol.
□ Postoji blagi bol koji ne zahteva upotrebu lekova.
□ Imam umereni bol koji zahteva upotrebu lekova (analgetika).
□ Imam jak bol koji zahteva upotrebu lekova (trodona/narkotika).
□ Imam jak bol koji ne prolazi na upotrebu lekova.

2. **Fizički izgled.** (Označite jedno polje: □)

□ Nema promena u mom fizičkom izgledu.
□ Postoje male promene u mom fizičkom izgledu.
□ Smeta mi fizički izgled, ali sam aktivan.
□ Osećam da mi je značajno ugrožen fizički izgled i ne mogu da sprovodim sve aktivnosti zbog toga.
□ Ne mogu da budem sa ljudima zbog svog fizičkog izgleda.

3. **Fizička aktivnost.** (Označite jedno polje: □)

□ Fizički sam aktivan kao što sam i ranije bio.
□ Postoje trenuci kada ne mogu da održim svoj stari tempo, ali ne često.
□ Često sam umoran i smanjio sam svoje aktivnosti i dalje sam fizički aktivan.
□ Nisam fizički aktivan jer nemam snage.
□ Obično sam u krevetu ili stolici i ne izlazim iz kuće.

4. **Rekreacija.** (Označite jedno polje: □)

□ Ne postoje ograničenja za rekreaciju kod kuće ili van kuće.
□ Postoji nekoliko stvari koje ne mogu da uradim, ali ipak izlazim i uživam u životu.
□ Mnogo puta bih voleo da mogu da izlazim više, ali ne mogu.
□ Postoje ozbiljna ograničenja za ono što mogu da radim, uglavnom ostajem kod kuće i gledam TV.
□ Ne mogu da radim ništa sa uzivanjem.

5. **Gutanje.** (Označite jedno polje: □)

□ Mogu da gutam kao što sam i ranije.
□ Ne mogu da progutam određenu čvrstu hranu.
□ Mogu samo da gutam tečnu hranu.
□ Ne mogu da progutam jer „ide pogrešnim putem“ i guši me.

6. **Žvakanje.** (Označite jedno polje: □)

□ Mogu da žvaćem kao što sam i ranije.
□ Mogu da jedem mekšu čvrstu hranu, ali ne mogu da sažvaćem neke od namirnica.
□ Ne mogu čak da žvaćem ni meku hranu.

7. **Govor.** (Označite jedno polje: □)

□ Moj govor je isti kao i uvek.
□ Imam poteškoća da izgovorim neke reči, ali se mogu razumeti.
□ Samo moja porodica i prijatelji mogu da me razumeju.
□ Ne mogu me razumeti.

8. **Rame.** (Označite jedno polje: □)

□ Nemam problema sa ramenom.
□ Moje rame je ukočeno, ali to ne utice na moju aktivnost ili snagu.
□ Bol ili slabost u ramenu doveli su do toga da promenim svoj posao.
□ Ne mogu da radim zbog problema sa ramenom.

9. **Ukus.** (Označite jedno polje: □)

□ Osećam sve ukuse.
□ Osećam skoro sve ukuse.
□ Osećam samo neke ukuse.
□ Ne osećam ukus hrane.

10. **Pljuvačka.** (Označite jedno polje: □)

□ Moja pljuvačka je normalne konzistencije.
□ Imam manje pljuvačke nego inače, ali dovoljno je.
□ Imam premalo pljuvačke.
□ Nemam pljuvačke.

11. **Raspoloženje.** (Označite jedno polje: □)

□ Moje raspoloženje je odlično i na njega karcinom ne utiče.
□ Moje raspoloženje je generalno dobro, samo povremeno na njega utiče karcinom.
□ Nisam ni raspoložen ni depresivan zbog svog karcinoma.
□ Pomalo sam depresivan zbog svog karcinoma.
□ Izuzetno sam depresivan zbog svog karcinoma.

12. **Anksioznost.** (Označite jedno polje: □)

□ Nisam zabrinut zbog svog karcinoma.
□ Malo sam zabrinut zbog svog karcinoma.
□ Zabrinut sam zbog svog karcinoma.
□ Veoma sam zabrinut zbog svog karcinoma.

Koja pitanja su Vam bila najvažnija u proteklih 7 dana?
Označite □ do 3 polja.

□ Bol	□ Gutanje	□ Ukus
□ Fizički izgled	□ Žvakanje	□ Pljuvačka
□ Fizička aktivnost	□ Govor	□ Raspoloženje
□ Rekreacija	□ Rame	□ Anksioznost

OPŠTA PITANJA

U poređenju sa mesecom pre nego što vam je dijagnostikovan karcinom, kako biste ocenili kvalitet svog života u vezi sa zdravljem? (označite jedno polje: □)

□ Mnogo bolje
□ Nešto bolje
□ Otprilike isto
□ Nešto gore
□ Mnogo gore

Uopšteno govoreći, da li biste rekli da je Vaš **kvalitet života u vezi sa zdravljem** tokom proteklih 7 dana bio: (označite jedno polje: □)

□ Odlično
□ Vrlo dobro
□ Dobro
□ Manje dobro
□ Loše
□ Veoma loše

Ukupan kvalitet života uključuje ne samo fizičko i mentalno zdravlje, već i mnoge druge faktore, kao što su porodica, prijatelji, duhovnost ili lične aktivnosti u slobodno vreme. Uzimajući u obzir sve u Vašem životu što doprinosi Vašem ličnom blagostanju, ocenite svoj **ukupni kvalitet života** tokom poslednjih 7 dana. (označite jedno polje: □)

□ Odlično
□ Vrlo dobro
□ Dobro
□ Manje dobro
□ Loše
□ Veoma loše

_____

Molimo Vas da opišete sva druga pitanja (medicinska ili nemedicinska) koja su važna za Vaš kvalitet života i koja nisu adekvatno obrađena u našim pitanjima (možete priložiti dodatne listove ako je potrebno).

ORIGINAL ARTICLE

UDC: 616.314-089
DOI: https://doi.org/10.2298/VSP231201007M

The impact of flap design on swelling, trismus, and pain after the lower third molar surgery: buccal triangular flap vs. envelope flap

Uticaj dizajna režnja na otok, trizmus i bol posle hirurgije trećih donjih molara: bukalni triangularni režanj vs. „envelop" režanj

Stevo Matijević*†, Filip Djordjević‡, Mila Vukašinović‡, Zoran Bukumirić§, Dejan Dubovina‡

***University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; †Military Medical Academy, Dental Clinic, Department of Oral Surgery, Belgrade, Serbia; ‡University of Priština in Kosovska Mitrovica, Faculty of Medicine, Department of Oral Surgery, Kosovska Mitrovica, Serbia; §University of Belgrade, Faculty of Medicine, Belgrade, Serbia**

Abstract

Background/Aim. Swelling, trismus, and pain (STP) are the most common complications that occur after the surgical extraction of impacted lower third molars (LTM). Buccal triangular and envelope flaps are the two most commonly used mucoperiosteal flaps in LTM surgery. The aim of this study was to compare the possible impact of these two types of flaps on the occurrence and intensity of postoperative STP after the surgical extraction of impacted LTMs. **Methods.** The study included 30 adult patients of both genders, with fully impacted LTMs in vertical position according to Winter classification and class I or II, and position A or B, according to Pell and Gregory classification. All patients were randomly divided into two groups depending on the type of the applied mucoperiosteal flap (triangular or envelope type). The degree of edema, interincisal distance (trismus), and the level of pain were evaluated preoperatively and at each follow-up (on the first, second, and seventh day postoperatively). **Results.** No statistically significant difference was found among the examined groups in terms of STP reduction in the postoperative period ($p > 0.05$). **Conclusion.** The choice of mucoperiosteal flap design, buccal triangular or envelope, during the surgical extraction of impacted LTMs has no impact on the intensity of postoperative STP.

Key words:
edema; molar, third; oral surgical procedures; pain; postoperative complications; surgical flaps; tooth, impacted; trismus.

Apstrakt

Uvod/Cilj. Otok, trizmus i bol (OTB) su najčešće komplikacije nakon hirurške ekstrakcije impaktiranih donjih trećih molara (DTM). Bukalni triangularni i „envelop" režanj su dva najčešće primenjivana mukoperiostalna režnja u hirurgiji DTM. Cilj istraživanja bio je da se uporedi mogući uticaj te dve vrste korišćenih mukoperiostalnih režnjeva na intenzitet OTB nakon hirurške ekstrakcije impaktiranih DTM. **Metode.** Studijom je obuhvaćeno 30 odraslih pacijenata oba pola, sa potpuno impaktiranim DTM u vertikalnoj poziciji prema Winterovoj klasifikaciji i klase I ili II i pozicije A ili B, prema klasifikaciji Pell-a i Gregory-a. Svi pacijenti su nasumično podeljeni u dve grupe, u zavisnosti od primenjenog mukoperiostalnog režnja (triangularni ili „envelop" tip). Stepen prisutnog otoka, interincizalno rastojanje i nivo bola određivani su preoperativno i pri svakoj kontrolnoj poseti (prvog, drugog i sedmog postoperativnog dana). **Rezultati.** Nije utvrđena statistički značajna razlika između ispitivanih grupa u pogledu smanjenja OTB u postoperativnom periodu ($p > 0,05$). **Zaključak.** Izbor vrste mukoperiostalnog režnja, bukalni triangularni ili „envelop" tip, prilikom hirurške ekstrakcije impaktiranih DTM nema uticaja na stepen inteziteta postoperativnog OTB.

Ključne reči:
edem; molar, treći; hirurgija, oralna, procedure; bol; postoperativne komplikacije; režnjevi, hirurški; zub, impakcija; trizmus.

Correspondence to: Stevo Matijević, University of Defence, Faculty of Medicine of the Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: drmatijevic@yahoo.com

Introduction

Surgical extraction of impacted lower third molars (LTM) can be accompanied by a large number of postoperative complications, the most common and almost inevitable being postoperative swelling, trismus, and pain (STP). The occurrence and intensity of these complications are influenced by numerous factors, primarily the applied surgical technique. Selection of an appropriate mucoperiosteal flap design can directly affect the visibility and accessibility of the operative field, influencing the degree of postoperative trauma and consequent STP [1–3]. Buccal triangular and envelope flaps are the two most commonly used mucoperiosteal flaps in LTM surgery [4]. Although most often described in the literature, there is still no consensus on the choice of flap design regarding the reduction of postoperative complications – data from the literature are sometimes conflicting.

The aim of this prospective study was to examine the possible impact of different mucoperiosteal flap designs (buccal triangular vs. envelope) used for the impacted LTM surgery on the occurrence and intensity of postoperative STP.

Methods

The study was approved by the Ethics Committee of the Faculty of Medical Sciences, University of Priština in Kosovska Mitrovica, Serbia (No. 09-453/2021) and is part of a research project that consisted of two mutually independent studies [5].

This randomized prospective study included a total of 30 patients of both genders, aged 18 and above, with impacted LTMs (class I or II and position A or B according to Pell and Gregory [6] classification, and vertical position according to Winter [7] classification). The position of the impacted LTM was analyzed using panoramic radiography. All patients were randomly divided into two groups, 15 patients in each group, depending on the applied mucoperiosteal flap design. Hence, in the first group (the triangular group), a standard buccal triangular flap was applied, while in the second group (the envelope group), an envelope flap was used.

The study excluded the following patients: those with deeply impacted teeth (Pell and Gregory [6] classification – class C tooth) and teeth in all other positions except for vertical according to Winter [7] classification; systemic diseases and therapy that affects immune response and wound healing; present pain sensations; local inflammation and preoperative trismus correlated with tooth impaction; patients with previous episodes of pericoronitis; patients with poor oral hygiene. Surgical interventions that lasted longer than 60 min and the occurrence of severe surgical complications were also reasons for exclusion from the study.

Surgical procedure

Surgical extractions were performed under local anesthesia – inferior alveolar nerve block with the additional plexus anesthesia for the buccal nerve branches (Ubistesin forte®, 1:100.000, Ultradent, Germany). After buccal mucoperiosteal flap elevation (triangular or envelope), depending on the group, alveolotomy and, if necessary, separation of the crown and roots of the impacted tooth were performed using round and fissured carbide rotary drills and mandatory cooling with saline solution. After the tooth extraction, all surgical wounds were primarily sutured. Patients were advised to use cold compresses postoperatively for six hours. No medications were prescribed to patients.

Postoperative analysis

Postoperative follow-up visits were done on the first, second, and seventh postoperative day in order to determine the degree of present STP sensations.

In order to determine the degree of postoperative swelling, the method of Schultze-Mosgau et al. [8] was used. Preoperatively, and at each follow-up visit, distances between certain facial points were measured: the tragus and the angle of the lips; the tragus and the pogonion; the lateral angle of the eye; the angle of the mandible. For this purpose, a silk thread was used to measure the distance between two points, and then it was transferred to a millimeter ruler. The mean value of the obtained values was calculated for each patient and compared afterward with the measurements obtained in the postoperative period.

The assessment of trismus (interincisal distance) was carried out as follows: first, preoperatively, the distance between the incisal edges of the upper and lower central incisors was clinically measured with a ruler to determine the basic value for subsequent comparisons with postoperative measurements. Afterwards, postoperatively, the extent of the present trismus was determined using the same method.

The level of postoperative pain was determined using a 10 cm long visual-analog scale (VAS), with a score range from 0 to 10, where grade 0 presented total absence of pain and grade 10 presented unbearable pain.

Statistical analysis

The *t*-test was used to assess the significance of the difference in the preoperative values of swelling and trismus. Repeated ANOVA test and linear mixed model were used (where trismus and VAS pain scale over time were dependent variables in relation to the type of flap) to model the relationship between swelling volumes of two groups, and $p = 0.05$ was taken as the level of statistical significance. All data were processed in the IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) software package and the R-3.6.3 software environment (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Swelling

There was no statistically significant difference in the extent of swelling between the groups preoperatively (tri-

Table 1

Values of the postoperative swelling

Postoperative day	Group		*p*-value between groups
	triangular	envelope	
1st	13.0 ± 0.5	12.1 ± 1.7	
2nd	13.1 ± 0.5	12.1 ± 1.7	0.149
7th	12.0 ± 0.5	11.4 ± 1.6	
p-value in time series		$p < 0.001$	

Results (in mm) are shown as mean ± standard deviation.

Table 2

Values of postoperative interincisal distance

Postoperative day	Group		*p*-value between groups
	triangular	envelope	
1st	3.1 ± 0.6	3.6 ± 0.5	
2nd	3.1 ± 0.6	3.6 ± 0.5	0.129
7th	4.0 ± 0.5	3.9 ± 0.5	
p-value in time series		$p < 0.001$	

Results (in mm) are shown as mean ± standard deviation.

Table 3

Values and variations of pain level measured by visual analog scale

Postoperative day	Group		*p*-value between groups
	triangular	envelope	
1st	3 (1–7)	4 (3–8)	
2nd	3 (0–7)	3.5 (1–8)	0.333
7th	0 (0–1)	0 (0–2)	
p-value in time series		$p < 0.001$	

Results are shown as mean (minimum-maximum).

angular group – 11.9 ± 0.5 mm; envelope group – 11.4 ± 1.6 mm; $p = 0.354$). Postoperatively, the swelling significantly decreased in both groups ($p < 0.001$), but comparing the groups mutually, no statistically significant difference was found ($p = 0.149$) (Table 1).

Trismus (interincisal distance)

There was no statistically significant difference in the values of interincisal distance between the groups preoperatively (triangular group – 4.0 ± 0.5 mm; envelope group – 3.8 ± 0.7 mm; $p = 0.52$). Postoperatively, the interincisal distance significantly increased in both groups ($p < 0.001$), but comparing the groups mutually, no statistically significant difference was found ($p = 0.129$) (Table 2).

Postoperative pain measured by VAS

Postoperatively, the pain level significantly decreased in both groups ($p < 0.001$), but comparing the groups mutually, no statistically significant difference was found ($p = 0.333$) (Table 3).

Discussion

STP are the most common and almost unavoidable postoperative complications of LTM surgery. Although transitory, they significantly affect the quality of life of patients in the early postoperative period. Several intraoperative and postoperative procedures have been shown to be relevant in reducing complications of this type [9, 10]. Some authors consider that the choice of mucoperiosteal flap can affect the occurrence and degree of postoperative STP [11, 12].

The main difference between the envelope and the buccal triangular flap is the vertical incision in the buccal area of the lower second molar done for raising the buccal triangular flap. This vertical incision might lead to greater trauma of the periosteum and buccal muscle fibers, which may contribute to a greater degree of postoperative edema and trismus. Koyuncu and Cetingül [13], as well as Tareen et al. [14], consider that due to the presence of a vertical relaxation incision of the buccal triangular flap, its repositioning and suturing is somewhat more difficult, which results in a longer overall duration of the operation. This may further cause more intensive release of inflammatory mediators and, consecutively, a significantly higher degree of swelling. Therefore, some authors point out that the degree of swelling and trismus is significantly lower when an envelope flap is used compared to a buccal triangular one [15–18]. Similarly, Rabi et al. [19] concluded that the degree of trismus is higher when the buccal triangular flap is applied, while there is no significant difference in terms of edema.

In a large meta-analysis that involved 20 studies, no significant difference was found between these two flap designs in terms of postoperative complications, although a slight advantage could be given to the envelope flap in terms

of swelling and trismus [20]. Abandansari and Foroughi [21] also pointed out that there is no statistically significant difference in the degree of STP when applying the envelope flap compared to the buccal triangular flap and considered that the choice of flap design solely depends on the surgeon's attitude.

Analyzing the results of our study, it can be concluded that the degree of swelling and trismus was slightly lower in the envelope group than in the triangular group. However, there was no statistically significant difference in the observed parameters between the two types of flaps examined in this study.

Comparing the levels of postoperative pain sensations, the results of our study are in agreement with numerous studies that state that there is no statistically significant difference between the examined types of mucoperiosteal flaps [4, 22]. Yet, some authors still prefer a buccal triangular flap in terms of reducing postoperative pain. Thus, Sandhu et al. [23] concluded that the occurrence of postoperative pain is observed more often when an envelope flap is used. Such conclusions, in some studies, might be explained by the fact that the occurrence of postoperative wound dehiscence, as well as alveolar osteitis, is more common when an envelope flap is used [11, 15, 24].

The choice of flap may also have an impact on the appearance of other postoperative complications that are not covered by this study: dehiscence, alveolar osteitis, hematoma, and change in the periodontal status of the lower second molar. Bearing all this in mind, as well as the results of this study and the inconsistency of results in similar studies by other authors, it can be said that the choice of flap design should solely depend on the attitude and personal experience of the surgeon.

Conclusion

We have concluded that there is no significant difference between using buccal triangular and envelope flap in the LTM surgery regarding the intensity of postoperative STP sensations.

REFERENCES

1. *Yolcu Ü, Acar AH.* Comparison of a new flap design with the routinely used triangular flap design in third molar surgery. Int J Oral Maxillofac Surg 2015; 44(11): 1390–7.
2. *Dolanmaz D, Esen A, Isik K, Candirli C.* Effect of 2 flap designs on postoperative pain and swelling after impacted third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol 2013; 116(4): e244–6.
3. *Kirk DG, Liston PN, Tong DC, Love RM.* Influence of two different flap designs on incidence of pain, swelling, trismus and alveolar osteitis in the week following third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 104(1): e1–6.
4. *Monaco G, Daprile G, Tavernese L, Corinaldesi G, Marchetti C.* Mandibular third molar removal in young patients: an evaluation of 2 different flap designs. J Oral Maxillofac Surg 2009; 67(1): 15–21.
5. *Djordjević F, Bubalo M, Perić D, Mihailović Dj, Bukumirić Z, Dubovina D.* Effectiveness of submucosal, oral, and intramuscular routes of dexamethasone administration in trismus, swelling, and pain reduction after the third lower molar surgery. Vojnosanit Pregl 2023; 80(4): 337–42.
6. *Pell GJ, Gregory GT.* Impacted mandibular third molars: Classification and modified technique for removal. Dent Dig 1933; 39(9): 330–8.
7. *Winter GB.* Principles of exodontia as applied to the impacted mandibular third molar: a complete treatise on the operative technic with clinical diagnoses and radiographic interpretations. St. Louis, USA: American Medical Book Company; 1926. p. 835.
8. *Schultze-Mosgau S, Schmelzeisen R, Frölich JC, Schmele H.* Use of ibuprofen and methylprednisolone for the prevention of pain and swelling after removal of impacted third molars. J Oral Maxillofac Surg 1995; 53(1): 2–7; discussion 7–8.
9. *Royal College of Surgeons of England – Faculty of Dental Surgery.* Parameters of care for patients undergoing mandibular third molar surgery [Internet]. The Royal College of Surgeons of England; 2020 [accessed on: 2023 December 25]. Available from: https://www.rcseng.ac.uk/-/media/files/rcs/fds/guidelines/3rd-molar-guidelines--april-2021.pdf
10. *Sifuentes-Cervantes JS, Carrillo-Morales F, Castro-Núñez J, Cunningham LL, Van Sickels JE.* Third molar surgery: Past, present, and the future. Oral Surg Oral Med Oral Pathol Oral Radiol 2021; 132(5): 523–31.
11. *Mohajerani H, Esmaeelinejad M, Jafari M, Amini E, Sharabiany SP.* Comparison of envelope and modified triangular flaps on incidence of dry socket after surgical removal of impacted mandibular third molars: a double-blind, split-mouth study. J Contemp Dent Pract 2018; 19(7): 836–41.
12. *Glera-Suárez P, Soto-Peñaloza D, Peñarrocha-Oltra D, Peñarrocha-Diago M.* Patient morbidity after impacted third molar extraction with different flap designs. A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal 2020; 25(2): e233–9.
13. *Koyuncu BÖ, Cetingül E.* Short-term clinical outcomes of two different flap techniques in impacted mandibular third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol 2013; 116(3): e179–84.
14. *Tareen MK, Hamad J, Saleem SM, Ahmad S.* To compare the triangular flap to envelope flap for the removal of impacted mandibular last molar. Pak J Med Health Sci 2015; 9: 434–6.
15. *Alqahtani NA, Khaleelahmed S, Desai F.* Evaluation of two flap designs on the mandibular second molar after third molar extractions. J Oral Maxillofac Pathol 2017; 21(2): 317–8.
16. *Erdogan O, Tatli U, Ustün Y, Damlar I.* Influence of two different flap designs on the sequelae of mandibular third molar surgery. Oral Maxillofac Surg 2011; 15(3): 147–52.
17. *Borgonovo AE, Giussani A, Grossi GB, Maiorana C.* Evaluation of postoperative discomfort after impacted mandibular third molar surgery using three different types of flap. Quintessence Int 2014; 45(4): 319–30.
18. *Baqain ZH, Al-Shafii A, Hamdan AA, Sawair FA.* Flap design and mandibular third molar surgery: a split mouth randomized clinical study. Int J Oral Maxillofac Surg 2012; 41(8): 1020–4.
19. *Rabi A, Haris PMM, Panickal DM, Ahamed S, Pulikkottil VJ, Haris KTM.* Comparative Evaluation of Two Different Flap Designs and Postoperative Outcome in the Surgical Removal of Impacted Mandibular Third Molar. J Contemp Dent Pract 2017; 18(9): 807–11.
20. *Lopes da Silva BC, Machado GF, Primo Miranda EF, Galvão EL, Falci SGM.* Envelope or triangular flap for surgical removal of third molars? A systematic review and meta-analysis. Int J Oral Maxillofac Surg 2020; 49(8): 1073–86.

21. *Abandansari SA, Foroughi R*. The effect of releasing incision on the postoperative complications of mandibular third molar surgery. Int J Adv Biotechnol Res 2016; 7: 1144–51.
22. *Chen YW, Lee CT, Hum L, Chuang SK*. Effect of flap design on periodontal healing after impacted third molar extraction: A systematic review and meta-analysis. Int J Oral Maxillofac Surg 2017; 46(3): 363–72.
23. *Sandhu A, Sandhu S, Kaur T*. Comparison of two different flap designs in the surgical removal of bilateral impacted mandibular third molars. Int J Oral Maxillofac Surg 2010; 39(11): 1091–6.
24. *Zhu J, Yuan X, Yan L, Li T, Guang M, Zhang Y*. Comparison of Postoperative Outcomes Between Envelope and Triangular Flaps After Mandibular Third Molar Surgery: A Systematic Review and Meta-Analysis. J Oral Maxillofac Surg 2020; 78(4): 515–27.

Received on December 1, 2023
Revised on December 20, 2023
Accepted on January 9, 2024
Online First February 2024

ORIGINAL ARTICLE

UDC: 617.7-007.681:616.89-008.454
DOI: https://doi.org/10.2298/VSP230831008C

Assessment of depression in patients with open-angle glaucoma

Procena depresije kod bolesnika sa glaukomom otvorenog ugla

Aleksandra Cvetković, Sunčica Srećković, Svetlana Paunović

University of Kragujevac, Faculty of Medical Sciences, Department of Ophthalmology, Kragujevac, Serbia; University Clinical Center Kragujevac, Clinic of Ophthalmology, Kragujevac, Serbia

Abstract

Background/Aim. Depression can be caused by a life situation. The aim of the study was to determine the influence of glaucomatous damage on the frequency of occurrence of depression, as well as to determine the risk factors for the onset of depression in patients with open-angle glaucoma (OAG). **Methods.** The study was designed as a clinical, observational study (cross-sectional study). The research included 150 patients of both genders over the age of 40 with a confirmed diagnosis of OAG. Anamnestic and sociodemographic data were collected by a questionnaire and detailed ophthalmological examinations were performed. The Beck Depression Inventory-II scale was used as a measurement instrument to assess depression. **Results.** A high (51.3%) prevalence of depressive symptoms in patients with OAG was confirmed. The patients who suffered from depression more often were women, people with lower monthly earnings, and lower mean deviation values of the visual field index. In patients with advanced glaucoma, a significantly higher frequency of depressive symptoms was observed. **Conclusion.** Due to the high prevalence of depressive symptoms, it is important to introduce a multidisciplinary approach to treatment by ophthalmologists and psychiatrists. Detecting and treating depressive symptoms at an early stage of the disease leads to a significant reduction in treatment costs and patient disability.

Key words:
age factors; depression; glaucoma, open-angle; socioeconomic factors; risk factors; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Depresija može biti izazvana nekom životnom situacijom. Cilj rada bio je da se utvrdi uticaj oštećenja izazvanog glaukomom na učestalost pojave depresije, kao i da se utvrde faktori rizika za nastanak depresije kod pacijenata sa glaukomom otvorenog ugla (GOU). **Metode.** Studija je dizajnirana kao klinička, opservaciona studija (studija preseka). Istraživanje je obuhvatilo 150 bolesnika oba pola, starijih od 40 godina, sa potvrđenom dijagnozom GOU. Obavljeni su detaljni oftalmološki pregledi, a anamnestički i sociodemografski podaci su prikupljeni putem upitnika. Kao instrument merenja za procenu depresije, korišćena je skala *Beck Depression Inventory-II*. **Rezultati.** Potvrđena je visoka (51,3%) prevalenca simptoma depresije kod bolesnika sa GOU. Od depresije su češće obolevale žene, osobe sa nižom mesečnom zaradom i nižim vrednostima srednje devijacije indeksa vidnog polja. Kod bolesnika sa uznapredovalim glaukomom, uočena je značajno viša učestalost simptoma depresije. **Zaključak.** Zbog visoke prevalencije simptoma depresije, važno je uvođenje multidisciplinarnog pristupa lečenju od strane oftalmologa i psihijatra. Otkrivanje i lečenje simptoma depresije u ranoj fazi bolesti dovodi do značajnog smanjenja troškova lečenja i onesposobljenosti bolesnika.

Ključne reči:
uzrast, faktor; depresija; glaukom, otvorenog ugla; socijalno-ekonomski faktori; faktori rizika; ankete i upitnici.

Introduction

Glaucoma is a chronic, progressive optic neuropathy that occurs as a result of the death of retinal ganglion cells and their axons. It is manifested by characteristic morphological changes in the optic nerve head and corresponding visual field defects (VFDs). Glaucoma is the leading cause of irreversible blindness around the world [1]. The prevalence of glaucoma is 3.54% in people aged 40–80 years [1–3]. Primary open-angle glaucoma (OAG) is the most common form of glaucoma worldwide [4].

Correspondence to: Aleksandra Cvetković, University of Kragujevac, Faculty of Medical Sciences, Department of Ophthalmology, Svetozara Markovića 69, 34 000 Kragujevac, Serbia. University Clinical Center Kragujevac, Clinic of Ophthalmology, Zmaj Jovina 30, 34 000 Kragujevac, Serbia. E-mail: dr.aleksandracvetkovic@gmail.com

Depression can be genetic, with an imbalance of neuroactive substances. Yet, it can also be caused by a life situation. Previous studies have shown a relatively high prevalence of depression (10–57%) and anxiety (13–33%) among glaucoma patients (GPs) [5–7]. However, an Israeli study found similar rates of depression in GPs and the general population [8]. In recent Serbian clinical research, none of the investigated clinical ophthalmological characteristics emerged as risk factors for depression, but the following did: low economic status, poor health, presence of comorbidities such as cardiovascular diseases, history of surgeries, and non-beneficial lifestyle habits of GPs. These findings suggest that objective measures of glaucoma severity may not be as important to the mental health of GPs as their perception of illness and disability [9]. Research shows that depression and anxiety can be caused by being diagnosed with glaucoma due to the fear of potential blindness, sociodemographic factors, daily lifelong antiglaucoma therapy, or multiple surgeries [1, 3]. Evidence has shown that GPs often have problems with essential daily activities such as walking, driving, or reading, especially when perimetric damage is advanced or when both eyes are affected [2]. Moreover, they reported that VFDs were associated with greater depression. It has been previously published that VFDs were associated with a greater risk of a significant reduction in patients' daily activities. Both have been associated with depression [10]. DiMatteo et al. [11] have shown in their meta-analysis that adherence to medication therapy is worse in the treatment of various diseases in patients with depressive symptoms. Adherence was found to be 38 times lower in depressed patients compared to non-depressed Mexican GPs [12]. More recent research shows that GPs with poor compliance have more symptoms of depression compared to patients with good compliance [13]. Research shows that GPs on long-term topical therapy with β-blockers (BB) are at a higher risk of developing depressive disorders [14, 15].

The main aim of the study was to determine the impact of glaucomatous damage on the frequency of depression and to assess the risk factors for depression in patients with OAG.

Methods

The research was conducted according to the principle of a clinical observational study (cross-sectional study) [16].

The study was approved by the Ethics Committee of the University Clinical Center Kragujevac (No 01/18/3740 from September 25, 2018). All patients signed an informed consent before inclusion in the study. The research included 150 patients of both genders, ages over 40. All the patients had a confirmed OAG diagnosis and were treated at the Ophthalmology Clinic of the University Clinical Center in Kragujevac, Serbia. Patients diagnosed with primary OAG, pseudoexfoliative glaucoma (PEX), and pigmentary glaucoma (PIG), with at least one year from diagnosis, were included in the study. The criteria for exclusion from the study were pregnancy, breastfeeding, and the presence of other types of eye diseases (primary angle closure glaucoma, secondary glaucoma, senile macular degeneration, uveitis, diabetic maculopathy, corneal diseases, and cataracts except for initial nuclear condensations). Anamnestically obtained data on the presence of coexisting psychological conditions before diagnosis (anxiety/depression, psychosis), abuse of alcohol and narcotics, use of drugs that are known to affect the patient's cognitive abilities or mental state (digoxin, corticosteroids), simultaneous participation in clinical studies that involve testing drugs or medical devices upto 30 days before the research were also exclusionary factors.

The study did not exclude patients using topical BB or carbonic anhydrase inhibitors (CAI_s) due to the interest in investigating their effect on the occurrence of anxiety and depressive symptoms.

The ophthalmological examination included: determination of best-corrected visual acuity (VA) – BCVA according to Snellen, detailed examination on a biomicroscope, measurement of intraocular pressure (IOP) with a Goldmann applanation tonometer, gonioscopy, examination of the fundus (with a non-contact glass for fundus examination with sufficient magnification on a biomicroscope or direct contact glass for fundus examination on a biomicroscope), and standard automated perimetry (SAP). SAPwas performed on a Humprey apparatus (Carl Zeiss Meditec AG, Jena, Germany) program 30-2 or 24-2.

OAG was diagnosed based on optic disk appearance and VFD [17]. In the case of the presence of disease in both eyes, the patient was grouped based on the data from the eye showing the worse clinical findings, BCVA, and mean deviation (MD) of the visual field index. A minimum of one year of disease duration and a minimum of three perimetric findings of standard automatic perimetry were selected for reliable determination of disease stage. The severity of glaucoma was determined based on the perimetric findings and MD index values according to Hoddap's classification [18]. Based on the severity of the perimetric damage, the patients were divided into three groups of 50 patients each. The first groupconsisted of patients with an early stage of glaucoma [MD < 6 decibels (dB)], the second groupof patients was with a moderate stage of glaucoma (MD > 6 dB), and the third groupwas with an advanced stage of glaucoma (MD > 12 dB).

Sociodemographic data were obtained by filling out a questionnaire by the first researcher during a conversation with the patient at the ophthalmology clinic.

The questionnaire included age, gender, marital status (single/married/divorced/widowed), level of education (illiterate/primary/secondary/high), occupation, employment (employed/unemployed/retired), economic status (total monthly household income < 20,000, from 20,001 to 40,000, from 40,001 to 60,000, from 60,001 to 80,000, and > 80,000 Serbian dinars.

The Beck Depression Inventory-II (BDI-II) assessment scale was used in our study. It is one of the most widely used instruments for measuring the intensity and symptoms of depression in the clinical and general population, sufficiently sensitive and specific for diagnosing depression [19, 20]. In 2010, it was translated into Serbian and confirmed in our

population [20]. All patients were personally interviewed without paraphrasing by the first researcher during control examinations at the Ophthalmology Clinic of the University Clinical Center Kragujevac.

The BDI-II consists of 21 items, and the score can range from 0 to 63. Scores 0–9 indicate no depression, 10–16 indicate mild mood disorder, 17–20 indicate mild to moderate depression, 21–30 moderate depression, 31–40 severe depression, and over 40 indicate extreme depression.

Statistical data processing

The following descriptive statistical methods were used: measures of central tendency (arithmetic mean, median), measures of variability (standard deviation, range), and indicators of structure expressed as percentages. Correlation between variables in which the distribution of data was normal was examined using Pearson's rank correlation. It has a value between -1 and 1. The sign indicates the direction of correlation. The strength was determined according to the division proposed by Cohen [21] (1988): small 0.10–0.29, medium 0.30–0.49, and large 0.5–1.0. The Kruskal-Wallis test was used to compare different groups of glaucoma. The Mann-Whitney *U* test for continuous variables and Pearson's Chi-square test or Fisher's exact probability test for categorical variables were used to test the difference. Univariate logistic regression was used to analyze the impact of risk factors (sociodemographic, clinical characteristics) on the occurrence of depression. Statistically significant risk factors ($p < 0.05$) with the outcome in univariate analysis were then selected for multivariate logistic regression analysis. The results of the regression models have been presented as an odds ratio with a 95% confidence interval (CI). A value of $p < 0.05$ is considered statistically significant. All data were processed with the SPSS 20 statistical program.

Results

In the overall study sample, the mean age was 73.0 ± 10.5 years (range 42 to 98 years). The average age was 67.04 ± 10.40 years (range 42 to 88) in the groupwith early glaucoma, 76.22 ± 9.64 years (range 52 to 93) in the groupwith moderate glaucoma, and 75.78 ± 8.84 years (range 54 to 98) in the groupwith advanced glaucoma.

The largest number of patients [88 (58.7%)] were female. Early-stage glaucoma was present in 35 (70%) women. In the advanced stage group, the majority of patients were [28 (56%)] men. Out of the total of 150 patients, 103 (68.7%) were married; 80 (53.3%) patients had secondary education and 48 (32%) had high education. Most [107 (71.3%)] of the patients were retired; 24 (16%) patients had the lowest income (Table 1).

Table 1

Sociodemographic characteristics of patients with open-angle glaucoma (OAG)

Characteristics	Group			Total
	Early OAG MD < 6 dB	Moderate OAG MD < 12 dB	Advanced OAG MD > 12 dB	
Age, years	67.04 ± 10.4 (42–88)	76.22 ± 9.64 (52–93)	75.78 ± 8.84 (54–98)	73.01 ± 10.48 (42–98)
Gender				
male	15 (30)	19 (38)	28 (56)	62 (41.3)
female	35 (70)	31 (62)	22 (44)	88 (58.7)
Marital status				
single	0 (0)	0 (0)	1 (2)	1 (0.7)
married	40 (80)	31 (62)	32 (64)	103 (68.7)
widowed	4 (8)	15 (30)	13 (26)	32 (21.3)
divorced	4 (8)	15 (30)	13 (26)	32 (21.3)
Education				
basic	2 (4)	5 (10)	14 (28)	21 (14)
secondary	18 (36)	31 (62)	31 (62)	80 (53.3)
high	30 (60)	14 (28)	4 (8)	48 (32)
illiterate	0 (0)	0 (0)	1 (2)	1 (0.7)
Employment status				
employed	21 (42)	8 (16)	5 (10)	35 (22.7)
unemployed	0 (0)	1 (2)	8 (16)	9 (6)
pensioner	29 (58)	41 (82)	37 (74)	107 (71.3)
Monthly salary, Serbian dinars				
< 20,000	1 (2)	5 (10)	18 (36)	24 (16)
20,000–40,000	16 (32)	26 (52)	25 (50)	67 (44.7)
40,001–60,000	21 (42)	12 (24)	7 (14)	40 (26.7)
60,001–80,000	10 (20)	6 (12)	0 (0)	16 (10.7)
> 80,001	2 (4)	1 (2)	0 (0)	3 (2)

MD – mean deviation; dB – decibel. Number of patients = 50 in each group.

All values are expressed as numbers (percentages), except for age which is shown as mean ± standard deviation (range).

All patients had bilaterally developed disease. The BCVA of 150 patients with OAG in their worse-seeing eye was 0.61 ± 0.38 (range 0–1.0). The mean IOPin the worse eye was 19.61 ± 5.58 (range 10–50). The mean cupto disc ratio (C/D) value in the worse eye was 0.66 ± 0.26 (range 0.2–1.0). The average number of glaucoma surgeries performed was 0.12 ± 0.1 (range 0–2). The most performed surgery was argon laser trabeculoplasty (ALT) in ten patients, followed by trabeculectomy in eight patients (Table 2).

Some form of depressive symptoms was found in 77 (51.3%) patients. All seven patients with extreme depression had advanced-stage glaucoma (Table 3).

A high positive correlation was observed between the stage of glaucoma and the level of depression (Pearson's correlation coefficient +0.608).

The frequency of depression among three different groups of OAG, early glaucoma, moderate glaucoma, and advanced glaucoma, was statistically significant, $p = 0.002$. It shows that the severity of glaucoma affects the occurrence of depression (Table 3).

Table 2

Clinical characteristics of patients with open-angle glaucoma (OAG)

Clinical characteristics	Group			Total
	Early OAG MD < 6 dB	Moderate OAG MD < 12 dB	Advanced OAG MD > 12 dB	
BCVA, mean ± SD (range)				
worse eye	0.92 ± 0.12 (0.5–1.0)	0.74 ± 0.22 (0.3–1.0)	0.16 ± 0.24 (0–0.8)	0.61 ± 0.38 (0–1.0)
better eye	0.99 ± 0.03 (0.8–1.0)	0.89 ± 0.16 (05–1.0)	0.57 ± 0.28 (0–1.0)	0.69 ± 0.28 (0–1.0)
IOP, mean ± SD (range)				
worse eye	18.44 ± 4.3 (11–33)	18.28 ± 3.58 (11–28)	22.1 ± 7.33 (10–50)	19.61 ± 5.58 (10–50)
better eye	16.67 ± 2.9 (10–21)	16.86 ± 3.31 (10–22)	16.54 ± 4.68 (4–28)	16.69 ± 3.69 (4–28)
C/D, mean ± SD (range)				
worse eye	0.41 ± 0.11 (0.2–0.7)	0.63 ± 0.2 (0.2–1.0)	0.93 ± 0.11 (0.6–1.0)	0.66 ± 0.26 (0.2–1.0)
better eye	0.35 ± 0.09 (0.2–0.6)	0.5 ± 0.18 (0.2–0.9)	0.69 ± 0.22 (0.1–1.0)	0.51 ± 0.22 (0.1–1.0)
Laterality of the disease, n (%)				
bilateral	50 (100)	50 (100)	50 (100)	150 (100)
one-sided	0 (0)	0 (0)	0 (0)	0 (0)
Number of anti-glaucoma drops *per* eye, mean ± SD (range)	2.12 ± 1.39 (1–6)	2.38 ± 1.82 (1–12)	3.78 ± 2.0 (1–10)	2.76 ± 1.9 (1–12)
Anti-glaucoma eye drops, n				
prostaglandin analogues	35	41	28	104
β-adrenergic blockers	15	21	16	52
carbonic anhydrase inhibitors	11	12	34	57
α-2 selective adrenergic agonists	11	10	26	47
cholinergic agonists	1	0	3	4
Number of antiglaucoma operations, mean ± SD (range)	0.0 ± 0.0 (0–0)	0.16 ± 0.1 (0–2)	0.2 ± 0.1 (0–1)	0.12 ± 0.1 (0–2)
Kind of antiglaucoma operations, n				
argon laser trabeculoplasty	0	6	4	10
trabeculectomy	0	2	6	8

BCVA – best-corrected visual acuity; IOP– intraocular pressure; C/D – cupto disc ratio; SD – standard deviation; n – number. Number of patients = 50 in each group.

Table 3

Mental health of patients with open-angle glaucoma (OAG)

Depression (BDI) (points)	Early OAG 1º MD < 6 dB	Moderate OAG 2º MD < 12 dB	Advanced OAG 3º MD > 12 dB	*p*
Absent (0–9)	46 (92)	20 (40)	7 (14)	0.02
Mild mood disorder (10–16)	1 (2)	12 (24)	10 (20)	
Borderline (17–20)	2 (4)	6 (12)	3 (6)	
Moderate (31–30)	1 (2)	7 (14)	16 (32)	
Severe (31–40)	0 (0)	5 (10)	7 (14)	
Extreme (> 40)	0 (0)	0 (0)	7 (14)	

BDI – Beck Depression Inventory; MD – mean deviation. Kruskal Wallis test.

All values are expressed as numbers (percentages). Number of patients = 50 in each group.

The association of depression with sociodemographic and clinical characteristics of patients with OAG is presented in Table 4.

A significant association of depression with gender was observed in our study (p = 0.043), BCVA of the worse eye (p = 0.043), MD of the worse eye (p = 0.048), and C/D of the worse eye (p = 0.049). No statistical significance of the difference was obtained for the other variables.

Risk factors associated with depression in patients with OAG are presented in Table 5.

Table 4

Factors associated with depression in patients with open-angle glaucoma

Parameter	No depression (n = 73)	With depression (n = 77)	*p*
Age, years	72.04 (42–98)	74.04 (45–98)	0.33*
Gender, n (%)			
male	36 (49.3)	26 (33.8)	0.043**
female	37 (50.7)	51 (66.2)	
Marital status			
single	1 (1.4)	0 (0)	0.536**
married	47 (64.4)	56 (72.7)	
widowed	18 (24.7)	14 (18.2)	
divorced	7 (9.6)	7 (9.1)	
Education			
basic	11 (15.1)	10 (13)	0.120**
medium	44 (60.3)	36 (46.8)	
high	17 (23.3)	31 (40.3)	
illiterate	1 (1.4)	0 (0)	
Employment status			
employed	20 (26)	14 (16.5)	0.563**
unemployed	5 (6.5)	4 (5.5)	
pensioner	52 (67.5)	55 (75.3)	
Monthly salary, Serbian dinars			
< 20,000	10 (13)	14 (19.2)	0.122**
20,000–40,000	32 (41.6)	35 (47.9)	
40,001–60,000	20 (26)	20 (27.4)	
60,001–80,000	13 (16.9)	3 (4.1)	
> 80,001	2 (2.6)	1 (1.4)	
Best-corrected visual acuity			
worse eye	0.66 (0–1)	0.54 (0–1)	0.043*
better eye	0.84 (0–1)	0.79 (0.01–1)	0.283*
Intraocular pressure			
worse eye	19.51 (10–34)	19.71 (11–50)	0.320*
better eye	16.57 (4–23)	16.81 (8–28)	0.784*
Mean deviation			
worse eye	-8.47 (-28–10)	-10.41 (-28–10)	0.048*
better eye	-6.01 (-26– -0.06)	-6.53 (-28.4–0.84)	0.656*
Cupto disc ratio			
worse eye	0.617 (0.2–1)	0.699 (0.2–1)	0.049*
better eye	0.48 (0.2–1)	0.55 (0.1–1)	0.060*
Number of anti-glaucoma drops *per* eye	2.75 (1–10)	2.77 (1–12)	0.806*
Type of anti-glaucoma eye drops			
prostaglandin analogues	50 (26)	54 (74)	0.230**
β-adrenergic blockers	23 (26.7)	29 (39.7)	0.205**
carbonic anhydrase inhibitors	28 (36.4)	29 (39.7)	0.672**
α-2 selective adrenergic agonists	25 (32.5)	22 (30.1)	0.758**
cholinergic agonists	3 (3.9)	1 (1.4)	0.337**
Number of antiglaucoma operations	0.11 (0–2)	0.14 (0–1)	0.394*
Kind of antiglaucoma operation			
argon laser trabeculoplasty	4 (5.2)	6 (8.2)	0.753**
trabeculectomy	4 (5.2)	4 (5.2)	0.753**

***Mann-Whitney *U* test; **Pearson Chi-square test.**

Values are given as mean (range) or numbers (percentages).

Patients with OAG who suffered from depression more often were women (p = 0.044) and those who had lower monthly earnings (p = 0.028) and lower MD (p = 0.046). The chance of depression was 1.04 for advanced-stage glaucoma (MD > 12 dB), 0.597 for moderate-stage glaucoma (MD < 12 dB), and 0.495 for early-stage glaucoma (MD < 6 dB).

Multivariate logistic regression analysis showed that the MD in the worse eye was a clinically significant (p = 0.047) risk factor for depression, as well as monthly earnings (p = 0.030) (Table 6).

Table 5

Risk factors associated with depression in patients with open-angle glaucoma - univariate logistic regression

Parameter	Depression 95%			*p****
	odds	lower	upper	
Age, years				
< 55	0.083	0.003	2.046	
56–70	0.312	0.083	1.168	
71–85	1.397	0.594	3.284	0.184
≥ 86	0.333	0.04	2.769	
Gender				
male/female	0.688	0.361	1.308	0.044
Marital status				
[Δ]single				
married	0.808	0.371	1.758	0.576
widowed	0.750	0.184	3.057	
divorced	0.125	0.009	1.671	
Education				
basic	1.200	0.216	6.676	
medium	0.504	0.206	1.232	0.136
high	0.926	0.283	3.034	
[Δ]illiterate				
Employment status				
employed	0.500	0.125	1.999	
unemployed	1.500	0.106	21.312	0.291
pensioner	0.714	0.334	1.529	
Monthly salary, Serbian dinars				
< 20,000	6.000	0.859	41.902	
20,000–40,000	0.203	0.070	0.584	
40,001–60,000	1.222	0.353	4.235	0.028
60,001–80,000	0.429	0.031	5.985	
> 80,001	2.000	0.500	7.997	
Best-corrected visual acuity				
worse eye	0.682	0.271	1.745	0.153
better eye	1.394	0.352	6.308	0.716
Intraocular pressure				
worse eye	1.019	0.305	3.872	0.101
better eye	0.295	0.153	0.569	0.696
Mean deviation, dB				
< 6	0.495	0.153	1.606	
< 12	0.597	0.193	1.843	0.046
> 12	1.04	0.339	3.19	
Cupto disc ratio on the worse eye	0.536	0.208	1.993	0.380
Number of anti-glaucoma drops *per* eye	0.745	0.266	2.282	0.181
Type of anti-glaucoma eye drops				
prostaglandin analogues	0.540	0.248	1.177	0.233
β-adrenergic blockers	0.522	0.172	1.588	0.207
carbonic anhydrase inhibitors	0.929	0.328	2.628	0.674
α-2 selective adrenergic agonists	0.675	0.209	2.177	0.760
cholinergic agonists				0.340
Number of antiglaucoma operations	0.559	0.281	1.112	0.560
Kind of antiglaucoma operation				
there were no surgeries	0.541	0.271	1.079	
argon laser trabeculoplasty	6.000	0.354	101.568	0.793
trabeculectomy	6	0.221	162.53	

***** Analysis of variance.**

Note: Since there was only one patient who was single and one who was illiterate, they were excluded from the univariate analysis.

Table 6

Risk factors associated with depression in patients with open-angle glaucoma - multivariate logistic regression

Parameter	Depression 95%			*p*
	odds	lower	upper	
[Δ]Age	-	-	-	-
[Δ]Gender				
male/female	0.697	0.357	1.311	0.044
[Δ]Education	-	-	-	-
[Δ]Employment status	-	-	-	-
Monthly salary	0.673	0.471	0.962	0.030
[Δ] Best-corrected visual acuity				
worse eye	-	-	-	-
better eye	-	-	-	-
[Δ] Intraocular pressure				
worse eye	-	-	-	-
Mean deviation on the worse eye	1.5	1.006	2.239	0.047
[Δ]Cupto disc ratio on the worse eye	-	-	-	-
[Δ]Number of anti-glaucoma drops *per* eye	-	-	-	-

Note: [Δ]Data were excluded from multivariate logistic regression because their statistical significance was not determined in the univariate logistic regression.

Discussion

In our study, the prevalence of depressive symptoms in OAG patients was 51.3%. As glaucoma is a chronic disease, it has been the focus of many studies exploring depression. The prevalence of depression in Serbia among patients with diabetes mellitus is 16.7% [22], and among patients with rheumatoid arthritis, it is 42% [23]. In the recently published study by Serbian authors, depression was identified in 41% of GPs [9]. In a similar study conducted in Singapore, the prevalence of depression was 30%. The prevalence of depression in our patients is much higher than in Singapore [5].

Due to the difficulty of detecting depressive symptoms and preventing the occurrence of depression, in our research, we observed all patients with pronounced symptoms of depression as well as those with clinically significant depression. The cut-off score was > 9. According to data from the literature, the cut-off score for patients with clinically significant depression is > 20 [19, 20]. Clinically significant depression was experienced by 43 (28.67%) patients in OAG patients. In the groupof patients with early OAG, there was 1 (2%) patient with clinically significant depression, 12 (24%) were in the groupwith moderate OAG, and 30 (60%) were in the groupwith advanced OAG with clinically significant depression. Differences in prevalence can be attributed to different study designs. In Turkey, the depression occurrence among GPs was 57% [24], and in Australia, it was 19.09% [25]. In Hungary, 12.1% of GPs suffered from depression [26], and in America [27] and Japan [28], depression occurrence was registered in 10% of the population [9]. The lower prevalence of depression in America and Japan is explained by the earlier initiation of treatment, which prevents the progression of the disease and the emergence of psychiatric comorbidities. Depression was also found to affect 32.1% of patients with severe glaucomatous disease [14]. Our research showed that patients suffering from a more severe stage of glaucoma show a higher level of depression. This connection has been confirmed in other scientific works [6, 7].

Through research, we found that women, patients with lower monthly incomes, and lower MD values are more likely to suffer from depression, which is in line with the results of the connection between glaucoma and depression, shown by Stamatiou et al. [6]. The authors reviewed the literature (587 abstracts and 32 studies) and determined the connection between glaucoma and depression, while the advanced stage of the disease, older age, female gender, and faster progression of vision loss were recognized as potential risk factors for depression in GPs [6]. A low MD as a risk factor for depression indicates the importance of SAPin the evaluation of GPs.

Contrary to our results, in a recent Serbian study, none of the examined clinical ophthalmological characteristics appeared as a risk factor for depression. Like us, they confirmed that low economic status is a risk factor for depression in GPs. They also found that poor health, the presence of comorbidities such as cardiovascular diseases, a history of surgeries, and non-beneficial lifestyle habits like coffee consumption are the main risk factors for depression in GPs [9].

There was no statistically significant association between the use of topical BB and CAI_s and depression in our study group. In most studies, no effect of BB on depressive symptoms was observed [29]. There is data in the literature that BB and CAI_s inhibit monoamine anhydrase and worsen depressive symptoms [14]. By reviewing the literature and summarizing the cumulative published experience for a small part of those treated with topical BB, the neuropsychiatric spectrum that resolves after stopping the drug is mentioned as an adverse event [30]. Individual susceptibility cannot be ruled out, so clinicians should be cautious with patients who have had a positive personal or family history of depression [29].

The prognosis of blindness in GPs causes worries and fear of loss of independence, which increases the risk of developing anxiety and depression. Depression can be not

only a consequence but also a risk factor for the onset and worsening of glaucoma [4, 31, 32]. Furthermore, adherence is 38 times lower in GPs with depression compared to patients without depression, which increases the need for operative treatment [12].

Timely identification of the problem affects the course and prognosis of the glaucoma disease, adherence to medication therapy, and long-term improvement of the quality of life of GPs [33, 34]. Further research should determine the underlying pathophysiological mechanisms of the connection between glaucoma and depression [16].

Conclusion

A high (51.3%) prevalence of depressive symptoms in patients with OAG was confirmed. The patients who suffer from depression more often are women, patients with lower monthly earnings, and lower MD.

It is necessary that ophthalmologists understand the clinical importance of the multidisciplinary approach to GPs. Identifying and treating GPs with depressive disorders, as well as coordinating their therapy, is essential.

Acknowledgement

We would like to express our gratitude to M.Sc. Eng Marko Minić D.O.O. PRIZMA Kragujevac for technical support.

Conflict of interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Tahir A, Ahmed MW, Khan S, Zafar O, Sarfraz MH, Tarar MS*. Depression and anxiety in glaucoma patients using mono drug therapy vs polydrug therapy. J Rawalpindi Med Coll 2023; 27(2).
2. *Rulli E, Quaranta L, Riva I, Poli D, Hollander L, Galli F,* et al. Visual field loss and vision-related quality of life in the Italian Primary Open Angle Glaucoma. Scientific Reports 2018; 8(1): 619.
3. *Riva I, Legramandi L, Katsanos A, Oddone F, Rulli E, Roberti G*, et al. Influence of sociodemographic factors on disease characteristics and vision-related quality of life in primary open-angle glaucoma patients: the Italian Primary Open Angle Glaucoma Study (IPOAGS). J Glaucoma, 2018; 27(9): 776–84.
4. *Garcia-Villanueva C, Milla E, Bolarin JM, García-Medina JJ, Cruz-Espinosa J, Benítez-Del-Castillo J*, et al. Impact of Systemic Comorbidities on Ocular Hypertension and Open-Angle Glaucoma, in a Population from Spain and Portugal. J Clin Med 2022; 11(19): 5649.
5. *Lim NC, Fan CH, Yong MK, Wong EP, YipLW*. Assessment of Depression, Anxiety, and Quality of Life in Singaporean Patients With Glaucoma. J Glaucoma 2016; 25(7): 605–12.
6. *Stamatiou ME, Kazantzis D, Theodossiadis P, Chatziralli I*. Depression in glaucoma patients: A review of the literature. Semin Ophthalmol 2022; 37(1): 29–35.
7. *Dayal A, Sodimalla KVK, Chelerkar V, Deshpande M*. Prevalence of Anxiety and Depression in Patients With Primary Glaucoma in Western India. J Glaucoma 2022; 31(1): 37–40.
8. *Weiss GA, Goldich Y, Bartov E, Burgansky-Eliash Z*. Compliance with eye care in glaucoma patients with comorbid depression. Isr Med Assoc J 2011; 13(12): 730–4.
9. *Marić V, Božić M, Marjanović I, Stamenković M*. Risk factors for depression in glaucoma patients. Serbian Archives of Medicine 2023; 151(5–6): 314–20.
10. *Diniz-Filho A, Abe RY, Cho HJ, Baig S, Gracitelli CP, Medeiros FA*. Fast Visual Field Progression Is Associated with Depressive Symptoms in Patients with Glaucoma. Ophthalmology 2016; 123(4): 754–9.
11. *DiMatteo MR, Lepper HS, Croghan TW*. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000; 160(14): 2101–7.
12. *Gamiochipi-Arjona JE, Azses-Halabe Y, Tolosa-Tort P, Lazcano-Gómez G, Gonzalez-Salinas R, Turati-Acosta M,* et al. Depression and Medical Treatment Adherence in Mexican Patients With Glaucoma. J Glaucoma 2021; 30(3): 251–6.
13. *Pappa C, Hyphantis T, Pappa S, Aspiotis M, Stefaniotou M, Kitsos G*, et al. Psychiatric manifestations and personality traits associated with compliance with glaucoma treatment. J Psychosom Res 2006; 61(5): 609–17.
14. *Bali SJ, Parmar T, Arora V, Ichhpujani P, Sagar R, Dada T*. Evaluation of major depressive disorder in patients receiving chronic treatment with topical timolol. Ophthalmologica 2011; 226(3): 157–60.
15. *Berchuck S, Jammal A, Mukherjee S, Somers T, Medeiros FA*. Impact of anxiety and depression on progression to glaucoma among glaucoma suspects. Br J Ophthalmol 2021; 105(9): 1244–9.
16. *Grujičič SŠ, Nikolić A*. Cross-section studies: advantages and disadvantages. Health Care 2021; 50(4): 43–54.
17. *European Glaucoma Society*. Terminology and Guidelines for Glaucoma. 5th Ed. Savona, Italy: European Glaucoma Society; 2020.
18. *Ng M, Sample PA, Pascual JP, Zangwill LM, Girkin CA, Liebmann JM,* et al. Comparison of visual field severity classification systems for glaucoma. J Glaucoma 2012; 21(8): 551–61.
19. *Novović Z, Mihić Lj, Tovilović S, Jovanović V, Biro M*. Psychometric characteristics of the Beck depression inventory on a Serbian student sample. Psychology 2011; 44(3), 225–43. (Serbian)
20. *Timotijević I, Paunović V*. Clinical assessment instruments in psychiatry. Beograd: Our book; 2010. p. 215.
21. *Cohen J*. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988. p. 567.
22. *Fisekovic Kremic MB*. Factors associated with depression, anxiety and stress among patients with diabetes mellitus in primary health care: Many questions, few answers. Malays Fam Physician 2020;15(3): 54–61.
23. *Golubović S, Ilić T, Golubović B, Gajić M, Gajić Z*. The occurrence of depressive symptoms in rheumatoid arthritis: a cross-sectional study. Vojnosanit Pregl 2023; 80(2): 128–35.
24. *Tastan S, Iyigun E, Bayer A, Acikel C*. Anxiety, depression, and quality of life in Turkish patients with glaucoma. Psychol Rep2010; 106(2): 343–57.
25. *Skalicky S, Goldberg I*. Depression and quality of life in patients with glaucoma: a cross-sectional analysis using the Geriatric Depression Scale-15, assessment of function related to vision,

and the Glaucoma Quality of Life-15. J Glaucoma 2008; 17(7): 546–51.

26. *Holló G, Kóthy P, Géczy A, Vargha P.* Personality traits, depression, and objectively measured adherence to once-daily prostaglandin analog medication in glaucoma. J Glaucoma 2009; 18(4): 288–92.
27. *Wang SY, Singh K, Lin SC.* Prevalence and predictors of depression among participants with glaucoma in a nationally representative population sample. Am J Ophthalmol 2012; 154(3): 436–44.e2.
28. *Mabuchi F, Yoshimura K, Kashiwagi K, Shioe K, Yamagata Z, Kanba S,* et al. High prevalence of anxiety and depression in patients with primary open-angle glaucoma. J Glaucoma 2008; 17(7): 552–7.
29. *Verbeek DE, van Riezen J, de Boer RA, van Melle JP, de Jonge P.* A review on the putative association between beta-blockers and depression. Heart Fail Clin 2011; 7(1): 89–99.
30. *Cimolai N.* Neuropsychiatric Adverse Events from Topical Ophthalmic Timolol. Clin Med Res 2019; 17(3–4): 90–6.
31. *Shin DY, Jung KI, Park HYL, Park CK.* The effect of anxiety and depression on progression of glaucoma. Sci Rep2021; 11(1): 1769.
32. *Wändell P, Carlsson AC, Ljunggren G.* Systemic diseases and their association with open-angle glaucoma in the population of Stockholm. Int Ophthalmol 2022; 42(5): 1481–9.
33. *Tharmathurai S, Huwaina AS, Azhany Y, Razak AA, Che-Hamzah J, Fazilawati Q,* et al. Quality of Life of Older Adults with Primary Open Angle Glaucoma using Bahasa Malaysia Version of Glaucoma Quality of Life 36 Questionnaire. Curr Aging Sci 2022; 15(2): 147–62.
34. *Sesar I, Pušić-Sesar A, Jurišić D, Sesar A, Merdžo I, Ćavar I.* Health-related quality of life in primary open-angle glaucoma patients. Acta Clin Croat 2020; 59(4): 623–31.

Received on August 31, 2023
Revised on October 30, 2023
Revised on December 22, 2023
Accepted on January 9, 2024
Online First February 2024

LETTER TO THE EDITOR

UDC: 578.5:616-036.22
DOI: https://doi.org/10.2298/VSP231026001G

Examination of the prevalence of high-risk human papillomavirus genotypes among women on the territory of Belgrade

Ispitivanje zastupljenosti visokorizičnih genotipova humanog papiloma virusa kod žena na teritoriji Beograda

To the Editor:

Cervical cancer is the fourth most common malignant tumor after breast cancer, colorectal cancer, and lung cancer, which threatens the health of women worldwide [1]. Persistent infections by specific high-risk (HR) human papillomavirus (HPV) – HR-HPV strains are the leading cause of cervical cancer and precancerous lesions [2].

HPV infection has the highest transmission rate among sexually transmitted diseases caused by viral agents [3]. HPV is an etiological factor in the development of malignant lesions of the anogenital tract, cervix, vagina, vulva, and penis, as well as the head and neck region, that is, the pharynx, larynx, mouth, esophagus, and respiratory tract [4]. Most HPV infections are self-limiting and remain at the individual level for 15–18 months until the immune system develops a defensive response to the presence of the pathogen. The infection caused by HPV is most often asymptomatic [5].

Based on a direct causal link between HPV infection and cancer development, the American Society for Colposcopy and Cervical Pathology guidelines, World Health Organization, European Society Gynecological Oncology, and European Federation of Colposcopy, suggest HPV deoxyribonucleic acid (DNA) testing as the primary method of HPV detection [6–8].

The advantage of this method is the high sensitivity of polymerase chain reaction (PCR) molecular tests, which ensure the identification of different HPV types, primarily HR-HPV 16 and HR-HPV 18, with a small number of false negative results, which can, with high reliability, declare a low risk for the development of cervical intraepithelial neoplasia 3 (CIN 3) lesions in persons with a negative HPV result [9]. Approximately 52% of CIN 3 lesions are associated with HPV 16 and 18 and represent HR lesions corresponding to precancerous disease [10].

Based on the report of the International HPV Reference Center, there are more than 200 different genotypes of HPVs [11]. HPV genotypes are classified based on the potential to cause the development of malignancy into HR-HPV and low-risk (LR) HPV – LR-HPV types [12]. Of this number of different genotypes, only 50 can induce infection of the cervical epithelium. However, only 14 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) were classified as HR types [12].

The presented study aims to assess the prevalence of HR-HPV genotypes among women who have undergone regular gynecological examinations in the territory of Belgrade, Serbia. The study included the analysis of 847 clinical samples, collected from May to October 2023, aged 19 to 60 years. The samples were collected and analyzed at the Institute of Public Health of Serbia "Dr. Milan Jovanović Batut". Viral DNA extraction was performed on a KingFisher Duo Prime (Thermo Fisher Scientific, Inc.) using the RealLine DNA – Extraction 3 magnetic extraction kit (Bioron diagnostics) [13, 14]. The applied test for DNA detection of 14 HR-HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) was Viasure High-Risk Human Papilloma Virus diagnostic test (CerTest Biotec, S.L.) [15]. By analyzing collected samples, 271 (32%) were positive, while the remaining 570 (68%) were negative for any HPV genotype.

Among the positive samples, only one HPV genotype (HPV 16 or HPV 18 or one of the groups of HR-HPV genotypes) was detected in some of the samples, and, in the rest of the samples, more than one HR-HPV genotype, i.e., co-infection, were detected. Within the positive samples, the genotype HPV 16 was detected in 74 (27%) samples regarding single infection and co-infection. The genotype HPV 18 was detected in 31 samples regarding single infection and co-infection and showed a frequency of 11%. The HPV group (31, 39, 56) showed the highest rate of detections, 126 (47%)

Correspondence to: Hristina Gospodinović, Institute of Public Health of Serbia "Dr. Milan Jovanović Batut", Petra Konjovića 12e, 11 090 Belgrade, Serbia. E-mail: hristina_gospodinovic@batut.org.rs

samples when it comes to single-type infections and co-infections by other HPV groups and HPV 16 and 18.

Based on the presented results, the highest prevalence was shown by the genotype of the HPV group (31, 39, 56), followed by HPV genotype 16, in all the positive samples. The presented results also indicate that a very high percentage of women who have undergone regular gynecological examinations on the territory of Belgrade are infected with some of the HR-HPV genotypes. The positive results according to detected HPV genotypes are equally distributed among all of the age-related groups of women analyzed in this study. Thirty-two percent of randomly selected women is a relatively worrying figure. The high prevalence of HR-HPV genotypes represents an indicator of recognition of the need for a wider area of education and prevention of the general population of women.

HPV genotyping promises the potential to refine the algorithm for the management of HR-HPV-positive women after treatment. Risk stratification allows suitable recommendations for colposcopies and treatments to women with the highest risk of cervical diseases, while women with the lowest risk of pathological changes should be re-examined at short intervals. This would utilize healthcare resources more effectively and reduce patients' psychological anxiety.

Hristina Gospodinović*, Edita Grego*, Sofija Jovanović†, Ljiljana Pavlović*
***Institute of Public Health of Serbia "Dr. Milan Jovanović Batut", Belgrade, Serbia; †University of Belgrade, Faculty of Medicine, Belgrade, Serbia**

R E F E R E N C E S

1. *Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J,* et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health 2020; 8(2): e191–203.
2. *Su P, Ma J, Yu L, Tang S, Sun P.* Clinical significance of extended high-risk human papillomavirus genotyping and viral load in cervical cancer and precancerous lesions. Gynecol Obstet Clin Med 2023; 3(1): 22–9.
3. *Moussavou PB, Koumakpayi IH, Nkili-Meyong AA, Labouba I, Bisvigou U, Chansi JK,* et al. Molecular analysis of human Papillomavirus detected among women positive for cervical lesions by visual inspection with acetic acid/Lugol's iodine (VIA/VILI) in Libreville, Gabon. Infect Agent Cancer 2016; 11(1): 50.
4. *Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C.* Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. J Clin Oncol 2015; 33(29): 3235–42.
5. *Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM.* Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010; 401(1): 70–9.
6. *Moussavou-Boundzanga P, Koumakpayi IH, Labouba I, Leroy EM, Belembaogo E, Berthet N.* Human papillomavirus detection using the Abbott RealTime high-risk HPV tests compared with conventional nested PCR coupled to high-throughput sequencing of amplification products in cervical smear specimens from a Gabonese female population. Virol J 2017; 14(1): 241.
7. *Kyrgiou M, Arbyn M, Bergeron C, Bosch FX, Dillner J, Jit M,* et al. Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC). Br J Cancer 2020; 123(4): 510–7.
8. *World Health Organization.* WHO recommends DNA testing as a first-choice screening method for cervical cancer prevention [Internet]. World Health Organization; 2021 [accessed on: 2023 December 25]. Available from: https://www.who.int/europe/news/item/11-09-2021-who-recommends-dna-testing-as-a-first-choice-screening-method-for-cervical-cancer-prevention
9. *Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L,* et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol 2011; 12(7): 663–72. Erratum in: Lancet Oncol 2011; 12(8): 722.
10. *Martin CM, O'Leary JJ.* Histology of cervical intraepithelial neoplasia and the role of biomarkers. Best Pract Res Clin Obstet Gynaecol 2011; 25(5): 605–15.
11. *Bzhalava D, Eklund C, Dillner J.* International standardization and classification of human papillomavirus types. Virology 2015; 476: 341–4.
12. *IARC Working Group on the Evaluation of Carcinogenic Risks to Humans.* Human papillomaviruses. IARC Monogr Eval Carcinog Risks Hum 2007; 90: 1–636.
13. *Bioron diagnostics.* RealLine DNA – Express [Internet]. BIORON Diagnostics GmbH; 2022 [accessed on: 2023 December 25]. Available from: https://www.bioron.de/wpcontent/uploads/2022/10/B_2IFU.Express_VBC8899-R_Rev01_1022_EN_GLU.pdf
14. *ThermoFisher Scientific.* KingFisher Duo Prime Purification System [Internet]. Thermo Fisher Scientific Inc; 2022 [accessed on: 2023 December 25]. Available from: https://assets.thermofisher.com/TFS-Assets/BID/brochures/kingfisher-duo-prime-purification-system-brochure.pdf
15. *CerTest.* VIASURE Real Time PCR Detection Kits – High Risk Papilloma [Internet]. Spain: Certest Biotec SL [accessed on: 2023 December 25]. Available from: https://www.certest.es/products/high-risk-papilloma/

Received on October 26, 2023
Revised on November 26, 2023
Revised on December 22, 2023
Accepted on January 9, 2024
Online First January 2024

CASE REPORTS

UDC: 578.834:616.24-002-053.32-08
DOI: https://doi.org/10.2298/VSP230427006R

Challenges in therapy of severe COVID-19 pneumonia with giant pneumatocele in a preterm newborn: how to optimize mechanical ventilation?

Izazovi u terapiji teške COVID-19 pneumonije sa džinovskom pneumatocelom kod preterminskog novorođenčeta: kako optimizovati mehaničku ventilaciju?

Snežana Rsovac*†, Mina Čobeljić*, Nadja Vukašinović*, Katarina Milošević†‡

University Children's Hospital, *Department of Pediatric and Neonatal Intensive Care, ‡Department of Pulmonology, Belgrade, Serbia; †University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Abstract

Introduction. Coronavirus disease 2019 (COVID-19) pneumonia is a potentially life-threatening condition that can require the use of mechanical ventilation (MV) and is rare in the neonatal population. Giant pneumatocele is an extremely rare complication of MV, which is practically unknown in neonates. **Case report.** We report a case of a two-week-old premature infant who developed severe acute respiratory distress syndrome (ARDS) due to COVID-19 and pneumatocele as a complication of MV. The newborn was admitted in a life-threatening condition with persistent hypercapnia, which, therefore, required prolonged MV. Chest computed tomography (CT) was done to assess the degree of fibrosis caused by COVID-19, and as an accidental finding, a pneumatocele was observed. The patient was immediately started on high-frequency oscillatory ventilation as a way of conservative treatment. After prolonged duration and gradual separation from MV, the patient was extubated, and oxygen therapy was gradually discontinued. The patient was discharged in good condition, and the follow-up chest CT showed complete regression of pneumatocele. **Conclusion.** Optimization of MV parameters and adequate treatment of complications such as ARDS or giant pneumatocele in neonates is an area that still requires further research, primarily due to the specificity of the neonatal age compared to adult patients.

Key words:
computed tomography; covid-19; infant, premature; pneumonia; respiratory distress syndrome, newborn; ventilator-induced lung injury.

Apstrakt

Uvod. Pneumonija u sklopu koronavirusne bolesti 2019 (COVID-19) je stanje koje je potencijalno opasno po život u čijem lečenju može biti neophodna primena mehaničke ventilacije (MV), ali se retko javlja u neonatalnoj populaciji. Džinovske pneumatocele su izuzetno retka komplikacija MV, praktično nepoznata kod novorođenčadi. **Prikaz bolesnika.** Prikazan je slučaj prevremeno rođenog novorođenčeta starosti dve nedelje, kod koga se u okviru COVID-19 razvio težak akutni respiratorni distres sindrom (ARDS) i pneumatocela nastala kao komplikacija MV. Novorođenče je primljeno u životno ugrožavajućem stanju sa perzistentnom hiperkapnijom zbog čega je bila neophodna produžena MV. Urađena je kompjuterizovana tomografija (KT) grudnog koša kako bi se procenio stepen fibroze izazvane COVID-19 i tom prilikom uočena je pneumatocela. Odmah je, kao metod konzervativnog lečenja, započeta visokofrekventna oscilatorna ventilacija. Nakon produženog trajanja i postepenog odvajanja od MV, bolesnik je ekstubiran i postepeno mu je ukinuta i terapija kiseonikom. Bolesnik je otpušten u dobrom opštem stanju, a kontrolnom KT utvrđena je kompletna regresija pneumatocele. **Zaključak.** Optimizacija parametara MV i adekvatno lečenje komplikacija kao što su ARDS ili džinovska pneumatocela kod novorođenčadi je oblast koja zahteva dalje istraživanje, prevashodno zbog specifičnosti neonatalnog uzrasta u odnosu na odrasle bolesnike.

Ključne reči:
tomografija, kompjuterizovana; covid-19; nedonošče; pneumonija; novorođenče, respiratorni distres sindrom; pluća, oštećenje izazvano respiratorom.

Correspondence to: Nađa Vukašinović, University Children's Hospital, Department of Pediatric and Neonatal Intensive Care, Tiršova 10, 11 000 Belgrade, Serbia. E-mail: nadjavukasinovic@gmail.com

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across the globe since it was first identified in Wuhan, China, in December 2019. So far, it has affected over 600 million people and caused 6 million deaths worldwide [1]. However, not all age groups are affected in the same way. The pediatric population is shown to have an asymptomatic or mild clinical presentation, shorter disease duration, and positive outcomes with seldom-seen complications [2]. Amongst this population, SARS-CoV-2 infected newborns might be observed as a separate group with its specific traits, including possible methods of transmission, ranging from intrauterine, intrapartum, to postnatal transmission [3, 4]. Even though maternal SARS-CoV2 infection has been associated with higher rates of preterm delivery and newborns' admission to the neonatal intensive care unit (NICU), no differences were observed in neonatal mortality or length of hospital stay [4]. In the majority of cases, newborns had an asymptomatic, mild, or atypical clinical presentation, including fever, rhinorrhea, feeding difficulties, tachypnea, and dyspnea [5]. However, severe cases of neonatal COVID-19 have also been reported, with neonates requiring NICU stay and, in some cases, even noninvasive or invasive ventilation [6]. Invasive mechanical ventilation (MV) can lead to several complications, one of them being the development of pulmonary pneumatoceles, thin-walled air-containing cystic formations within the lung parenchyma. Pneumatoceles in neonatal age are usually caused by inadequate delivery of volumes or pressures during MV. Pneumatoceles are mostly asymptomatic but sometimes can have grave complications due to lung and mediastinum compression. We present a preterm newborn with severe COVID-19, requiring invasive ventilation, who developed a pneumatocele as a complication of MV.

Case report

A late preterm male neonate was born in 35/36 gestational week *via* an uncomplicated vaginal delivery to a COVID-19-positive mother, with a birthweight of 2,580 g and an Apgar score of 9. Due to the transient tachypnea of the newborn, he required oxygen supplementation during the first 24 hrs of life but had no further complications. On the 7th day of life, he was discharged from the hospital in a good clinical condition. The baby was tested for SARS-CoV-2 at birth and at discharge from the hospital using reverse transcription polymerase chain reaction tests. Both results were positive, but the baby had no symptoms of COVID-19 or any other infection.

On the 12th day of life, the baby developed feeding difficulties, became hypothermic (33 °C), and was tachypneic. Grunting and acrocyanosis were also observed, as well as a drop in oxygen saturation (SpO_2) (58%, normal values for SpO_2 are > 92%). After the initial workup at the regional medical center, the baby was urgently transferred to the COVID-19 NICU of the University Children's Hospital, Belgrade, Serbia.

On admission, the newborn was afebrile, tachypneic, and moderately dyspneic with mild subcostal retractions. Examination of the respiratory system revealed symmetrical lower-intensity breathing sounds followed by inspiratory crackles. The rest of the physical exam findings were unremarkable. Thorough laboratory as well as radiographic examinations were performed. Antigen test for SARS-CoV-2 was positive, C-reactive protein value was within the normal range (< 10 mg/L), procalcitonin, interleukin (IL)-6, and fibrinogen values were slightly above the upper limit [reference range (RR) < 0.5 ng/mL, 0–7 pg/mL, and 3.1–6.1 g/L, respectively]. Ferritin and D-dimer were elevated (2,056.3 ug/L and 6.9 mg/L, RR 13–150 ug/L and < 0.5 mg/L, respectively). Chest X-ray revealed bilateral lung opacities. Continuous fentanyl sedation and low molecular weight heparin were started. Due to the worsening of the baby's breathing pattern shortly after admission, as well as respiratory acidosis observed in arterial blood gases (ABGs), oxygen therapy *via* nasal cannulas was aborted, and the patient non-invasive ventilation (NIV) was started. Soon after, he was orally intubated, and pressure control – assist control mode of MV was introduced with initial settings raised to peak inspiratory airway pressure of 20 cm H_2O and a fraction of inspired oxygen (FiO_2) of 100% (Table 1). Twenty-four hours after starting the treatment, his ABG values improved, showing a lowering of hypercapnia but also persistent moderate hypoxia. This allowed for a change in the mode of MV to pressure control – synchronized intermittent mandatory ventilation (PC-SIMV) with a reduction of ventilation parameters (Figure 1). Systemic corticosteroids were started in regular therapy.

On the 4th day of hospitalization, significant acute respiratory distress syndrome (ARDS) progression was observed (with zones of hypoventilation, hyperinflation, and consolidation on chest X-ray). Hence, surfactant was administered, methylprednisolone dosage was increased, and immunoglobulins were started. Despite all undertaken measures, respiratory failure progressed even further over the next two days. Parameters of MV had to be significantly increased [peak inspiratory pressure of 25 mm H_2O (RR 20–25 cm H_2O), positive end-expiratory pressure of 7 mm H_2O (RR 4–6 cm H_2O), and FiO_2 of 100%] with a change in the mode of ventilation to pressure control – continuous mandatory ventilation. Second and third doses of surfactant were administered, and the dose of systemic corticosteroid was further increased. Only four days after, inhaled nitric oxide (iNO) therapy of 20 ppm was initiated as well due to suprasystemic pulmonary tension. The unwavering requirement for high MV parameters, persistent bilateral lung opacities observed on the follow-up chest X-ray, and unchanging clinical findings on the examination of the respiratory system led to a decision to apply the fourth dose of surfactant on the 11th day of hospitalization. This caused a significant increase in oxygenation, with SpO_2 values mostly above 92%. Throughout the hospitalization, the patient required intermittent administration of furosemide in order to maintain adequate diuresis, short-term inotropic support due to hypotension, as well as several erythrocyte transfusions due to anemia verified in complete blood count. Sildenafil was included in regular

Table 1

Breaking points of the patient's stay in the Intensive Care Unit

Parameter	Day of hospitalization												
	1	2	4	6	10	12	14	40	56	62	81	84	89
SPO_2 (%)	80%		90–98	77–92	77–96	88%	94%	75–82	86–92	85–99		85%	88–100
CRP (mg/L)		2.1						168.5	54.3			3.5	
Surfactant		1st dose		2nd & 3rd dose		4th dose		5th dose					
Antibiotics			amikacin ampicillin					ciprofloxacin vancomycin	amikacin piperacillin				
Corticosteroids (mg/kg of BW)		1	2	3		2							
Dobutamine						5 mcg/kg/min		starting again 7 mcg/kg/min					
Sildenafil								starting		ex			
iNO (ppm)					20		10	ex					
Immunoglobulins		pentaglobine						pentaglobine					
Mode of MV	PC-AC	PC-SIMV		CMV	CMV		SIPPV	HFOV	HFOV	SIMV	CPAP/PSV	HFNC	NC
PIP	21	26		28	23		23			23			
PEEP	5	6		6	6		5			6	7		
FiO_2	80	100		100	100		90	100	60	85	75		
OI	9	13.62		16.66	14.42		13.48	27.04	12.2	9.6	5.5		
Amplitude								45	38				
CDP								24	19				
Flow (L/min)												10	3
pH	7.27	7.31		7.46	7.44		7.34	7.27	7.32	7.43	7.43	7.41	
pCO_2 (mmHg)	55	45		47	48		59	94	88	71	44	63	
pO_2 (mmHg)	40	64		62	71		77	77	99	77	79	92	

Note: reference range (RR) for dobutamine is 2–25 mcg/kg/min, OI < 17, CDP 12–17 cm H_2O, amplitude 20–40 cm H_2O, flow for HFNC 6–10 L/min, pH 7.35–7.45, pCO_2 35–45 mmHg, pO_2 50–80.

SPO_2 – oxygen saturation; CRP – C-reactive protein; BW – body weight; iNO – inhaled nitric oxide; MV – mechanical ventilation; PIP – peak inspiratory pressure; PEEP – positive end-expiratory pressure; FiO_2 – fraction of inspired oxygen; OI – oxygenation index; CDP – continuous distending pressure; pH – potential of hydrogen; pCO_2 – partial pressure of carbon dioxide; pO_2 – partial pressure of oxygen; PC-AC – pressure control assist control; PC-SIMV – pressure control – synchronized intermittent mandatory ventilation; CMV – continuous mandatory ventilation; SIPPV – synchronized intermittent positive pressure ventilation; HFOV – high-frequency oscillatory ventilation; CPAP/PSV – continuous positive airway pressure/pressure support ventilation; HFNC – high flow nasal cannula; NC – nasal cannula.

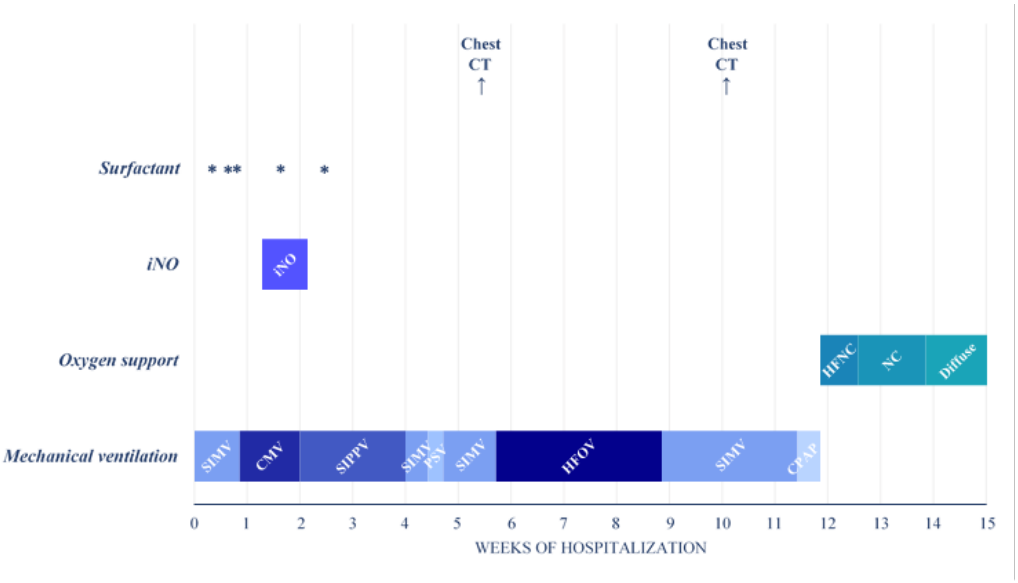


Fig. 1 – Timeline of the patient's stay in the Intensive Care Unit.
CT – computed tomography; Diffuse – diffuse oxygen therapy; * – administration of surfactant; For other abbreviations, see Table 1.

therapy on the 14th day, and usage of iNO was aborted the day after. The described improvement of oxygenation was short-lived, and on the 17th day, the 5th dose of surfactant was administered, and beta-2 agonist-anticholinergic inhalations were started. Acetylcysteine inhalation was also administered to help eliminate the abundance of secretion present in the airways from the start of the treatment. Compensated respiratory acidosis with refractory hypercapnia and hypoxemia was a persistent finding in ABGs. During the next ten days, ventilatory support was gradually reduced all the way down to pressure support ventilation mode, and both corticosteroid and sildenafil doses were decreased. However, on the 32nd day of hospitalization, the patient's clinical aspect worsened due to developing sepsis, so the requirement for ventilatory support once again increased, and he was changed back to PC-SIMV mode of ventilation. The obtained chest X-ray showed no signs of improvement in comparison to previous X-rays, and the image of the III phase of ARDS was still present.

In order to evaluate the degree of lung fibrosis, on the 36th day of hospitalization, a chest computed tomography (CT) scan was obtained, which corresponded to the already established diagnosis of ARDS. Additionally, it showed a large air collection (pneumatocele) in the anterior part of the right hemithorax with a polycyclic outline, spreading from the diaphragm to the upper half of the sternum and communicating with airways (Figure 2). Diffuse bilateral ground glass lung opacities and thickened peribronchial connecting tissue were noted as well.

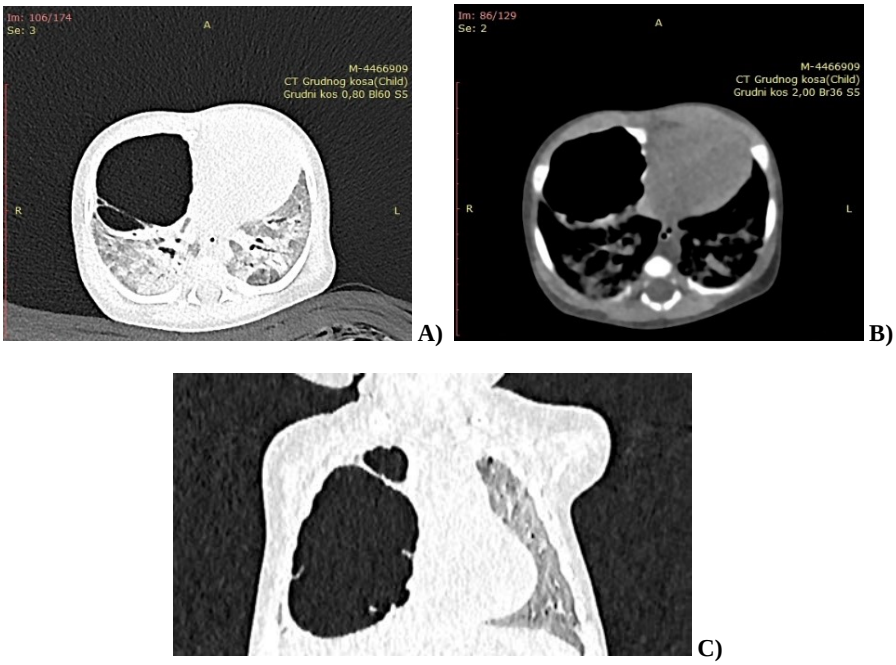


Fig. 2 – Computed tomography of the chest. Pneumatocele observed in transverse (A and B) and coronal plane (C).

The high-frequency oscillatory ventilation (HFOV) mode was started and kept for the next 22 days. This gradually led to an improvement in gas exchange and made it possible for ventilatory support to be reduced first to PC-SIMV. Over the next 19 days, it dropped down to pressure-controlled – continuous positive airway pressure. Even though follow-up chest CT scan findings showed further progression of the changes in the lung parenchyma, the clinical aspect of the patient, as well as his oxygenation and ventilation, were good enough to allow for extubation after 83 days of MV. Complete supportive therapy was initiated to improve respiratory function (such as beta-2 agonist-anticholinergic inhalations, corticosteroid inhalations, aminophylline, and IV corticosteroids). Oxygen support was gradually decreased from high flow nasal cannula to diffuse application of 4 L/min of oxygen. The baby was discharged from the Intensive Care Unit after 106 days (Table 1, Figure 1) and moved to the Pulmonology Department for further treatment using inhaled and systemic corticosteroids, a decrease in oxygen therapy, and physical rehabilitation.

The third chest CT scan performed was the first to show an improvement. Findings described in previous CT scans were in regression – pneumatocele was smaller, but ground glass opacities were persistent with fibroadhesive strips and consequential bronchiectasis. At no time was there any indication for an operative approach to the described pneumatocele. Considering that the mother was trained during the hospitalization to provide adequate physical rehabilitation treatment, as well as percutaneous drainage of secretion from the airways and application of oxygen therapy, and seeing that the clinical aspect of the patient was significantly improved, the baby was discharged home after 144 days in the hospital, from October 2021 to April 2022.

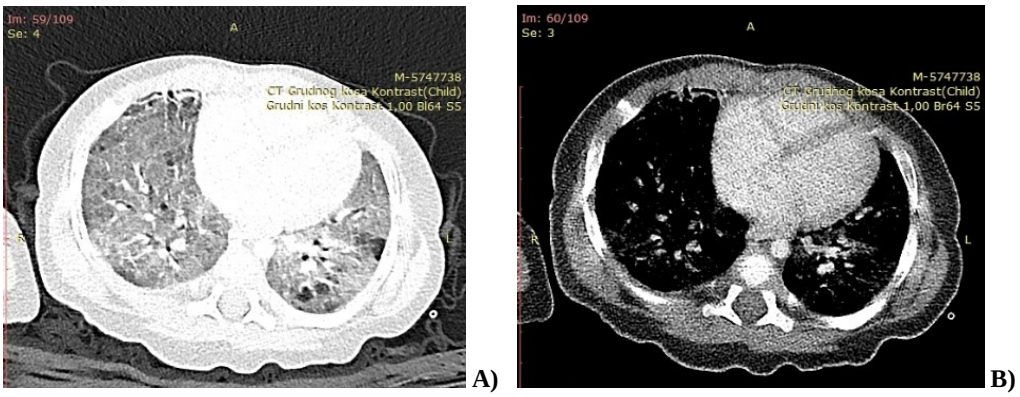
Systemic and inhaled corticosteroids were prescribed in regular therapy, along with the usage of a home oxygen concentrator as required.

Follow-up chest CT performed two months after hospital discharge showed no signs of previously described pneumatocele and no change in the rest of the findings regarding lung fibrosis (Figure 3). On the follow-up examination five months after discharge, the mother reported that the baby did not require oxygen support, so systemic corticosteroid therapy was aborted, and inhaled corticosteroids were tapered off.

Discussion

The available literature on severe cases of COVID-19 in newborns is scarce since clinical presentation in this population is usually asymptomatic or mild, with the most common symptoms being fever, rhinorrhea, feeding difficulties, and cough [5]. Severe cases of pulmonary involvement require respiratory support, but oxygen therapy or noninvasive ventilation is mostly a sufficient manner of respiratory treatment [7]. Only a small number of critically ill newborns require invasive MV [7]. Changes in lung radiographs, such as ground glass opacities, were also commonly described in patients with pulmonary involvement and severe clinical presentation. However, even though it has been one of the most common clinical entities observed in severe COVID-19 patients over the previous three years, not many newborns were classified as having ARDS since this diagnosis is not so common during the neonatal period. The Montreux definition of neonatal ARDS states that ARDS is characterized by qualitative or quantitative surfactant dysfunction and extensive lung tissue inflammation. It has acute onset from a known or suspected clinical insult. Conditions such as respiratory distress syndrome, transient tachypnea of the newborn, or congenital anomalies have to be excluded as a primary cause of acute respiratory condition [8].

MV is an important method of ARDS treatment when NIV is insufficient, but it must be highlighted that the lungs of these patients are even more prone to ventilator-induced lung injuries (VILI): volumes/pressures required to expand collapsed alveoli lead to overexpansion of normal, unaffected alveoli and cause lung injuries such as pneumothorax or pneumatocele. Therefore, a crucial point in ARDS treatment is balancing MV parameters with low tidal volume (4 mL/kg) and limited platform pressure (up to 25 mm H_2O) to provide adequate ventilation and oxygenation, prevent respiratory acidosis, and, on the other hand, avoid any potential VILIs [9]. MV leads to an increase in levels of pro-inflammatory cytokines (IL-6, IL-8 and tumor necrosis factor-α) and a decrease of anti-inflammatory cytokine IL-10, which, in addition to already elevated levels of pro-inflammatory cytokines due to primary disease, increases lung vulnerability and propensity towards complications [10].



A) **B)**

Fig. 3 – Follow-up computed tomography of the chest. No signs of pneumatocele were observed (A and B).

Additionally, in newborns, especially premature infants, MV carries even higher risks since it can potentially harm lung development and lead to histological changes in airways and alveoli [11]. Pneumothorax has been described in the literature as a complication of MV in SARS-CoV-2 positive newborns [6], but to our knowledge, pneumatocele in newborns has not been described in relation to COVID-19 so far.

Pulmonary pneumatoceles in neonatal age are most commonly caused by MV, specifically by inadequate delivery of volumes or pressures. They are typically observed in the right lower lobe or the right middle lobe due to the anatomy of airways and distribution of ventilatory pressure and volumes [10]. Pneumatoceles are mostly asymptomatic and discovered as incidental findings on chest X-rays. However, they can sometimes compress the adjacent lung and the mediastinum, leading to the development of atelectasis of the lung parenchyma, consequential respiratory failure, pulmonary hypertension, and death. Common complications are the rupture of the pneumatocele into the pleural space, tension pneumothorax, and secondary infection. It is, therefore, important to start adequate treatment for pneumatocele as soon as the diagnosis is established. Although there are no clear guidelines, therapeutic options range from conservative management, such as lung protective ventilation strategies, unilateral intubation, positioning of the patient, and fluid restriction, to invasive approaches, such as percutaneous drainage, lobectomy, or even pneumonectomy for patients who develop complications refractory to conservative management [10, 12]. Lung protective ventilation strategies imply the reduction of mean airway pressure and the usage of HFOV or volume-controlled modes as a guarantee of adequate volume delivery. HFOV delivers small tidal volumes, maintains constant alveolar inflation, prevents the lung "inflate-deflate" cycle, and improves oxygenation [13]. This ventilation mode uses the effects of permissive hypercapnia to provide ventilation support while maintaining normal cellular function and potential of hydrogen value. It is the best ventilation mode to reduce the risk of VILI as it improves lung recruitment while avoiding overdistension. HFOV is also the best and most recommended conservative treatment method in patients with pneumatocele, where it is usually the only method of treatment. It may take up to several months for complete resolution, but in cases of uncomplicated pneumatoceles, complete recovery with no residues is the most common outcome [10].

Conclusion

This case report provides insight into severely ill COVID-19 newborns requiring intensive respiratory support and developing lung complications. Even though they are described in the adult population, entities such as pneumatocele, COVID-19-caused ARDS, and respiratory insufficiency in newborns are still an area that lacks clear guidelines and requires further research.

Acknowledgement

A signed informed consent for writing and publishing this paper was obtained from the patient's legal guardian (parent).

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. *World Health Organization*. WHO Coronavirus (COVID-19) Dashboard [Internet]. Geneva: World Health Organization; 2022 [cited 2022 Oct 20; accessed 2023 Dec 18]. Available from: https://covid19.who.int/
2. *Martins MM, Prata-Barbosa A, da Cunha AJLA*. Update on SARS-CoV-2 infection in children. Paediatr Int Child Health 2021; 41(1): 56–64.
3. *Ryan L, Plötz FB, van den Hoogen A, Latour JM, Degtyareva M, Keuning M,* et al. Neonates and COVID-19: state of the art: Neonatal Sepsis series. Pediatr Res 2022; 91(2): 432–9.
4. *Perlman JM, Salvatore C*. Coronavirus Disease 2019 Infection in Newborns. Clin Perinatol 2022; 49(1): 73–92.
5. *Spoulou V, Noni M, Koukou D, Kossyvakis A, Michos A*. Clinical characteristics of COVID-19 in neonates and young infants. Eur J Pediatr 2021; 180(9): 3041–5.
6. *Pakdel M, Pouralizadeh N, Faramarzi R, Boskabadi H, Mamouri G*. Neonates with Covid-19 infection: Is there any different treatment process? J Pediatr Surg Case Rep 2022; 77: 102148.
7. *Nyholm S, Edner A, Myrelid Å, Janols H, Dörenberg R, Diderholm B*. Invasive mechanical ventilation in a former preterm infant with COVID-19. Acta Paediatr 2020; 109(10): 2141–3.
8. *De Luca D, van Kaam AH, Tingay DG, Courtney SE, Danhaive O, Carnielli VP*, et al. The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity. Lancet Respir Med 2017; 5(8): 657–66.
9. *Mengyue H, Hua M, Chunzhi L*. Research Progress of Neonatal Acute Respiratory Distress Syndrome. Biomed J Sci Tech Res 2019; 22(5): 16994–17001.
10. *Rocha G*. Pulmonary pneumatoceles in neonates. Pediatr Pulmonol 2020; 55(10): 2532–41.
11. *De Bisschop B, Peeters L, Sonnaert M*. Successful conservative managements of extensive pneumatoceles in a preterm girl: A case report. J Neonatal Perinatal Med 2021; 14(1): 139–42.
12. *Al-Ghafri M, Al-Hanshi S, Al-Ismaily S*. Two cases of pneumatoceles in mechanically ventilated infants. Oman Med J 2015; 30(4): 299–302.
13. *Meyers M, Rodrigues N, Ari A*. High-frequency oscillatory ventilation: A narrative review. Can J Respir Ther 2019; 55: 40–6.

Received on April 27, 2023
Revised on October 2, 2023
Revised on December 17, 2023
Accepted on December 19, 2023
Online First February 2024

CASE REPORT

UDC: 616-056.7:616.28-008.14
DOI: https://doi.org/10.2298/VSP221026066O

Cochlear implantation for severe mixed hearing loss caused by Treacher Collins syndrome – a case report

Primena kohlearnog implanta kod bolesnika sa teškim mešovitim oštećenjem sluha izazvanim sindromom Tričer Kolins

Sanja Ostojić-Zeljković, Mina Nikolić, Sanja Djoković

University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia

Abstract

Introduction. Treacher Collins syndrome (TCS) is a rare genetic condition characterized by typical head and neck malformations occurring in 1:50,000 newborns. Permanent conductive or mixed hearing loss of various degrees is diagnosed in 50% of individuals with TCS. A prerequisite for speech and language development in children with permanent mixed hearing impairment is the application of one of the bone conduction hearing aids. Choosing an adequate hearing aid in this case depends primarily on the degree of hearing impairment and the type of ear malformation. **Case report.** We present a female patient with multiple genetic malformations due to TCS. The patient was, immediately after birth, referred for audiological evaluation because of considerable ear and face malformations. Using a hearing test battery, permanent mixed, predominantly conductive, bilateral hearing loss of severe degree was diagnosed. The use of bone conduction hearing aids (including the Vibrant® Soundbridge middle ear implant) in the patient did not give the expected results – sufficient amplification for adequate speech and language development. Only after cochlear implantation at the age of nine did the patient's hearing threshold stabilize and her communication and academic potential develop to full capacity. **Conclusion.** If a middle ear implant is not sufficient for adequate amplification, cochlear implantation should be considered as an appropriate solution for treating severe permanent mixed hearing impairment in patients with TCS.

Key words:
bone diseases, developmental; cochlear implants; genetic diseases, inborn; hearing loss; prostheses and implants.

Apstrakt

Uvod. Tričer Kolins sindrom (TKS) je retko genetsko oboljenje koje karakterišu prepoznatljive malformacije u predelu glave i vrata, a javlja se kod 1:50 000 novorođene dece. Kod 50% osoba sa TKS dolazi do trajnog mešovitog oštećenja sluha različitog stepena. Preduslov za pojavu govora i jezika kod dece sa trajnim mešovitim oštećenjem sluha je primena nekog od slušnih aparata za koštanu provodljivost. Odabir adekvatnog slušnog pomagala u ovom slučaju zavisi pre svega od stepena oštećenja sluha i tipa malformacije organa čula sluha. **Prikaz bolesnika.** Prikazujemo bolesnicu sa mnogobrojnim genetskim malformacijama nastalim usled TKS. Bolesnica je zbog značajnih malformacija uva i lica odmah po rođenju upućena na audiološku procenu. Korišćenjem baterije za ispitivanje sluha dijagnostikovan je trajni mešoviti, obostrani, pretežno provodljivi gubitak sluha teškog stepena. Primena aparata za koštanu provodljivost (uključujući Vibrant® Soundbridge implantat srednjeg uva) kod bolesnice nije dovela do očekivanih rezultata – dovoljno pojačanje za odgovarajući razvoj govora i jezika. Tek nakon kohlearne implantacije u uzrastu od devet godina, kod bolesnice je došlo do stabilizacije praga sluha i razvoja komunikacijskih i akademskih potencijala do punog kapaciteta. **Zaključak.** Ukoliko implantat srednjeg uva nije dovoljan za adekvatno pojačanje, treba razmotriti kohlearnu implantaciju kao odgovarajuće rešenje za lečenje trajnog mešovitog oštećenja sluha teškog stepena kod bolesnika sa TKS.

Ključne reči:
kosti, bolesti, razvojne; kohlea, implantat; genetičke bolesti, urođene; sluh, gubitak; proteze i implantati.

Introduction

Treacher Collins syndrome (TCS) is a rare genetic condition characterized by typical malformations of the head and neck, occurring in 1:50,000 newborns [1]. Malformations of the outer, middle, and occasionally inner ear in 50% of TCS could cause permanent, usually conductive, hearing loss [2]. Diagnosis and treatment of those patients is

Correspondence to: Sanja Ostojić Zeljković, University of Belgrade, Faculty of Special Education and Rehabilitation, Visokog Stevana 2, 11 000 Belgrade, Serbia. E-mail: snjostojic@gmail.com

overly complex and requires a coordinated multidisciplinary approach and support during their lifetime. The evaluation protocol should include multiple audiological tests for estimating the type and degree of hearing loss to define a rehabilitation plan by a multidisciplinary team (an ear, nose, and throat doctor, an audiologist, and a surdologist) in order to enable normal speech and language development in those patients [3–5]. In TCS children with conductive or mixed hearing loss, adequate amplification using bone conduction hearing aids, such as bone anchored hearing aid (BAHA) or Vibrant® Soundbridge (VSB), is a prerequisite for speech and language development. Cochlear implantation (CI) for TCS patients with permanent severe mixed hearing loss is seldom mentioned in the literature as a suitable solution. Over the last four years, 659 publications have been cited in the Google Scholar database, and only nine of them have analyzed the rehabilitation effects in TCS patients with cochlear implants. In the patient presented in this paper, only CI has provided stable and sufficient amplification and subsequent progress of speech and language skills. Therefore, we report a case of a patient with TCS who showed considerable progress in listening and speech-language development after CI. This paper focuses on seeking an adequate amplification solution in the first nine years of the patient's life.

The research was approved by the Academic Council and Ethics Committee of the Faculty of Special Education and Rehabilitation, University of Belgrade, Serbia (No 89/1-1), and the parents' consent for this case report was obtained.

Case report

Medical status

The patient was a girl, born from a regularly monitored pregnancy, delivered at term with an Apgar score of 7/8. The following severe malformations were observed immediately after birth: microtia and severe stenosis of the outer ear canal, lack of the zygomatic bones, gothic palate, atresia of the anus, labia minor adhesions, and absent nipples. Neurologic findings included microcephaly, craniofacial dysmorphism, and slight hypotonia. The findings were suggestive of TCS. Genetic analysis showed inversion of chromosome 9 [karyotype 46, XX; Inv (9) (p12q13)]. Surgical treatment of congenital malformations commenced soon after birth. Anal atresia was operated on three times, as well as gynecological malformation of the labia minor. The girl had the ileus surgery at the age of ten months. She was treated twice for sepsis using combined antibiotic therapy over a prolonged period, and some of those antibiotics were ototoxic.

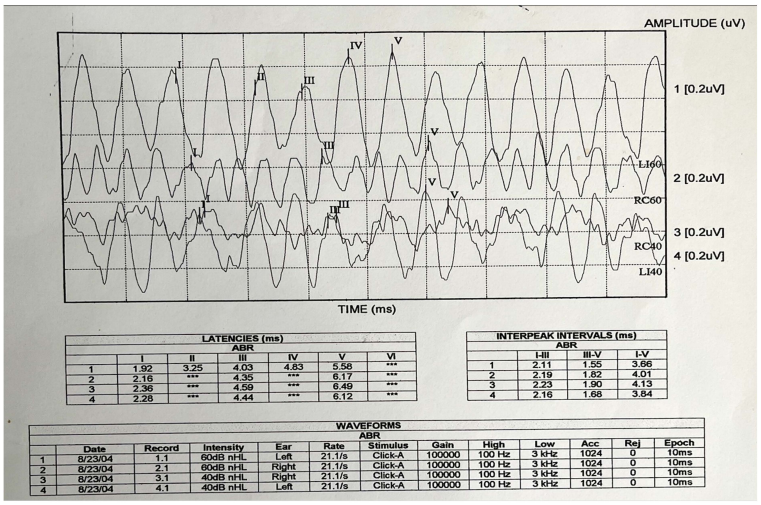
The first audiological evaluation was performed at the age of two months using behavior observation and a battery of electrophysiology tests [brainstem evoked response audiometry (BERA), otoacoustic emissions] (Figure 1A). However, the amplification and rehabilitation process had to be postponed because of the surgical treatment of life-threatening conditions. Periodic audiological check-ups have been conducted once a year using the aforementioned battery of audiological tests. At the age of three years and five months, the BERA test with click stimuli at 40 to 80 dB stimuli intensity confirmed moderate to severe mixed hearing loss with predominant conductive component due to outer and middle ear malformations (Figure 1B). Control BERA at the age of four years and eleven months confirmed previous findings with slight maturation of central auditory pathways (Figure 1C).

Amplification modalities

Although the hearing loss was diagnosed soon after birth, amplification had to be postponed until the age of 18 months due to numerous surgeries and recurrent life-threatening infections in this little girl. The girl used the BAHA® Softband and was enrolled in speech therapy. The device is considered suitable for mild to moderate conductive or mixed hearing loss, but this girl could only identify some isolated sounds with the device. She depended on the lip-reading support for speech understanding and remained quite passive. Surdologist reports based on standardized speech and language tests (Articulation test, Picture describing test, Vocabulary test by Vasić [6]) showed poor results and considerable delay. The delay in speech and language development, as well as in listening skills, became even more obvious over the next three years despite the intensive speech therapy. Since the girl had normal intellectual capacity, it became obvious that she was not amplified adequately. Pure tone audiometry (PTA) at the age of five years and five months showed severe mixed, predominantly conductive hearing loss (Figure 2). The BAHA® Intenso Softband device was provided. Although some progress was observed, surgical implantation of the device was needed to provide optimal amplification.

Eighteen months later, a multidisciplinary team consisting of an otological surgeon, an audiologist, a radiologist, a surdologist, and a psychologist discussed the options for surgical treatment. Multislice computed tomography of the temporal bone has shown good anatomical prerequisites for the implantation of the VSB middle ear implant in the right ear, which could provide better amplification and conditions for further speech and language development. The surgery was uneventful, but the listening improvement after the switch-on was not impressive, as shown in the PTA results. Seven months after the surgery, the hearing threshold started to fluctuate and deteriorate, and the rehabilitation progress was severely affected. That caused severe emotional distress in the nine-year-old girl and her parents. The fluctuation of hearing thresholds with VSB over time is shown in Figure 3 A–D.

Total hearing loss was observed seven months after the switch-on, with partial recovery three months later, but only up to 2 kHz and still with an ascendant curve. Fluctuations of the hearing threshold in PTA were the result of an effort to adjust the hearing map in the VSB processor with the aim of establishing the listening function that was expe-



LATENCIES (ms) ABR

	I	II	III	IV	V	VI
1	1.92	3.25	4.03	4.83	5.58	***
2	2.16	***	4.35	***	6.17	***
3	2.36	***	4.59	***	6.49	***
4	2.28	***	4.44	***	6.12	***

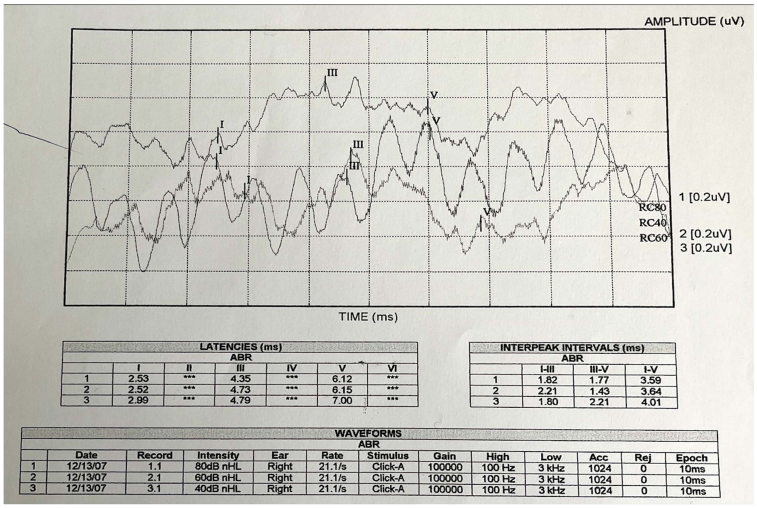
INTERPEAK INTERVALS (ms) ABR

	I-III	III-V	I-V
1	2.11	1.55	3.66
2	2.19	1.82	4.01
3	2.23	1.90	4.13
4	2.16	1.68	3.84

WAVEFORMS ABR

	Date	Record	Intensity	Ear	Rate	Stimulus	Gain	High	Low	Acc	Rej	Epoch
1	8/23/04	1.1	60dB nHL	Left	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms
2	8/23/04	2.1	60dB nHL	Right	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms
3	8/23/04	3.1	40dB nHL	Right	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms
4	8/23/04	4.1	40dB nHL	Left	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms

A)



LATENCIES (ms) ABR

	I	II	III	IV	V	VI
1	2.53	***	4.35	***	6.12	***
2	2.52	***	4.73	***	6.15	***
3	2.99	***	4.79	***	7.00	***

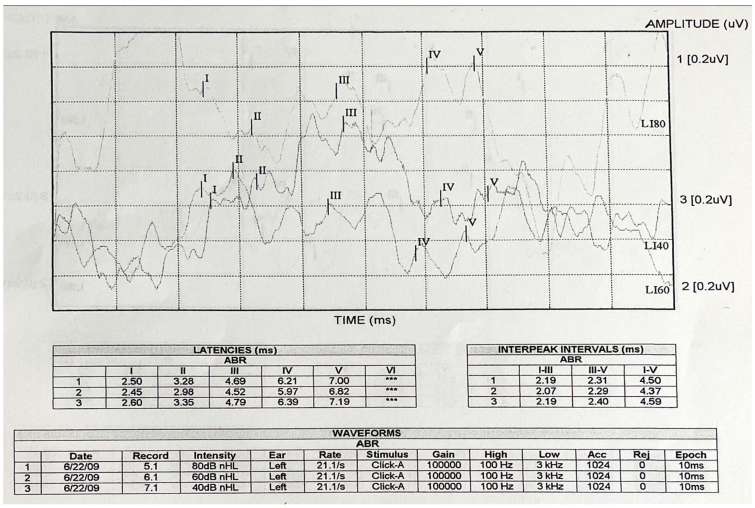
INTERPEAK INTERVALS (ms) ABR

	I-III	III-V	I-V
1	1.82	1.77	3.59
2	2.21	1.43	3.64
3	1.80	2.21	4.01

WAVEFORMS ABR

	Date	Record	Intensity	Ear	Rate	Stimulus	Gain	High	Low	Acc	Rej	Epoch
1	12/13/07	1.1	80dB nHL	Right	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms
2	12/13/07	2.1	60dB nHL	Right	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms
3	12/13/07	3.1	40dB nHL	Right	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms

B)



LATENCIES (ms) ABR

	I	II	III	IV	V	VI
1	2.50	3.28	4.69	6.21	7.00	***
2	2.45	2.98	4.52	5.97	6.82	***
3	2.60	3.35	4.79	6.39	7.19	***

INTERPEAK INTERVALS (ms) ABR

	I-III	III-V	I-V
1	2.19	2.31	4.50
2	2.07	2.29	4.37
3	2.19	2.40	4.59

WAVEFORMS ABR

	Date	Record	Intensity	Ear	Rate	Stimulus	Gain	High	Low	Acc	Rej	Epoch
1	6/22/09	5.1	80dB nHL	Left	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms
2	6/22/09	6.1	60dB nHL	Left	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms
3	6/22/09	7.1	40dB nHL	Left	21.1/s	Click-A	100000	100 Hz	3 kHz	1024	0	10ms

C)

Fig. 1 – A) Brainstem evoked response audiometry (BERA) at the age of 2 months shows a pathological auditory function with a lowered hearing threshold in both ears, which was determined by a click stimulus with an intensity of 40 and 60 dB. The absolute latencies of the I, III, and V waves are prolonged (normally expected 2, 4, and 6 ms), and the inter-wave intervals of the I–V waves are relatively preserved (up to 4 ms), with worse findings in the right ear. B) and C) The control BERA at the age of 3 years and 5 months and 4 years and 11 months, respectively, shows a moderate to severe hearing loss threshold (click stimulus 40 to 80 dB), with the delay of absolute latency and relatively preserved inter-wave intervals, indicating a mixed hearing impairment with a predominant conductive component.

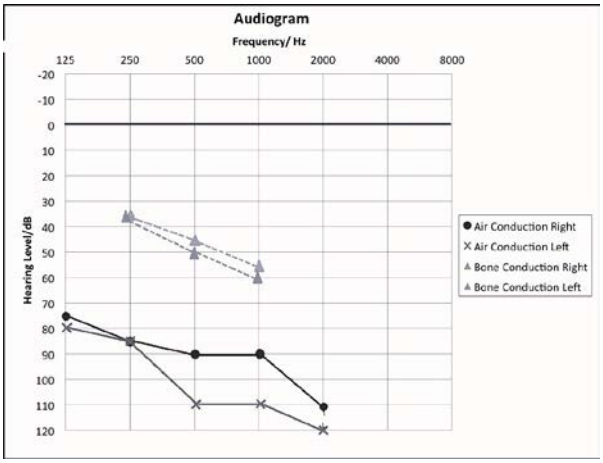


Fig. 2 – Pure tone audiometry at the age of 5 years and 5 months shows severe mixed, predominantly conductive hearing loss.

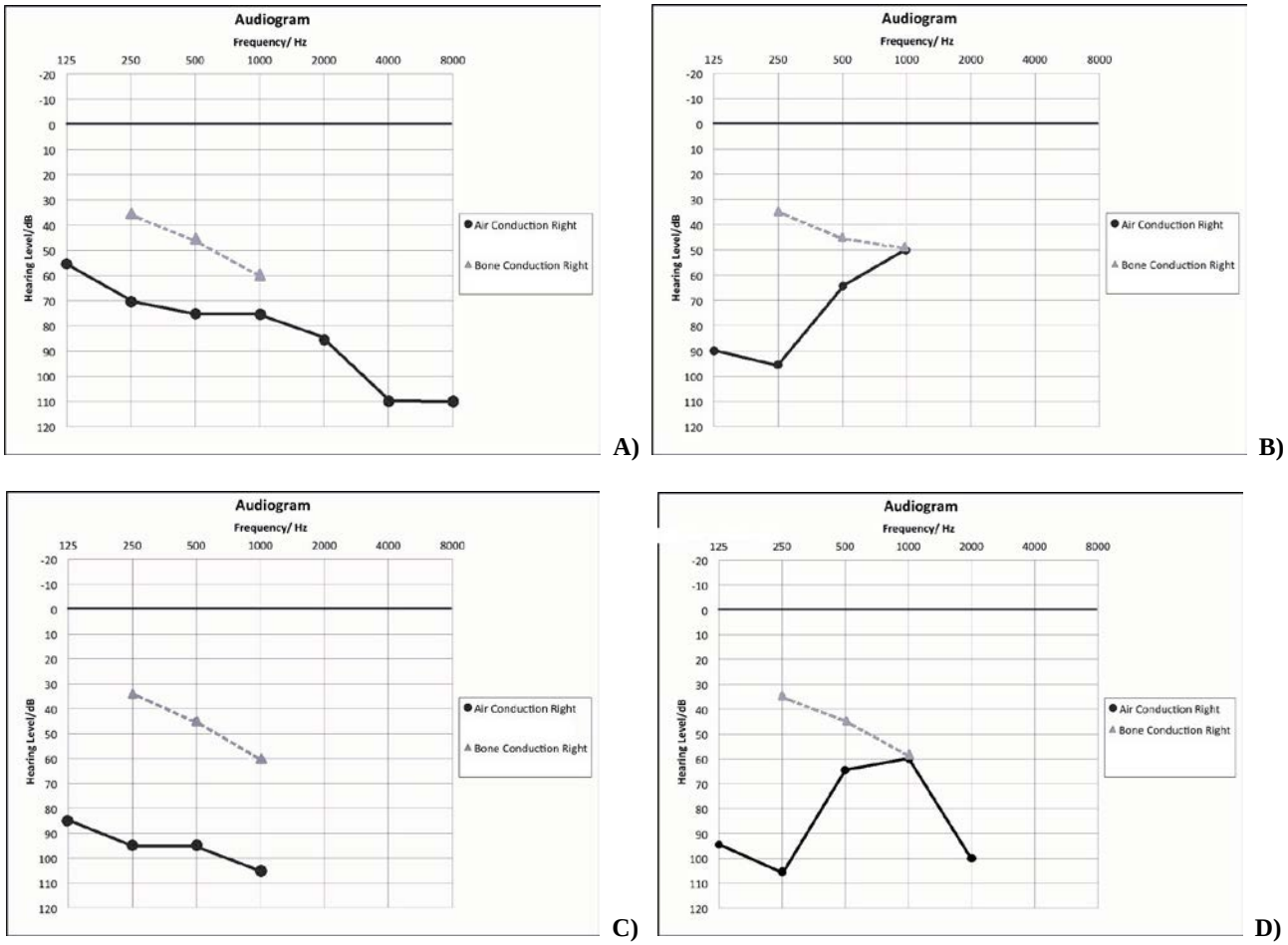


Fig. 3 – Pure tone audiometry of the right ear shows the fluctuation of hearing thresholds with Vibrant® Soundbridge (VSB) over time: A) 2 weeks after switch-on of VSB; B) 4 months after VSB use; C) 7 months after VSB use; D) 10 months after VSB use.

cted after the implantation. This did not provide functional hearing sufficient for speech and hearing development.

That situation called for further consultations of the multidisciplinary team, including engineers from the VSB Med-El® manufacturer, with the parents of the nine-year-old girl with TCS, and a consensus over the fact that CI was necessary was reached. The surgery was successful, and a Med-El® Sonata implant with a shorter Flex 28 electrode was implanted. Four weeks later, the implant was activated, and the Rondo® processor was fitted. The audiometry (Figure 4)

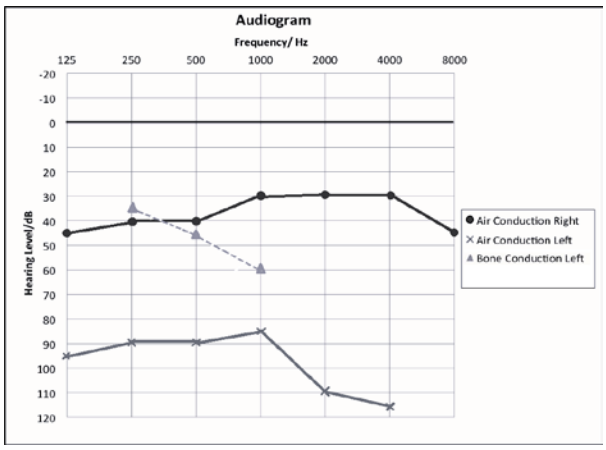


Fig. 4 – Pure tone audiometry with Rondo® processor and cochlear implant in the right ear shows a satisfactory aided hearing threshold (40 to 30 dB).

showed a satisfactory aided hearing threshold (40 to 30 dB) with a processor. Improved aided threshold provided satisfactory hearing and enabled further development of verbal communication. The girl attends a mainstream school with an individual education program and personal assistant.

Discussion

The motivation for reviewing this case is the rare example of CI in a patient with permanent mixed, predominantly sensorineural, with significant conductive component, hearing impairment caused by TCS [6–8]. TCS is a genetic disorder with characteristic malformations of the ears, face, eyes, and jaws, causing the impairment of respiration, speech, and sleep, frequently associated with psychological and behavioral issues due to strange appearance [8, 9]. Expression of various features and symptoms of TCS can differ considerably among patients depending on gene mutations with autosomal dominant or autosomal recessive inheritance [9]. Half of the patients with TCS could have some degree of hearing loss depending on the outer, middle, and/or inner ear malformation [10]. The choice of the amplification device depends on the anatomy of the ear and the degree of the hearing impairment. Bone conduction hearing instruments, external or implantable, are usually the best choice. The first bone conduction aids were mechanical vibrators, but the development of electronic devices improved bone conduction amplification considerably. Most of those devices are surgically implanted in the mastoid bone (BAHA®, Ponto, Bone Bridge) or the middle ear (VSB). Air-conduction hearing aids could be used only occasionally if the anatomy of the auricle and meatus is normal. BAHA® was introduced in 1984, supplying helpful solutions for conductive or mixed hearing loss of mild to moderate degree. Babies and infants could wear the device on a soft band before they are old enough for surgical implantation of the device in the mastoid bone (5–6 years of age) [5]. The surgical procedure is easy, and the percentage of complications is low. Most professionals dealing with the rehabilitation of children and adults with conductive or mixed hearing loss have a positive experience with BAHA® and VSB [11–14]. In most patients, BAHA® and VSB contribute to the improvement of auditory skills, speech, language, and communication development [14].

A cochlear implant is an electronic device suitable for profound sensorineural hearing loss. Over the last 30 years, it has enormously improved the speech and hearing rehabilitation of children with congenital or early acquired deafness. The selection criteria for CI are clearly listed [15, 16], and this patient did not meet the usual requirements from that list. Extended indications for CI in severe to profound mixed hearing loss in progressive otosclerosis have been introduced recently, but the indication for CI in children with similar hearing loss due to congenital malformation of the outer, middle, and/or inner ear has been rarely considered. Unable to achieve satisfactory amplification with a middle ear implant and dealing with constant fluctuation of the hearing threshold, our multidisciplinary team concluded that CI would be the only possible solution in this specific case. In children with congenital or early acquired deafness, the implantation age is a critical factor for the successful outcome of CI [17]. According to the Joint Committee on Infant Hearing, the optimal age for CI in congenital deafness is between 12 and 24 months [18, 19]. However, our patient was implanted at the age of nine. Her listening skills, communication, and academic achievement at that moment did not make her an ideal candidate for CI. However, she met the following criteria for the procedure: hearing threshold > 90 dB at 0.5, 1, and 2 kHz and no measurable hearing on higher frequencies; no benefit from other types of amplification – BAHA® Softband for three years, BAHA® Intenso Softband for 1.5 years and VSB for two years; open set test performance < 50%.

Conclusion

Although CI is rarely considered as a solution for permanent mixed, predominantly conductive hearing loss, such as in TCS, and the selection criteria for the procedure could

only partially be met, our patient with a cochlear implant achieved good and stable aided threshold, improved listening skills, speech, and communication capacity. Based on this experience, the authors would recommend CI as an ultimate solution for cases of TCS with severe to profound mixed hearing loss when all other bone conduction hearing aids fail to provide sufficient amplification for the development of auditory skills and speech, thus obstructing the achievement of the full communication capacity of a child. Selection criteria should be taken into consideration and adjusted individually in each specific case.

Acknowledgment

This paper was funded by the Ministry of Education, Science, and Technological Development of the Republic of Serbia (contract No. 451-03-47/2023-01) within the project "Influence of Cochlear Implantation on Education of Deaf and Hearing Impaired Individuals" (grant No. 179055).

Conflict of interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Wang P*, *Fan X*, *Fan Y*. The research progress of Treacher Collins syndrome. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2016; 30(4): 333–8. (Chinese)
2. *Chow K*, *Tepper* R, *Frankneckt J*, *Kaplan L*, *Cosetti M*. Hearing Loss and Aural Rehabilitation in Patients with Treacher Collins Syndrome. In: *Yates DM, Markiewicz MR,* editors. Craniofacial Microsomia and Treacher Collins Syndrome. New York: Springer International Publishing; 2022. p. 447–58.
3. *Rosa F*, *Coutinho MB*, *Ferreira JP*, *Sousa CA*. Ear malformations, hearing loss and hearing rehabilitation in children with Treacher Collins syndrome. Acta Otorrinolaringol Esp 2016; 67(3): 142–7. (English, Spanish)
4. *Ostojić S*, *Mikić B*, *Mirić D*. Hearing impairment in children with Treacher Collins syndrome - specifics of the rehabilitation process. In: *Karić J, Ostojić S, Radić-Šestić M,* editors. Collection of papers: Specificity of hearing loss. Belgrade: Faculty of Special Education and Rehabilitation, University of Belgrade; 2014. p. 43–7. (Serbian)
5. *Hylton JB*, *Leon-Salazar V*, *Anderson GC*, *De Felippe NL*. Multidisciplinary treatment approach in Treacher Collins syndrome. J Dent Child (Chic) 2012; 79(1): 15–21.
6. *Vasić S*. Speaking skills: Exercises and tests for children and adults. Belgrade: BIGZ; 1980. p. 202. (Serbian)
7. *Scott TM*. Case Study and Audiologic Management of a Child With Treacher Collins Syndrome. Perspect Hear Hear Dis: Res Diag 2002; 6(1): 15–7.
8. *Yates DM*, *Bufford S*. An Overview of Treatment Recommendations for the Treacher Collins Syndrome Patient. In: *Yates DM, Markiewicz MR,* editors. Craniofacial Microsomia and Treacher Collins Syndrome. New York: Springer International Publishing; 2022. p. 447–58.
9. *National Organization for Rare Disorders – NORD*. Treacher Collins Syndrome [Internet]. Quincy, MA: NORD; 2019 [updated 2023 Nov 1; cited 2023 Nov 22]. Available from: https://rarediseases.org/rare-diseases/treacher-collins-syndrome/
10. *Marres HA*. Hearing loss in the Treacher-Collins syndrome. Adv Otorhinolaryngol 2002; 61: 209–15.
11. *Rivas JA*, *Rivas A*, *Rincon LA*, *Tamayo CA*, *Forero VH*, *Rivas A*. Vibrant Soundbridge vs BAHA: outcomes comparison. Otolaryngology–Head and Neck Surgery 2012; 147(2 Suppl): P226.
12. *Marsella P*, *Scorpecci A*, *Pacifico C*, *Tieri L*. Bone-anchored hearing aid (Baha) in patients with Treacher Collins syndrome: tips and pitfalls. Int J Pediatr Otorhinolaryngol 2011; 75(10): 1308–12.
13. *Lesinskas E*, *Stankeviciute V*, *Petrulionis M*. Application of the Vibrant Soundbridge middle-ear implant for aural atresia in patients with Treacher Collins syndrome. J Laryngol Otol 2012; 126(12): 1216–23.
14. *Polanski JF*, *Plawiak AC*, *Ribas A*. Hearing rehabilitation in Treacher Collins Syndrome with bone anchored hearing aid. Rev Paul Pediatr 2015; 33(4): 483–7. (Portuguese)
15. *Ostojić-Zeljković S*, *Đoković S*. Cochlear implantation outcome and perspective. Belgrade: University of Belgrade – Faculty of Special Education and Rehabilitation; 2015. (Serbian)
16. *Ostojić S*, *Đoković S*, *Mirić D*, *Mikić B*, *Mikić M*. Effects of cochlear implantation in teenagers with congenital deafness. Specijalna edukacija i rehabilitacija 2010; 9(1): 51–64. (Serbian)
17. *Marschark M*, *Duchesne L*, *Pisoni D*. Effects of age at cochlear implantation on learning and cognition: a critical assessment. Am J Speech Lang Pathol 2019; 28(3): 1318–34.
18. *Mueller HG*, *Jorgensen LE*. Hearing aids for speech-language pathologists: A guide to modern rehabilitative audiology. San Diego: Plural Publishing; 2019. p. 445.
19. *Joint Committee on Infant Hearing*. Year 2019 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs. J Early Hear Detect Interv 2019; 4(2): 1–44. [accessed on 2023 Dec 5]. Available from: http://www.jcih.org/posstatemts.htm

Received on October 26, 2022
Revised on August 21, 2023
Revised on September 22, 2023
Revised on October 24, 2023
Accepted on November 7, 2023
Online First November 2023

INSTRUCTIONS TO THE AUTHORS

The VSP publishes only papers not published before, nor submitted to any other journals, in the order determined by the Editorial Board. Any attempted plagiarism or self-plagiarism will be punished. When submitting a paper to the VSP electronic editing system **(http://aseestant.ceon.rs/index.php)**, the following should be enclosed: a statement on meeting any technical requirements, a statement signed by all the authors that the paper on the whole and/or partly has not been submitted nor accepted for publication elsewhere, a statement specifying the actual contribution of each author, no conflict of interest statement that make them responsible for meeting any requirements set. What follows subsequently is the acceptance of a paper for further editing procedure. The manuscripts submitted to the VSP pass in-house and external peer review. All authors pay "Article Processing Charge" for coverage all editing and publishing expenses. Domestic authors pay 5,000 RSD, and those from aboard 150 euros. The editing and publishing fee is required for substantive editing, facts and references validations, copy editing, and publishing online and in print by editorial staff of the Journal. No additional fees, other than stated above, are required even if an author who already paid the fee would have more articles accepted for publishing in the year when fee was paid. All authors who pay this fee may, if want, receive printed version of the Journal in year when fee is payed. Please note that the payment of this charge does not guarantee acceptance of the manuscript for publication and does not influence the outcome of the review procedure. The requirement about paying "Article Processing Charge" does not apply to reviewers, members of the Editorial Board and the Publisher's Council of the Journal, young researchers and students, as well as any of the subscribers of the Journal.

The VSP publishes: **editorials, original articles**, **short communications**, **reviews**/**meta-analyses, case reports**, **medical history** (general or military), personal views, invited comments, letters to the editor, reports from scientific meetings, book reviews, and other. Original articles, short communications, meta-analyses and case reports are published with abstracts in both English and Serbian.

General review papers will be accepted by the Editorial Board only if the authors prove themselves as the experts in the fields they write on by citing not less than 5 self-citations.

Papers should be written on IBM-compatible PC, using 12 pt font, and double spacing, with at least 4 cm left margin. **Bold** and *italic* letters should be avoided as reserved for subtitles. Original articles, reviews, meta-analyses and articles from medical history should not exceed 16 pages; current topics 10; case reports 6; short communications 5; letters to the editor and comments 3, and reports on scientific meetings and book reviews 2.

All measurements should be reported in the metric system of the International System of Units (SI), and the standard internationally accepted terms (except for mmHg and °C).

MS Word for Windows (97, 2000, XP, 2003) is recommended for word processing; other programs are to be used only exceptionally. Illustrations should be made using standard **Windows** programs, **Microsoft Office** (**Excel**, **Word Graph**)**.** The use of colors and shading in graphs should be avoided.

Papers should be prepared in accordance with the **Vancouver Convention**.

Papers are reviewed anonymously by at least two editors and/or invited reviewers. Remarks and suggestions are sent to the author for final composition. Galley proofs are sent to the corresponding author for final agreement.

Preparation of manuscript

Parts of the manuscript are: **Title page; Abstract with Key words; Text; Acknowledgements** (to the authors' desire), **References**, **Enclosures**.

1. ***Title page***

a) The title should be concise but informative, while subheadings should be avoided;

b) Full names of the authors signed as follows: ***, †, ‡, §, ||, ¶, **, ††, ...** .

c) Exact names and places of department(s) and institution(s) of affiliation where the studies were performed, city and the state for any authors, clearly marked by standard footnote signs;

d) Conclusion could be a separate chapter or the last paragraph of the discussion;

e) Data on the corresponding author.

2. ***Abstract and key words***

The second page should carry a structured abstract (250-300 words for original articles and meta-analyses) with the title of the article. In short, clear sentences the authors should write the **Background**/**Aim**, major procedures – **Methods** (choice of subjects or laboratory animals; methods for observation and analysis), the obtained findings – **Results** (concrete data and their statistical significance), and the **Conclusion**. It should emphasize new and important aspects of the study or observations. A structured abstract for case reports (up to 250 words) should contain subtitles **Introduction, Case report, Conclusion**). Below the abstract **Key words** should provide 3–10 key words or short phrases that indicate the topic of the article.

3. ***Text***

The text of the articles includes: **Introduction**, **Methods**, **Results**, and **Discussion**. Long articles may need subheadings within some sections to clarify their content.

Introduction. After the introductory notes, the aim of the article should be stated in brief (the reasons for the study or observation), only significant data from the literature, but not extensive, detailed consideratuion of the subject, nor data or conclusions from the work being reported.

Methods. The selection of study or experimental subjects (patients or experimental animals, including controls) should be clearly described. The methods, apparatus (manufacturer's name and address in parentheses), and procedures should be identified in sufficient detail to allow other workers to reproduce the results. Also, give references to established methods, including statistical methods. Identify precisely all drugs and chemicals used, with generic name(s), dose(s), and route(s) of administration. State the approval of the Ethnics Committee for the tests in humans and animals.

Results should be presented in logical sequence in the text, tables and illustrations. Emphasize or summarize only important observations.

Discussion is to emphasize the new and significant aspects of the study and the conclusions that result from them. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data.

References

References should be superscripted and numerated consecutively in the order of their first mentioning within the text. All the authors should be listed, but if there are more than 6 authors, give the first 6 followed by *et al*. Do not use abstracts, secondary publications, oral communications, unpublished papers, official and classified documents. References to papers accepted but not yet published should be cited as "in press". Information from manuscripts not yet accepted should be cited as "unpublished data". Data from the Internet are cited with the date of citation.

Examples of references:

Jurhar-Pavlova M, Petlichkovski A, TrajkovD, Efinska-Mladenovska O, Arsov T, Strezova A, et al. Influence of the elevated ambient temperature on immunoglobulin G and immunoglobulin G subclasses in sera of Wistar rats. Vojnosanit Pregl 2003; 60(6): 657–612.

DiMaio VJ. Forensic Pathology. 2nd ed. Boca Raton: CRC Press; 2001.

Blinder MA. Anemia and Transfusion Therapy. In: Ahya NS, Flood K, Paranjothi S, editors. The Washington Manual of Medical Therapeutics, 30th edition. Boston: Lippincot, Williams and Wilkins; 2001. p. 413-28.

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG*, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Tables

Each table should be typed double-spaced 1,5 on a separate sheet, numbered in the order of their first citation in the text in the upper left corner and supplied with a brief title each. Explanatory notes are printed under a table. Each table should be mentioned in the text. If data from another source are used, acknowledge fully.

Illustrations

Any forms of graphic enclosures are considered to bi figures and should be submitted as additional databases in the System of Assistent. Letters, numbers, and symbols should be clear and uniform, of sufficient size that when reduced for publication, each item will still be legible. Each figure should have a label on its back indicating the number of the figure, author's name, and top of the figure (**Figure 1**, **Figure 2** and so on). If a figure has been published, state the original source.

Legends for illustrations are typed on a separate page, with Arabic numbers corresponding to the illustrations. If used to identify parts of the illustrations, the symbols, arrows, numbers, or letters should be identified and explained clearly in the legend. Explain the method of staining in photomicrographs.

Abbreviations and acronyms

Authors are encouraged to use abbreviations and acronyms in the manuscript in the following manner: abbreviations and acronyms must be defined the first time they are used in the text consistently throughout the whole manuscript, tables, and graphics; abbreviations should be used only for terms that appear more than three times in text; abbreviations should be sparingly used.

An alphabetical list of all abbreviations used in the paper, followed by their full definitions, should be provided on submission.

Detailed Instructions are available at the web site:

www.vma.mod.gov.rs/vsp

UPUTSTVO AUTORIMA

VSP objavljuje radove koji nisu ranije nigde objavljivani, niti predati za objavljivanje redosledom koji određuje uređivački odbor. Svaki pokušaj plagijarizma ili autoplagijarizma kažnjava se. Prilikom prijave rada u sistem elektronskog uređivanja „Vojnosanitetskog pregleda“**(http://aseestant.ceon.rs/index.php)** neophodno je priložiti izjavu da su ispunjeni svi postavljeni tehnički zahtevi uključujući i izjavu koju potpisuju svi autori da rad nije ranije ni u celini, niti delimično objavljen niti prihvaćen za štampanje u drugom časopisu. Izjavu o pojedinačnom doprinosu svakog od autora rada potpisanu od svih autora, treba skenirati i poslati uz rad kao dopunsku datoteku. Takođe, autori su obavezni da dostave i potpisanu izjavu o nepostojanju sukoba interesa čime postaju odgovorni za ispunjavanje svih postavljenih uslova. Ovome sledi odluka o prihvatanju za dalji uređivački postupak. Rukopisi pristigli u Redakciju časopisa podležu internoj i eksternoj recenziji. Svi autori dužni su da plate “Article Processing Charge” za pokriće troškova jezičke, stručne i tehničke obrade rukopisa, kao i njegovog objavljivanja. Domaći autori plaćaju iznos od 5 000 dinara, a inostrani 150 eura. Dodatna plaćanja nisu predviđena čak i u slučaju da autor koji je već prethodno platio traženi iznos, ima više prihvaćenih radova za objavljivanje u godini u kojoj je izvršio uplatu. Svi autori koji su platili “Article Processing Charge” mogu, ukoliko žele, dobijati štampanu verziju časopisa tokom godine u kojoj je izvršena uplata. Plaćanje ovog iznosa ne garantuje prihvatanje rukopisa za objavljivanje i ne utiče na ishod recenzije. Od obaveze plaćanja pokrića navedenih troškova oslobođeni su recenzenti, članovi Uređivačkog odbora i Izdavačkog saveta VSP, studenti i mladi istraživači, kao i pretplatnici časopisa.

U VSP-u se objavljuju **uvodnici**, **originalni članci, prethodna** ili **kratka saopštenja**, revijski radovi tipa **opšteg pregleda** (uz uslov da autori navođenjem najmanje 5 autocitata potvrde da su eksperti u oblasti o kojoj pišu), **aktuelne teme, metaanalize**, **kazuistika, seminar praktičnog lekara,** članci iz **istorije medicine**, lični stavovi, naručeni komentari, pisma uredništvu, izveštaji sa naučnih i stručnih skupova, prikazi knjiga i drugi prilozi. Radovi tipa originalnih članaka, prethodnih ili kratkih saopštenja, metaanalize i kazuistike **objavljuju se uz apstrakte na srpskom i engleskom jeziku**.

Rukopis se piše sa proredom 1,5 sa levom marginom od **4 cm**. Koristiti font veličine 12, a načelno izbegavati upotrebu **bold** i *italic* slova, koja su rezervisana za podnaslove. Originalni članci, opšti pregledi i metaanalize i članci iz istorije medicine ne smeju prelaziti 16 stranica (bez priloga); aktuelne teme – deset, seminar praktičnog lekara – osam, kazuistika – šest, prethodna saopštenja – pet, a komentari i pisma uredniku – tri, izveštaji sa skupova i prikazi knjiga – dve stranice.

U celom radu obavezno je korišćenje međunarodnog sistema mera (SI) i standardnih međunarodno prihvaćenih termina (sem mm Hg i °C).

Za obradu teksta koristiti program **Word for Windows** verzije 97, 2000, XP ili 2003. Za izradu grafičkih priloga koristiti standardne grafičke programe za **Windows**, poželjno iz programskog paketa **Microsoft Office** (**Excel, Word Graph**). Kod kompjuterske izrade grafika izbegavati upotrebu boja i senčenja pozadine.

Radovi se pripremaju u skladu sa **Vankuverskim dogovorom**.

Prispeli radovi kao anonimni podležu uređivačkoj obradi i recenziji najmanje dva urednika/recenzenta. Primedbe i sugestije urednika/recenzenata dostavljaju se autoru radi konačnog oblikovanja. Pre objave, rad se upućuje autoru određenom za korespodenciju na konačnu saglasnost.

Priprema rada

Delovi rada su: **naslovna strana, apstrakt sa ključnim rečima, tekst** rada, zahvalnost (po želji), literatura, prilozi.

1. ***Naslovna strana***

a) Poželjno je da naslov bude kratak, jasan i informativan i da odgovara sadržaju, podnaslove izbegavati.

b) Ispisuju se puna imena i prezimena autora sa oznakama redom: *, †, ‡, §, ‖, ¶, **, ††, ...

c) Navode se puni nazivi ustanove i organizacijske jedinice u kojima je rad obavljen mesta i države za svakog autora, koristeći standardne znake za fusnote.

d) Zaključak može da bude posebno poglavlje ili se iznosi u poslednjem pasusu diskusije.

e) Podaci o autoru za korespodenciju.

2. ***Apstrakt i ključne reči***

Na drugoj stranici nalazi se strukturisani apstrakt (250-300 reči za originalne članke i meta-analize) sa naslovom rada. Kratkim rečenicama na srpskom i engleskom jeziku iznosi se **Uvod/Cilj** rada, osnovne procedure **– Metode** (izbor ispitanika ili laboratorijskih životinja; metode posmatranja i analize), glavni nalazi **– Rezultati** (konkretni podaci i njihova statistička značajnost) i glavni **Zaključak**. Naglasiti nove i značajne aspekte studije ili zapažanja. Strukturisani apstrakt za kazuistiku (do 250 reči), sadrži podnaslove **Uvod, Prikaz bolesnika** i **Zaključak**). Ispod apstrakta, „Ključne reči“ sadrže 3–10 ključnih reči ili kratkih izraza koje ukazuju na sadržinu članka.

3. ***Tekst članka***

Tekst sadrži sledeća poglavlja: **uvod**, **metode**, **rezultate** i **diskusiju**. **Uvod.** Posle uvodnih napomena, navesti cilj rada. Ukratko izneti razloge za studiju ili posmatranje. Navesti samo važne podatke iz literature a ne opširna razmatranja o predmetu rada, kao ni podatke ili zaključke iz rada o kome se izveštava.

Metode. Jasno opisati izbor metoda posmatranja ili eksperimentnih metoda (ispitanici ili eksperimentne životinje, uključujući kontrolne). Identifikovati metode, aparaturu (ime i adresa proizvođača u zagradi) i proceduru, dovoljno detaljno da se drugim autorima omogući reprodukcija rezultata. Navesti podatke iz literature za uhodane metode, uključujući i statističke. Tačno identifikovati sve primenjene lekove i hemikalije, uključujući generičko ime, doze i načine davanja. Za ispitivanja na ljudima i životinjama navesti saglasnost nadležnog etičkog komiteta.

Rezultate prikazati logičkim redosledom u tekstu, tabelama i ilustracijama. U tekstu naglasiti ili sumirati samo značajna zapažanja.

U **diskusiji** naglasiti nove i značajne aspekte studije i izvedene zaključke. Posmatranja dovesti u vezu sa drugim relevantnim studijama, u načelu iz poslednje tri godine, a samo izuzetno i starijim. Povezati zaključke sa ciljevima rada, ali izbegavati nesumnjive tvrdnje i one zaključke koje podaci iz rada ne podržavaju u potpunosti.

Literatura

U radu literatura se citira kao superskript, a popisuje rednim brojevima pod kojima se citat pojavljuje u tekstu. Navode se svi autori, ali ako broj prelazi šest, navodi se prvih šest i *et al*. Svi podaci o citiranoj literaturi moraju biti tačni. Literatura se u celini citira na engleskom jeziku, a iza naslova se navodi jezik članka u zagradi. Ne prihvata se citiranje apstrakata, sekundarnih publikacija, usmenih saopštenja, neobjavljenih radova, službenih i poverljivih dokumenata. Radovi koji su prihvaćeni za štampu, ali još nisu objavljeni, navode se uz dodatak „u štampi“. Rukopisi koji su predati, ali još nisu prihvaćeni za štampu, u tekstu se citiraju kao „neobjavljeni podaci“ (u zagradi). Podaci sa interneta citiraju se uz navođenje datuma pristupa tim podacima.

Primeri referenci:

Đurović BM. Endothelial trauma in the surgery of cataract. Vojnosanit Pregl 2004; 61(5): 491–7. (Serbian)

Balint B. From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

Mladenović T, Kandolf L, Mijušković ŽP. Lasers in dermatology. In: *Karadaglić Đ*, editor. Dermatology. Beograd: Vojnoizdavački zavod & Verzal Press; 2000. p. 1437–49. (Serbian)

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG*, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Tabele

Sve tabele pripremaju se sa proredom 1,5 na posebnom listu. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u levom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

Ilustracije

Slikama se zovu svi oblici grafičkih priloga i predaju se kao dopunske datoteke u sistemu **aseestant**. Slova, brojevi i simboli treba da su jasni i ujednačeni, a dovoljne veličine da prilikom umanjivanja budu čitljivi. Slike treba da budu jasne i obeležene brojevima, onim redom kojim se navode u tekstu (**Sl. 1; Sl. 2** itd.). Ukoliko je slika već negde objavljena, obavezno citirati izvor.

Legende za ilustracije pisati na posebnom listu, koristeći arapske brojeve. Ukoliko se koriste simboli, strelice, brojevi ili slova za objašnjavanje pojedinog dela ilustracije, svaki pojedinačno treba objasniti u legendi. Za fotomikrografije navesti metod bojenja i podatak o uvećanju.

Skraćenice i akronimi

Skraćenice i akronimi u rukopisu treba da budu korišćeni na sledeći način: definisati skraćenice i akronime pri njihovom prvom pojavljivanju u tekstu i koristiti ih konzistentno kroz čitav tekst, tabele i slike; koristiti ih samo za termine koji se pominju više od tri puta u tekstu; da bi se olakšalo čitaocu, skraćenice i aktinome treba štedljivo koristiti.

Abecedni popis svih skraćenica i akronima sa objašnjenjima treba dostaviti pri predaji rukopisa.

Detaljno uputstvo može se dobiti u redakciji ili na sajtu: www.vma.mod.gov.rs/vsp