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BIOMECHANICAL ASPECTS OF STATIC FOOT LOAD IN PHYSICALLY ACTIVE AND INACTIVE STUDENTS

BIOMEHANIČKI ODNOSI STATIČKOG OPTEREĆENJA STOPALA KOD FIZIČKI AKTIVNIH I NEAKTIVNIH STUDENATA

Siniša S. BABOVIĆ[1], Bojana S. KRSTONOŠIĆ[1], Aleksa D. NOVAKOVIĆ[1], Miljan M. SAVULJIĆ[1] and Miroslav MILANKOV[1,2]

Summary

Introduction. This study investigated the parameters of foot load, as one of the dimensions of foot biomechanics, using a new method of objectification of the measured values. The examined biomechanical parameters directly affect correct gait and posture. The aim of this research was to determine if there was a statistically significant difference in the forefoot and rearfoot load, as well as the load on the whole foot between physically active and inactive students. **Material and Methods.** The study included 91 students, of whom 44 were physically inactive and 47 were physically active. Measurements were performed by using a baropodometry platform (FreeMed Maxi, Sensor Medica, Rome, Italy) used for the first time in our population for objectification of the morpho-physiological parameters. All reference values were provided by the manufacturer as a part of the Freestep version 1.4.01 software. **Results.** Our results showed that physically active students have statistically significantly higher forefoot load values. Physically inactive students have statistically significantly higher rearfoot load values. Also, physically inactive students have statistically significantly higher deviations in most parameters from the reference values compared to physically active students. The percentage of physically inactive students with non-physiological values is higher in every parameter compared to the percentage of physically active students. However, this difference is statistically significant only for the load on the right forefoot in relation to both feet. **Conclusion.** Physically active students showed a physiologically better foot load distribution than physically inactive students.

Key words: Biomechanical Phenomena; Foot; Gait; Students; Exercise; Sedentary Behavior; Pressure; Posture

Sažetak

Uvod. U ovom istraživanju ispitivani su parametri opterećenja stopala, kao jedne od dimenzija biomehanike stopala, novom metodom objektivizacije merenih vrednosti. Izmereni parametri biomehanike imaju direktan uticaj na ispravan hod i pravilnu posturu. Cilj istraživanja bio je da se utvrdi da li postoji statistički značajna razlika u opterećenju prednjeg i zadnjeg dela stopala, kao i stopala u celini između fizički aktivnih i neaktivnih studenata. **Materijal i metode**. Uzorak je činio 91 student, od kojih je bilo 44 fizički neaktivinih, a 47 fizički aktivnih. Merenja su vršena na aparatu *freeMed Maxi* proizvođača *Sensor Medica, Italy*, koji je prvi put upotrebljen u našoj populaciji za objektivizaciju morfo-fizioloških parametara. Sve referentne vrednosti je dao proizvođač u okviru svog *freeStep v.1.4.01* programa. **Rezultati.** Rezultati istraživanja ukazuju na to da fizički aktivni studenti imaju statistički značajno veće vrednosti opterećenja prednjeg dela stopala. Fizički neaktivni studenti imaju statistički značajno veće vrednosti opterećenja zadnjeg dela stopala, a takođe, imaju statistički značajno veća odstupanja u većini parametara od referentnih vrednosti u odnosu na fizički aktivne studente. Procenat fizički neaktivnih studenata sa nefiziološkim vrednostima je za sve parametre veći nego kod fizički aktivnih studenata, iako je ova razlika statistički značajna samo za opterećenje prednjeg dela desnog stopala u odnosu na oba stopala. **Zaključak.** Fizički aktivni studenti su pokazali fiziološki bolju raspodelu opterećenja od fizički neaktivnih studenata.

Ključne reči: biomehanički fenomeni; stopalo; hod; studenti; fizička aktivnost; sedentarna aktivnost; pritisak; postura

Introduction

Despite a high incidence of foot deformities in the general population [1], they are not treated with the necessary attention. Foot deformities affect one of the basic foot functions – maintenance of the physiological relationship between the static load and its distribution on the ground. For better understanding of these deformities, one needs good knowledge of the foot anatomy and gait mechanics.

The foot (*pes*) is a distal part of the lower extremity which is in contact with the ground and forms a

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Abbreviations

F	– forefoot
R	– rearfoot
PIS	– physically inactive students
PAS	– physically active students
D	– right foot
S	– left foot
DF	– right forefoot
DR	– right rearfoot
SF	– left forefoot
SR	– left rearfoot

right angle with the shin. It can be divided into three regions: forefoot (F), midfoot and rearfoot (R). The F consists of toe bones and metatarsal bones; the midfoot consists of the navicular, cuboid and three cuneiform bones; the R includes the talus and calcaneus bones. In addition to the bones, each of these regions consists of muscles, tendons and other soft tissues [2, 3].

From morphological and physiological aspects, the feet are the foundation for both standing and walking. In a healthy foot, three main support points are distal extremities (heads) of the first and the fifth metatarsal bone, and the calcaneal tuberosity. Together, they make up the vertices of the so called "sustentation triangle" **(Figure 1)** [4]. The three vertices are connected by arches of the foot: transverse, medial longitudinal and lateral longitudinal. The most prominent arch is the medial longitudinal, with its highest point 15 – 18 mm above the surface, while the lateral longitudinal is 3 – 5 mm above the surface at its highest point [5]. In adults, the arches form an indentation on the medial plantar side of the foot called the plantar vault [4].

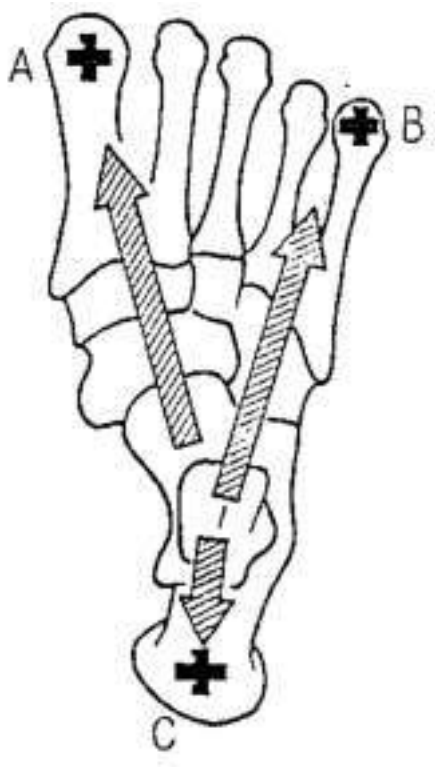


Figure 1. Sustentation triangle (drawing by the author)
Slika 1. *Trougao sustentacije (crtež autora)*

The morphology of the foot must be preserved in order to perform its function adequately. The shape is defined by the bones, the soft tissues and the forces that affect the foot. These morphological elements resist the pressure that is transferred from the shin and has a tendency to flatten the foot. They may be divided into passive and active components. Passive components or passive tensors of the foot vault are ligaments, while muscles are the active components [5]. Physical activity during the warm-up exercises significantly contributes to the tautness of the active tensors of the foot vaults, and thus maintains the morphology of the foot.

The foot is a key element of biomechanics of the human body because it has the following functions [6]:

- it maintains appropriate weight distribution and its transfer to the ground,
- it supports the body and allows maintenance of posture without extensive muscle use,
- it adapts to the irregularities of the surface while standing and walking,
- it acts like a spring and therefore can be separated from the surface while walking.

The most important forces which enable body movement are muscle activity, body weight and connective tissue elasticity. While analyzing gait biomechanics one should take into account both foot statics and dynamics.

The foot statics includes the influence of all forces that affect the foot while standing. The trabecular system of the bones follows the direction of these forces. One of these forces is the body weight, by which the body puts pressure on the surface. The body weight is transferred to the plantar vault via the tibiotalar articulation, in the direction of the mechanical axis of the leg, which is located between the medial two thirds and the lateral third of the articular surface of the tibiotalar joint. Half of the force is transferred to the subtalar joint, then to the sustentaculum tali, from which it is transferred to the plantar side of the calcaneal tuberosity and finally across the soft tissues to the ground. The rest is directed to the ground across the neck and the head of the talar bone to the navicular bone, then to the cuneal, cuboid and all five metatarsal bones, with the help of the soft tissues [4, 7, 8].

According to the Newton's third law of motion, there are forces by which the surface reactively affects the foot while it is on the ground. They are called ground reaction forces and are crucial in the development of the deformities of the locomotor apparatus. Each of these forces has three components: vertical, anteroposterior, mediolateral. The vertical component is of the highest magnitude, and can reach up to 150% of the body weight [9].

Foot dynamics includes the study of biomechanical forces on the foot in motion. From the aspect of dynamics, the foot is a 2nd class lever, which means that the resistive force to the body weight is located between the fulcrum (heads of the metatarsal bones) and the effort (Achilles tendon).

Table 1. Measured foot loads in PAS and PIS
Tabela 1. *Izmerene vrednosti opterećenja stopala PAS i PIS*

		N/*B*	$\bar{x}$	SD/*SD*	Minimum/*Minimum*	Maximum/*Maksimum*	t	p/*p*
R/F % DF	PIS	44	40.05	11.759	17	73	3.216	0.002
	PAS	47	47.13	9.164	27	66		
R/F % DR	PIS	44	59.95	11.759	27	83	3.216	0.002
	PAS	47	52.87	9.164	34	73		
R/F % SF	PIS	44	38.66	11.344	20	62	3.000	0.004
	PAS	47	44.85	8.188	23	62		
R/F % SR	PIS	44	61.34	11.344	38	80	3.000	0.004
	PAS	47	55.15	8.188	38	77		
load % DF	PIS	44	20.09	6.049	9	36	3.093	0.003
	PAS	47	23.66	4.931	13	35		
load % DR	PIS	44	30.09	6.261	13	43	3.114	0.002
	PAS	47	26.47	4.782	17	36		
Load % D	PIS	44	50.18	3.725	41	59	0.345	0.942
	PAS	47	50.13	3.340	40	58		
load % SF	PIS	44	19.23	5.701	10	32	2.931	0.004
	PAS	47	22.23	3.985	11	30		
load % SR	PIS	44	30.59	6.032	18	43	2.623	0.010
	PAS	47	27.64	4.660	18	37		
Load % S	PIS	44	49.82	3.725	41	59	0.073	0.942
	PAS	47	49.87	3.340	42	60		

Legend: F - forefoot; R – rearfoot; R/F % - F or R load percentage in relation to the whole foot; load % - F or R load percentage in relation to both feet; Load % - whole foot load percentage in relation to both feet; PAS - physically active students; PIS - physically inactive students; D – right foot; S – left foot; SD - standard deviation
Legenda: F - prednji deo stopala; R - zadnji deo stopala; R/F % - procenat opterećenja prednjeg. odnosno zadnjeg dela stopala u odnosu na celo stopalo; load% - procenat opterećenja prednjeg. odnosno zadnjeg dela stopala u odnosu na oba stopala; Load% - procenat opterećenja celog stopala u odnosu na oba stopala; PAS - fizički aktivni studenti; PIS - fizički neaktivni studenti; D - desno stopalo; S - levo stopalo, SD - standardna devijacija

Gait is a complex biomechanical process of refraction of force vectors. Apart from motion of the feet, this process includes both vertical and horizontal oscillations of the body and the head, which are followed by the postural adaptation. During gait, the gravity lines move a few centimeters from the center of gravity (located anteriorly to the promontorium). Although small, these movements are crucial during the absorption of reaction forces of the ground [10–12].

Material and Methods

The study included 91 students (n = 91, aged from 19 to 23 years) of the University of Novi Sad attending the Faculty of Medicine and the Faculty of Sport and Physical Education. A study on daily physical activities was conducted; each participant was asked if they got at least 150 minutes of moderate-intensity aerobic activity per week (this is the minimal weekly activity recommended by the World Health Organization) [13]. Based on their answers, the participants were divided into two categories: physically inactive students (PIS) of the Faculty of Medicine (n = 44) and physically active students (PAS) of the Faculty of Sport and Physical Education (n = 47). The PIS were active less than 150 minutes per week, while PAS had at least 150 minutes of physical activity per day. Of the total number of PIS, 21 were male and 23 female. Of the total number of PAS, 32 were male and 15 female.

All the participants were given detailed instructions regarding the research and all signed a written informed consent for participation in the study. Ethics Committee of the Faculty of Medicine in Novi Sad issued a written approval for this research.

Feet measurements were performed by using a baropodometry platform (FreeMed Maxi, Sensor Medica, Rome, Italy, owned by company "Dunav ortopedsko") and the included Freestep version 1.4.01 software. The platform is equipped with pressure sensors that can determine biometric parameters related to foot statics and dynamics. Measured data were transferred to a computer with the installed Freestep software. Numerical data of the examined parameters were processed in the software, as well as the isochromatic map of the foot sole, based on the foot load. Alongside the measured values, the software shows physiological data with a reference range recommended by the manufacturer.

In order to compare the load of participants' feet the following were used:

1. F or R load percentage in relation to the whole foot (R/F %),

Table 2. Deviation of measured values of the foot load from the reference values in PAS and PIS
Tabela 2. *Odstupanja izmerenih vrednosti opterećenja stopala od referentnih kod PAS i PIS*

		N/*B*	$\bar{x}$	SD/*SD*	Minimum/*Minimum*	Maximum/*Maksimum*	U/*U*	p/*p*
R/F % DF deviation	PIS	44	7.57	7.079	0	25	835.500	0.113
	PAS	47	4.91	5.081	0	18		
R/F % DR deviation	PIS	44	7.57	7.079	0	25	835.500	0.113
	PAS	47	4.91	5.081	0	18		
R/F % SF deviation	PIS	44	7.77	7.243	0	22	789.500	0.049
	PAS	47	4.57	5.274	0	29		
R/F % SR deviation	PIS	44	7.77	7.243	0	22	789.500	0.049
	PAS	47	4.57	5.274	0	29		
Load % DF deviation	PIS	44	2.93	3.302	0	11	657.500	0.003
	PAS	47	1.66	2.389	0	9		
Load % DR deviation	PIS	44	3.11	3.519	0	13	647.500	0.002
	PAS	47	1.55	2.124	0	7		
Load % D deviation	PIS	44	0.86	1.456	0	6	1024.00	0.936
	PAS	47	0.60	1.378	0	7		
Load % SF deviation	PIS	44	3.05	3.410	0	10	697.000	0.007
	PAS	47	1.06	1.686	0	9		
Load % SR deviation	PIS	44	3.20	3.488	0	13	721.000	0.013
	PAS	47	1.53	2.052	0	7		
Load % S deviation	PIS	44	0.86	1.456	0	6	1024.00	0.936
	PAS	47	0.60	1.378	0	7		

Legend: F - forefoot; R – rearfoot; R/F % - F or R load percentage in relation to the whole foot; load % - F or R load percentage in relation to both feet; Load % - whole foot load percentage in relation to both feet; PAS - physically active students; PIS - physically inactive students; D – right foot; S – left foot; SD - standard deviation; U - Mann-Whitney test
Legenda: F - prednji deo stopala; R - zadnji deo stopala; R/F % - procenat opterećenja prednjeg. odnosno zadnjeg dela stopala u odnosu na celo stopalo; load % - procenat opterećenja prednjeg. odnosno zadnjeg dela stopala u odnosu na oba stopala; Load % - procenat opterećenja celog stopala u odnosu na oba stopala; PAS - fizički aktivni studenti; PIS - fizički neaktivni studenti; D - desno stopalo; S - levo stopalo, SD - standardna devijacija, U - Man-Vitnijev test

2. F or R load percentage in relation to both feet (load %) and
3. Whole foot load percentage in relation to both feet (Load %).

The recommended reference range for the first parameter (R/F %) is 42 – 48% for F and 52 – 58% for R; for the second parameter (load %) it is 20 – 26% for F and 24 – 30% for R; the reference range for the third parameter (Load %) is 47 – 53%.

Measurements of height, weight and shoe size were conducted and these data were entered into the database. Then, the participants were submitted to baropodometry platform: they stood still for several seconds, until the machine finished reading the data.

After determining the parameters, the data were entered into the free program for statistical analysis of sampled data. The measured values were compared with the reference values. By doing so, we have established to what degree they deviated from the reference physiological values.

We examined:

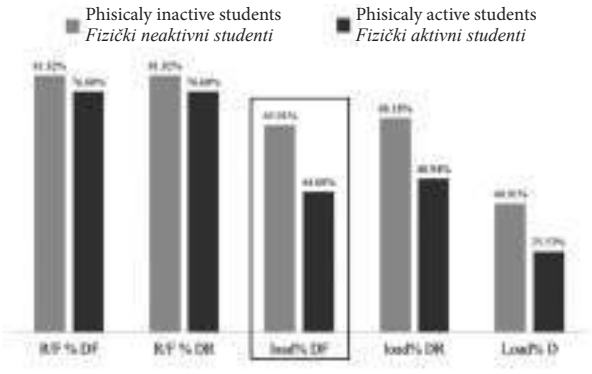
- The percentage of participants with non-physiological values in each of the groups,
- If there was a statistically significant difference in measured values between PIS and PAS,
- If there was a statistically significant difference in deviation from the reference values between PIS and PAS.

Student's t-test, Mann-Whitney U-test and Pearson's χ^2-test were used for statistical analysis.

Results

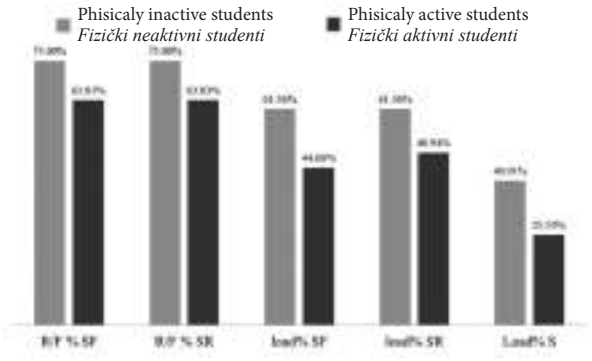
The statistical analysis showed that PAS have statistically significantly higher values of R/F % of the right forefoot (DF), R/F % of the left forefoot (SF), load % DF and load % SF. The PIS showed statistically significantly higher values of R/F % of the right rearfoot (DR), R/F % of the left rearfoot (SR), load % DR and load % SR. There were no statistically significant differences in values of Load % D and Load % S between PAS and PIS **(Table 1)**.

The PIS showed statistically significantly higher deviations from the reference values for the parameters R/F % SF, R/F % SR, load % DF, load % DR, load % SF and load % SR in comparison to PAS. There were no statistically significant differences in deviations from the reference values for parameters R/F % DF, R/F % DR, Load % D and Load % S in comparison to PAS **(Table 2)**.



Graph 1. Percentage of participants with non-physiological values for the right foot by groups; the selected part shows a statistically significant difference
Grafikon 1. *Procenat ispitanika sa nefiziološkim vrednostima po grupama ispitanika za desno stopalo. Označeni deo grafika pokazuje statistički značajnu razliku*

The percentage of PIS with non-physiological values was higher for all the parameters than in PAS. However, the difference was statistically significant only for the parameter load % DF **(Graphs 1 and 2)**.



Graph 2. Percentage of participants with non-physiological values for the left foot by groups
Grafikon 2. *Procenat ispitanika sa nefiziološkim vrednostima po grupama ispitanika za levo stopalo*

Discussion

The significance of this paper is reflected in the first attempt of representing objective parameters of the foot statics in our population using a new device - FreeMed Maxi. Such a sophisticated device was not accessible to researchers until now, therefore there was little to no possibility to compare our results with those of other researchers.

We have concluded that all the parameters of the F load (R/F % DF, R/F % SF, load % DF and load % SF) in PAS are statistically significantly higher in comparison to PIS. All the parameters of the R load (R/F % DR, R/F % SR, load % DR and load % SR) are statistically significantly higher in PIS than in PAS. According to these results, we may conclude that while standing, PAS use their F as the main support and PIS use their R as the main support. This can be partially explained by frequent exercise in PAS, mainly because during warm-up exerices (stretching and running) greater strain is exerted on the F, which was confirmed by authors who conducted research in this area [14–16].

We have established that there is a statistically significantly higher deviation for most parameters of foot load (R/F % SF, R/F % SR, load % DF, load % DR, load % SF and load % SR) in PIS in comparison to PAS. A possible explanation could be that physical activity significantly stretches the tendons of the muscles and the ligaments, and in that way contributes to maintaining healthy morpho-functional caracteristics of the foot [17, 18]. Apart from that, inadequate footwear and sedentary way of life of PIS are possible causes of these differences.

Even though a higher percentage of PIS deviates from physiological values in all the parameters in comparison to PAS, both groups showed a significant percentage of participants that deviated from the reference range. These results are quite unsatisfactory. The most probable causes for such results are genetic inheritance, damaging effects of inadequate footwear and differences in gait.

The limiting factor of this study is that there are no relevant data we can compare our results to. In addition, the significance of the inheritance factor for the development of foot deformities and load distribution was not taken into account, since the data regarding foot deformities of the participants' relatives were not acquired, as well as the type and quality of footwear and orthopedic aids which the participants may have used in their childhood. Finally, earlier foot and ankle injuries should have been taken into consideration.

Foot deformities are not only a medical but also a socioeconomic problem. Their early discovery and prevention is necessary, so that the damage to the locomotor apparatus, caused by inadequate force vector distribution, especially in young athletes and in older age, could be hindered. Consequently, it is crucial that medical professionals observe the development of child's feet through regular checkups and educate the population about the problems that may appear as a consequence of foot deformities.

Conclusion

Our study shows that physically active students have physiologically better foot load distribution than physically inactive students.

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HEALTH CONCERNS OF PATIENTS WITH RHEUMATOID ARTHRITIS DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC

ZABRINUTOST BOLESNIKA OBOLELIH OD REUMATOIDNOG ARTRITISA TOKOM PANDEMIJE IZAZVANE COVID-19 VIRUSOM

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Summary

Introduction. Rheumatoid arthritis is a symmetrical polyarticular arthritis that primarily affects the small joints of the hands and feet. Patients with rheumatoid arthritis have a significantly higher risk of developing serious infections that require hospitalization. The coronavirus disease 2019 pandemic was declared in 2019. The aim of this study was to examine the concerns of patients with rheumatoid arthritis during the coronavirus disease 2019 pandemic. **Material and Methods**. A prospective, randomized, cross-sectional study included 127 patients with rheumatoid arthritis treated with biological therapy at the Special Hospital for Rheumatic Diseases, Novi Sad, Serbia. Data were obtained by a questionnaire that included three sections: general information, data on the disease, and health concerns before and during the coronavirus disease 2019 pandemic. The data were collected in the period from 1 to 31 October, 2021. Statistical analysis was performed using the IBM SPSS Statistics for Windows, Ver. 25.0. **Results.** A total of 127 respondents participated in the study, 108 women (85%) and 19 men (15%). The average age of participants was 54.26 years. The statistical analysis showed that there were no statistically significant differences among the respondents in relation to sociodemographic characteristics, and that they all showed approximately the same level of concern for themselves and their loved ones during the coronavirus disease 2019 pandemic. Among the participants with rheumatoid arthritis, the health concerns during the coronavirus disease 2019 pandemic were more pronounced in patients with associated diseases: high blood pressure (3.43 [SD = 1.07] vs. 3.01 [SD = 1.09]; $p < 0.05$), heart failure (3.92 [SD = 0.82] vs. 3.07 [SD = 1.09]; $p < 0.05$) and thyroid disease (3.82 [SD = 0.97] vs. 3.04 [SD = 1.08]; $p < 0.01$), compared to those without comorbidities. The total health concerns of the respondents were higher during the coronavirus disease 2019 pandemic compared to the pre-pandemic period (3.16 [SD = 0.40] vs. 2.93 [SD = 0.35]; $p < 0.001$). **Conclusion**. The respondents expressed greater health concerns for both themselves and their loved ones during the pandemic compared to the pre-pandemic period.

Key words: Arthritis, Rheumatoid; COVID-19; Pandemics; Surveys and Questionnaires; Mental Health; Quality of Life; Stress, Psychological

Sažetak

Uvod. *Arthritis Rheumatoides* je simetrični poliartikularni artritis koji prvenstveno zahvata male zglobove šaka i stopala. Bolesnici oboleli od reumatoidnog artritisa imaju značajno veći rizik da razviju ozbiljne infekcije koje zahtevaju hospitalizaciju bolesnika. COVID-19 pandemija proglašena je 2019. godine. Cilj rada bio je ispitati zabrinutost bolesnika obolelih od reumatoidnog artritisa tokom pandemije COVID-19 virusa. **Materijal i metode**. Rad predstavlja prospektivnu, randomizovanu studiju preseka koja je obuhvatila 127 bolesnika obolelih od reumatoidnog artritisa lečenih u Specijalnoj bolnici za reumatske bolesti, Novi Sad, Srbija. Podaci su dobijeni popunjavanjem upitnika koji je sadržao opšti upitnik, upitnik sa podacima o bolesti i upitnik o zabrinutosti za zdravlje pre i tokom COVID-19 pandemije. Podaci su prikupljani u periodu od 1.10.2021. godine do 31.10.2021. godine. Za obradu podataka korišćen je statistički program *IBM SPSS Statistics for Windows, ver. 25.0*. **Rezultati**. U istraživanju je učestvovalo 127 ispitanika, 108 žena (85%) i 19 muškaraca (15%). Prosečna starost iznosila je 54,26 godina. Statistički testovi pokazali su da statistički značajnih razlika u odnosu na sociodemografske karakteristike nema, te da sve grupe ispitanika pokazuju približan nivo zabrinutosti za sebe i svoje bližnje tokom COVID-19 pandemije. Među ispitivanom populacijom obolelih od reumatoidnog artritisa zabrinutost tokom COVID-19 infekcije bila je izraženija među bolesnicima koji su od udruženih bolesti imali povišen krvni pritisak (3,43 [SD = 1,07] *vs.* 3,01 [SD = 1,09]; $p < 0,05$), srčanu slabost (3,92 [SD = 0,82] *vs.* 3,07 [SD = 1,09]; $p < 0,05$) i bolesti štitaste žlezde (3,82 [SD = 0,97] *vs.* 3,04 [SD = 1,08]; $p < 0,01$) u odnosu na osobe bez komorbiditeta. Ukupna zabrinutost ispitanika je bila veća u odnosu na prepandemijsko stanje (3,16 [SD = 0,40] *vs.* 2,93 [SD = 0,35]; $p < 0,001$). **Zaključak**. Ispitanici su pokazali veću zabrinutost kako za svoje tako i za zdravlje bližnjih tokom pandemije u odnosu na prepandemijsko stanje.

Ključne reči: reumatoidni artritis; covid-19; pandemija; ankete i upitnici; mentalno zdravlje; kvalitet života; psihološki stres

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Abbreviations

RA – rheumatoid arthritis
COVID-19 – coronavirus disease 2019
WHO – World Health Organization
SD – standard deviation

Introduction

Rheumatoid arthritis (RA) is a symmetrical polyarticular arthritis that primarily affects the small joints of the hands and feet. The prevalence of RA in the global population is 0.5 - 1.0%, even though the prevalence of this disease may have changed in Europe from the age of Renaissance until Garrod described RA as a separate entity in 1859 [1]. After the detection of a new coronavirus in China in December 2019, and its spreading all over the world, the World Health Organization (WHO) proclaimed a public health emergency of international importance on January 30, 2020. In Serbia, the first case of COVID-19 infection was registered on March 6, 2020. In Serbia, there were 1,174,333 confirmed cases of COVID-19 infection on November 5, 2021, and the number of deceased persons was 10,271 [2]. The relationship between RA and COVID-19 infection may be interpreted in two directions. Microorganisms may pose a potential cause of acute and chronic arthritis, whether through direct colonization of joints or through the host autoimmune mechanisms [3, 4]. A study conducted in Korea reported a link between the parainfluenza virus infection and coronavirus with newly occurring RA [5]. On the other hand, patients suffering from RA are at increased risk from COVID-19 infection compared to general population. Doran et al. proved that RA patients are at a significantly higher risk for developing serious infections requiring hospitalization [6]. Among the population with polyarthritis, the number of hospitalizations was four times higher compared to the general population [7]. A review published in 2011, including 6,242 stable patients from the Consortium of Rheumatology Research of North America (CORRONA) 2002 – 2007 registry, showed that each increase of 0.6 in disease activity score 28 responds to the increase of incidence rate requiring hospitalization by 25% and increase in clinical infections by 4% [8]. Until November 23, 2021 the WHO approved production of eight anti-COVID-19 vaccines including two messenger ribonucleic acid vaccines (mRNA), three non-replicating viral vector vaccines, and three inactivated virus vaccines [9]. Since we have been facing the COVID-19 infection issue for a prolonged period of time on a global level, the purpose of this paper was to investigate the health concerns of patients suffering from RA during the COVID-19 pandemic.

Material and Methods

A prospective, randomized, cross-sectional study included 127 patients with RA treated at the Special Hospital for Rheumatic Diseases, Novi Sad, Serbia. The data were collected in the period from 1 to 31 October, 2021 at the Daily Hospital of the Special Hospital for Rheumatic Diseases, Novi Sad, Serbia. A total of 125 patients were treated with biological therapy, while 2 patients received approval by the Republic Fund for biological therapy within the last two weeks. The study was approved by the Ethics Committee of the Special Hospital for Rheumatic Diseases, Novi Sad (number 14/29-1/1-21) and all the patients provided a written informed consent. Respondents completed a survey that covered several areas: a) general information, b) data on the disease and c) health concerns before and during the COVID-19 pandemic. General information included the following variables: sex (male/female), age (open question), level of formal education (elementary school/high school/junior college/higher education and over), marital status (married/single/divorced/widow), residence (city/village/suburban area), residential space (apartment/house), living with (immediate family/broader family/alone), living with persons over 70 years of age (yes/no), living with persons under 18 years of age (yes/no), employment (employed/unemployed/retired), type of job performed (physical work/work with a machine/work in trade/administrative work/work in health and/or social services/other), the number of people they come in contact with in everyday work (under 5 people/from 5 to 10 people, more than 10 people) and the means of transportation to work (bus/private vehicle/other). Data on the basic disease, RA and its therapy included: duration of the inflammatory rheumatic disease (open question), use of biological therapy (yes/no), duration of biological therapy (open question), drug administration schedule (regular/not regular/no administration). Data on comorbidities were collected by multiple choice questions. Comorbidities were classified into six categories: hypertension, heart diseases, chronic lung disease, diabetes, thyroid disease, and so on. The third part of the questionnaire collected data on health concerns of the participants for both their and health of their loved ones before and during the pandemic. The respondents answered these four questions:

– How concerned were you about your own health before the COVID-19 pandemic?
– How concerned were you about your own health during the COVID-19 pandemic?
– How concerned were you about the health of your loved ones before the COVID-19 pandemic?
– How concerned were you about the health of your loved ones during the COVID-19 pandemic?

Responses were ranked from 0 (not concerned at all) to 5 (very concerned). The total concern before the pandemic is a composite score of concerns related to one's own health and health of their loved ones before the pandemic. The total concern during the pandemic is a composite score of concerns related to one's own health and health of their loved ones during the pandemic. The composite score may range from 0 to 5, where higher values represent higher concern. The total concern before the pandemic showed satisfactory reliability (Cronbach's Alpha = 0.756) while excellent reliability was found for the composite score

of the total concern during COVID-19 pandemic (Cronbach's Alpha = 0.848). Social and demographic characteristics, data on the disease and health concerns of the respondents before and during the COVID-19 pandemic are presented through descriptive analysis. The results of these analyses are represented using frequencies and percentages for testing qualitative variables, mean value, and standard deviation (SD) for continuous variables. Independent sample T-test was used for testing differences between the two groups. Analysis of variance (ANOVA) was used to determine differences between three and more groups. To assess differences related to the level of concern about one's own health and health of their loved ones before and during the COVID-19 pandemic, the Paired Samples T-test was used. Correlation was tested using the Pearson's correlation coefficient. Reliability was tested using the Cronbach's alpha test. A probability level of $p \leq 0.05$ was considered statistically significant. Statistical analysis was performed using the IBM SPSS Statistics for Windows, Ver. 25.0.

Results

The **Table 1** presents general characteristics of patients with RA, as well as their health concerns during the COVID-19 pandemic. The study included 127 respondents (108 women - 85.0% and 19 men - 15%), with average age of 54.26 years (SD = 11.54), ranging from 22 to 87 years of age. The highest percentage of respondents was married (71.7%), while half of them lived in cities (56.7%). The majority of respondents

Table 1. General characteristics of the respondents and their health concerns during the COVID-19 pandemic
Tabela 1. *Opšte karakteristike ispitanika i njihova zabrinutost za zdravlje tokom COVID-19 pandemije*

General characteristics of the respondents *Opšte karakteristike ispitanika*	N/*B* = 127	Health concerns during the COVID 19 pandemic/*Zabrinutost za zdravlje tokom COVID 19 pandemije*	p/*p*
	N/*B* (%)	Mean ± SD/*Srednja ± Standardna devijacija*	
Gender/*Pol*			0.652[a]
Female/*Ženski*	108 (85.0%)	3.14 ± 1.06	
Male/*Muški*	19 (15.0%)	3.26 ± 1.33	
Age/*Starost*			0.187[b]
22 – 42	17 (13.4%)	2.65 ± 0.90	
43 – 52	33 (26.0%)	3.14 ± 1.22	
53 – 62	47 (37.0%)	3.23 ± 1.04	
63 – 87	30 (23.6%)	3.35 ± 1.13	
Marital status/*Bračno stanje*			0.373 [b]
Married/*Udata/oženjen*	91 (71.7%)	3.26 ± 1.12	
Widow(er)/*Udovac/udovica*	9 (7.1%)	2.83 ± 1.03	
Divorced/*Razveden/razvedena*	16 (12.6%)	2.84 ± 1.04	
Unmarried/*Nedudata/neoženjen*	11 (8.7%)	3.00 ± 1.10	
Type of residence/*Mesto življenja*			0.959 [b]
City/*Grad*	72 (56.7%)	3.16 ± 1.13	
Countryside/*Selo*	42 (33.1%)	3.18 ± 1.12	
Suburb/*Prigradsko naselje*	13 (10.2%)	3.08 ± 0.95	
Living space/*Stambeni prostor*			0.742 [a]
Apartment/*Stan*	33 (26.0%)	3.21 ± 0.94	
House/*Kuća*	94 (74.0%)	3.14 ± 1.16	
Living with/*Živim sa*			0.163 [b]
Family/*Porodicom*	100 (78.7%)	3.25 ± 1.16	
In a wider community/*U široj zajednici*	13 (10.2%)	2.65 ± 0.63	
Alone/*Sam/sama*	14 (11.0%)	3.00 ± 0.92	
There are people over 70 in the community *U zajednici ima starijih od 70 godina*			0.259 [a]
Yes/*Da*	27 (21.3%)	2.94 ± 0.91	
No/*Ne*	100 (78.7%)	3.22 ± 1.14	
There are children under the age of 18 in the community/*U zajednici ima mlađih od 18 godina*			0.061 [a]
Yes/*Da*	33 (26.0%)	2.85 ± 1.05	
No/*Ne*	94 (74.0%)	3.27 ± 1.10	

Education/*Obrazovanje*			0.902 [b]
Primary school/*Osnovna škola*	12 (9.4%)	3.08 ± 1.10	
High school/*Srednja škola*	83 (65.4%)	3.19 ± 1.15	
College/*Viša škola*	13 (10.2%)	3.23 ± 0.86	
University and above/*Visoka škola i više*	19 (15.0%)	3.00 ± 1.09	
Employment/*Radni odnos*			0.304 [a]
Yes/*Da*	64 (50.4%)	3.14 ± 1.10	
No/*Ne*	17 (13.4%)	2.82 ± 1.29	
Retiree/*Penzioner/ka*	46 (36.2%)	3.30 ± 1.02	
Job/*Posao koji obavljam je*			0.809 [b]
Physical work/*Fizički rad*	10 (15.4%)	3.10 ± 1.26	
Work with machinery/*Rad za mašinom*	4 (6.2%)	3.38 ± 1.25	
Trader/*Rad u trgovini*	13 (20.0%)	3.15 ± 1.07	
Administrative work/*Administrativni rad*	23 (35.4%)	2.98 ± 1.16	
Health care or social service *Rad u zdravstvu i socijalnoj službi*	7 (10.8%)	3.21 ± 1.07	
Other/*Drugo*	8 (12.3%)	3.61 ± 0.82	
While working I am in contact with *Pri radu dolazim u kontakt sa*			0.775 [b]
Less than 5 people/*Manjim brojem ljudi (do 5)*	11 (17.2%)	3.04 ± 1.34	
Between 5 and 10 people/*Umerenim brojem ljudi (5 do 10)*	11 (17.2%)	3.00 ± 1.05	
More than 10 people/*Većim brojem ljudi od 10*	42 (65.6%)	3.23 ± 1.05	
I usually go to work/*Na posao dolazim*			0.073 [a]
By bus/*Autobusom*	14 (21.9%)	3.07 ± 0.78	
By car/*Privatnim vozilom*	32 (50.0%)	3.45 ± 1.17	
Other/*Drugim vidom dolaska*	18 (28.1%)	2.72 ± 1.08	

Legend: [a] Independent Samples T-Test; [b] Analysis of variance (ANOVA); N - Number of respondents; The probability level of $p \leq 0.05$ was considered statistically significant

Legenda: [a] T-test za velike nezavisne uzorke; [b] Jednofaktorska analiza varijanse (ANOVA); B – broj ispitanika; Prihvaćen nivo statističke značajnosti je $p \leq 0,05$

were living in houses (74.0%), and 26% were living in apartments. A total of 78.7% of respondents were living with their immediate families, while 21.3% were living with family members aged 70 or above, and 26.0% of respondents were living with minors. There were 9.4% of respondents with elementary education, 65.4% graduated from high school, 10.2% of respondents graduated from junior college, while 15% of respondents had higher education. Half of the respondents were employed (50.4%), 65.6% of which were in contact with a larger number of people at work (more than 10). A total of 35.4% of respondents were administrative workers, 20% worked in trade, 15.4% were physical workers, 10.8% worked in health and social services, while 6.2% worked with machines. We examined differences between social and demographic groups of respondents related to health concerns during COVID-19 pandemic. Statistical analysis showed that there were no statistically significant differences, and that all groups showed approximately the same level of concern for themselves and their loved ones during the COVID-19 pandemic. The study included patients with RA with disease duration from 1 to 49 years and average duration of 12.45 (SD = 7.18) years. A total of 98.4% of respondents received biological therapy, whereas 16.8% of respondents received this therapy for less than a year. A total of 44.8% of respondents received therapy from 1 to 5 years, 29.6% received therapy from 6 to 10 years, while 8.8% of respondents received biological therapy for more than 11 years. As much as 97.6% of respondents received therapy regularly. Hypertension was present in 34.6% of respondents with RA, 15.0% had a thyroid disease, 9.4% had a heart diseases, and 6.3% of respondents had lung diseases and diabetes. Health concerns during the COVID-19 pandemic were more expressed in patients with hypertension compared to normotensive patients (3.43 [SD = 1.07] vs. 3.01 [SD = 1.09]; $p < 0.05$). Patients with RA and heart disease showed higher health concerns compared to those without this comorbidity (3.92 [SD = 0.82] vs. 3.07 [SD = 1.09]; $p < 0.05$) as well as patients with RA and a thyroid disease (3.82 [SD = 0.97] vs. 3.04 [SD = 1.08]; $p < 0.01$). Patients who were taking drugs regularly showed higher health concerns compared to those who took drugs irregularly (3.19 [SD=1.09] vs. 1.83 [SD = 0.76]; $p < 0.05$) (**Table 2)**.

A paired samples T-test was used to test the differences in the level of health concerns for themselves and their loved ones before and during the COVID-19 pandemic. The results showed higher health concerns for their own health during the pandemic than in the

Table 2. Data on the respondents' diseases and their health concerns during the COVID-19 pandemic
Tabela 2. *Podaci o bolesti kod ispitanika i njihova zabrinutost za zdravlje tokom COVID-19 pandemije*

Data on the diseases *Podaci o bolesti*	N/*B* = 127	Health concerns during the COVID-19 pandemic/*Zabrinutost za zdravlje tokom COVID-19 pandemije*	p/*p*
	N/*B* (%)	Mean ± SD/*Srednja ± Standardna devijacija*	
Duration of the inflammatory rheumatic disease *Dužina trajanja zapaljenske reumatske bolesti*			0.533 [b]
1 – 10	50 (39.4%)	3.26 ± 1.05	
11 – 20	68 (53.5%)	3.13 ± 1.15	
21+	9 (7.1%)	2.83 ± 1.09	
Comorbidities/*Komorbiditeti*			
Hypertension/*Povišeni krvni pritisak*	44 (34.6%)	3.43 ± 1.07	0.040 [a]
Heart disease/*Srčana bolest*	12 (9.4%)	3.92 ± 0.82	0.012 [a]
Chronic obstructive pulmonary disease *Hronična opstruktivna bolest pluća*	8 (6.3%)	3.63 ± 0.69	0.216 [a]
Diabetes/*Šećerna bolest*	8 (6.3%)	3.50 ± 1.16	0.366 [a]
Thyroid disease/*Bolest štitaste žlezde*	19 (15.0%)	3.82 ± 0.97	0.004 [a]
Other/*Drugo*	15 (11.8%)	3.57 ± 0.62	0.126 [a]
Biological therapy/*Biološka terapija*			0.839 [a]
Yes/*Da*	125 (98.4%)	3.16 ± 1.10	
No/*Ne*	2 (1.6%)	3.00 ± 1.41	
Duration of biological therapy/*Dužina trajanja biološke terapije*			0.114 [b]
< year/ < *1 godina*	21 (16.8%)	3.69 ± 1.03	
1 – 5	56 (44.8%)	3.05 ± 1.06	
6 – 10	37 (29.6%)	3.03 ± 1.15	
11+	11 (8.8%)	3.14 ± 1.12	
During COVID-19 pandemic I take my medications *Lekove u vremenu pandemije COVID-19 virusom uzimam*			0.035 [b]
On regular basis/*Redovno*	124 (97.6%)	3.19 ± 1.09	
Irregulary/*Neredovno*	3 (2.4%)	1.83 ± 0.76	
I do not take medications/*Ne uzimam*	0 (0%)	NA/*NP*	

Legend: [a] Independent Samples T-Test; [b] Analysis of variance (ANOVA); N - Number of respondents; The probability level of $p \leq 0.05$ was considered statistically significant (Note: Comorbidity is a variable offering multiple choice answers)
Legenda: [a] T-test za velike nezavisne uzorke; [b] Jednofaktorska analiza varijanse (ANOVA); B – broj ispitanika; Prihvaćen nivo statističke značajnosti je p ≤ 0,05 (Napomena: Komorbiditeti su varijabla sa mogućnošću višestrukog izbora)

Table 3. Difference in health concerns before and during the COVID-19 pandemic
Tabela 3. *Razlika u zabrinutosti za zdravlje pre i tokom COVID-19 pandemije*

		Mean ± SD/*Srednja ± Standardna devijacija*	p/*p*
Par 1 *Pair 1*	Concerns for ones own health before the COVID-19 pandemic *Zabrinutost za sopstveno zdravlje pre pandemije COVID-19*	2.71 ± 0.47	< 0.001
	Concerns for ones own health during the COVID-19 pandemic *Zabrinutost za sopstveno zdravlje za vreme pandemije COVID-19*	2.98 ± 0.68	
Par 2 *Pair 2*	Concerns for the health of loved ones before the COVID-19 pandemic *Zabrinutost za zdravlje bližnjih pre pandemije COVID-19*	3.16 ± 0.36	< 0.001
	Concerns for the health of loved ones during the COVID-19 pandemic *Zabrinutost za zdravlje bližnjih za vreme pandemije COVID-19*	3.33 ± 0.39	
Par 3 *Pair 3*	Total health concerns before the COVID-19 pandemic *Ukupna zabrinutost za zdravlje pre COVID-19 pandemije*	2.93 ± 0.35	< 0.001
	Total health concerns during the COVID-19 pandemic *Ukupna zabrinutost za zdravlje za vreme COVID-19 pandemije*	3.16 ± 0.40	

Legend: Paired samples t-test; The probability level of $p \leq 0.05$ was considered statistically significant
Legenda: T-test uparenih uzoraka; Prihvaćen nivo statističke značajnosti je p ≤ 0,05

pre-pandemic period (2.98 [SD = 0.68] vs. 2.71 [SD = 0.47]; $p < 0.001$). Health concerns for their loved ones were more statistically significant during than before the pandemic (3.33 [SD = 0.39] vs. 3.16 [SD = 0.36]; $p < 0.001$). The total concern is a composite score of concerns related to one's own health and health of their loved ones, where higher value implies higher concern. By comparing positive scores, our data showed higher total health concerns during the COVID-19 pandemic than in the pre-pandemic period (3.16 [SD = 0.40] vs. 2.93 [SD = 0.35]; $p < 0.001$) **(Table 3)**.

Discussion

The end of 2021 brought uncertainty. Epidemics and pandemics are a periodic phenomenon that is often associated with intense impact causing fear and consequently damaging human mental health [10]. The aim of our study was to examine health concerns of patients suffering from RA during the COVID-19 infection. Biological therapy is the optimal therapy for all patients with RA. For the purpose of selecting the best therapeutic option for RA patients, similar studies were conducted by Williams and Edwardson [11], Goekoop-Ruiterman [12], Chilton and Collet [13]. These studies concluded that patients were satisfied with biological therapy for RA treatment. Most patients started biological therapy for RA as the choice of treatment. According to most respondents, physicians and patients are involved in the decision-making process related to the drug selection. An online study from 2020, which included the population of India, dealt with the issue of human mental health during the pandemic. The participants were persons over the age of 18 with higher level of education. The study showed higher levels of health concerns in persons working in healthcare. Also, higher level of COVID-19 infection prevention was found among this population [14]. In our study, all patients showed equal level of concern for themselves and their loved ones during the COVID-19 pandemic, regardless of social and epidemiological features. The deviations in our results is explained by the fact that only 10.8% of the examined patients worked in healthcare services, while the largest number of respondents worked in administration. The COVID-19 infection may cause complications in certain groups of patients, while 11 – 24% of patients may experience long-term symptoms, up to three months after the confirmed infection [15–17]. Joint data from 12 studies conducted in the period from 2019 to 2021, dealing with the assessment of quality of life of patients suffering from COVID-19, show lower values of health-related quality of life (HRQoL) score (physical and mental component) in patients who were treated in intensive care units compared to those treated in general wards [18]. Therefore, COVID-19 infection may impact quality of life in short and long term. This raises concerns since more than half of patients over 15 years of age have one chronic disease [19]. It is known that increased level of stress is confirmed in people suffering from chronic diseases compared to general population [20]. Results of our study show that among patients suffering from RA, health concerns during COVID-19 infection were more pronounced among those with comorbidities, including hypertension, heart weakness and thyroid diseases. Similar results were found in a study conducted in Bangladesh during COVID-19 infection, where higher level of stress was recorded in patients suffering from heart weakness, lung diseases and diabetes [21]. Given the fact that the COVID-19 infection is widespread, epidemiologic measures for suppressing it are of utmost importance (restriction of movement, quarantine, isolation, etc.). In the aforementioned online study conducted in 2020 in India, these measures led to inappropriate behavior (rage, protests, concern) noticed in 1/6 of respondents. In the same study, preoccupation with COVID-19 pandemic was noticed in 1/3 of patients which resulted in posting on social media related to the current pandemic. Two thirds of patients felt the need to talk to someone regarding their concerns related to COVID-19 infection. Thus, people felt emotionally exhausted. More than three quarters of patients felt the need to seek professional help for the purpose of maintaining and improving their mental health [14]. Rheumatic and musculoskeletal diseases are the second factor contributing to the reduction of the quality of life and present global disability [22]. Along with this fact, patients with RA show reduced quality of life compared to general population and other chronic diseases [23, 24]. For the purpose of suppressing spreading of the COVID-19 infection, many institutions close their doors to patients that require face-to-face clinical treatment, including RA patients. To overcome this issue, healthcare system focused on online provision of health services. Videoconferencing psychotherapy showed promising results for anxiety and mood disorders [25], while therapist-guided online interventions proved even better for human mental health [26, 27]. Prevention of mental disorders should be ever present, especially in the era of COVID-19 pandemic, considering the fact that our patients showed more health concerns compared to the pre-pandemic period.

Conclusion

In accordance with high percentage of immunization and successful measures implemented by the Republic of Serbia in combating coronavirus disease 2019 pandemic, our study showed a statistical significance in linking coronavirus disease 2019 infection and health concerns of rheumatoid arthritis patients. Our respondents showed greater concern for their own health as well as the health of their loved ones compared to the pre-pandemic period, regardless of social and demographic features. Patients with comorbidities, such as heart weakness, hypertension and thyroid diseases, showed greater concern for their own health during the coronavirus disease 2019 pandemic compared to persons without or with some other comorbidities.

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PROGNOSTIC FACTORS AND TREATMENT OUTCOME IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

PROGNOSTIČKI FAKTORI I ISHOD LEČENJA U PEDIJATRIJSKOJ AKUTNOJ LIMFOBLASTNOJ LEUKEMIJI

Dejan DOBRIJEVIĆ[1] and Jovanka KOLAROVIĆ[1, 2]

Summary

Introduction. Acute lymphoblastic leukemia is a malignant, clonal proliferation of B or T lymphocyte precursors. Prognostic factors play an important role in the treatment of this disease. The objective of the study was to determine whether individual clinical and laboratory parameters may have a predictive significance for relapse and the disease outcome. **Material and Methods.** A retrospective study included 53 patients with acute lymphoblastic leukemia treated at the Institute for Child and Youth Health Care of Vojvodina. The following clinical and laboratory parameters were examined: gender, age at diagnosis, initial white blood cell count, peripheral blood blast percentage, bone marrow blast percentage, prednisone response on day 8 of treatment, immunophenotypic characteristics of leukemic blasts, and infiltration of the central nervous system. Relapses and lethal outcomes were analyzed as well. **Results.** The mean age at diagnosis was 6.4 ± 7.8 years. Prognostic factors associated with poor outcome were: age over 10 years, mature cell leukemia, and central nervous system involvement. Relapse was found in 6 children (11.3%). Lethal outcome was recorded in 7 children (13.2%). **Conclusion.** Treatment of childhood lymphoblastic leukemia should be based on the prognostic factors for each patient. The results of this study are consistent with the current literature.

Key words: Precursor Cell Lymphoblastic Leukemia-Lymphoma; Treatment Outcome; Prognosis; Child; Antineoplastic Protocols; Disease-Free Survival; Immunophenotyping

Sažetak

Uvod. Akutna limfoblastna leukemija predstavlja malignu, klonsku proliferaciju B ili T-limfocitnog prekursora. Prognostički faktori igraju važnu ulogu u tretmanu ove bolesti. Cilj istraživanja bio je utvrditi da li pojedini klinički i laboratorijski parametri mogu imati prediktivni značaj za relaps i ishod bolesti. **Materijal i metode.** Sprovedena je retrospektivna studija od 53 pacijenta na Institutu za zdravstvenu zaštitu dece i omladine Vojvodine. Posmatrane kliničke i laboratorijske varijable su uključivale pol, uzrast u vreme postavljanja dijagnoze, inicijalni broj leukocita, procenat blasta u perifernoj krvi, procenat blasta u koštanoj srži, prednizonski odgovor osmog dana terapije, imunofenotipske karakteristike leukemijskih blasta i infiltraciju centralnog nervnog sistema. Informacije o relapsu i smrtnom ishodu su takođe bile zabeležene i analizirane. **Rezultati.** Prosečan uzrast u vreme postavljanja dijagnoze bio je 6,4 ± 7,8 godina. Prognostički faktori povezani sa lošim ishodom bolesti bili su: uzrast preko 10 godina, leukemija zrelih ćelija i infiltracija centralnog nervnog sistema. Relaps je zabeležen kod 6 dece (11,3%). Smrtni ishod je zabeležen kod 7 dece (13,2%). **Zaključak.** Terapija pedijatrijske akutne limfoblastne leukemije treba biti bazirana na prognostičkim faktorima svakog pacijenta. Rezultati studije su u korelaciji sa aktuelnim literaturnim navodima iz literature.

Ključne reči: akutna limfoblastna leukemija; ishod lečenja; prognoza; dete; hemioterapeutski protokoli; preživljavanje bez bolesti; imunofenotipizacija

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant, clonal proliferation of B or T lymphocyte precursors [1]. It is the most common malignancy in pediatric oncology with an incidence of 3 – 4 cases per 100,000 children under the age of 15. Although it may affect children of all ages, it is known that its peak is between 2 and 5 years of age [2, 3].

The survival rate of childhood ALL has significantly improved over the last few decades, especially among patients with good prognosis [4]. Five-year survival rate is around 80% and more than 90% of children achieve remission [5]. Despite all improvements, pediatric ALL still remains the leading cause of mortality in pediatric oncology [6, 7].

The ALL is a heterogeneous disease and therefore, in order to apply the most suitable therapeutic protocol, patients are divided into risk groups based on various prognostic factors [8]. Significant prognostic factors for childhood ALL are: age at diagnosis, initial white blood cell (WBC) count, gender, ethnicity, extramedullary infiltration, immunophenotypic characteristics of leukemic blasts, early medullary response to induction therapy, bone marrow cellularity, prednisone response on day 8 of

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Abbreviations

ALL	– acute lymphoblastic leukemia
WBC	– white blood cells
CNS	– central nervous system
SR	– standard risk
IR	– intermediate risk
HR	– high risk
ALL IC-BFM	– Acute Lymphoblastic Leukemia Intercontinental Berlin-Frankfurt-Münster
EDTA	– ethylenediaminetetraacetic acid

treatment, and infiltration of the central nervous system (CNS) [6, 9]. Based on these factors, children are stratified into standard-risk (SR), intermediate-risk (IR) and high-risk (HR) groups, which determine the type of therapy and prognosis [10].

The aim of this study was to describe various clinical and laboratory features of children with ALL and to evaluate prognostic factors for the disease outcome.

Material and Methods

A single-center retrospective study included 53 children with a newly diagnosed ALL admitted to the Department of Hematology and Oncology of the Institute for Child and Youth Health Care of Vojvodina from May 2003 to November 2009. The patients were treated with Acute Lymphoblastic Leukemia Intercontinental Berlin-Frankfurt-Münster (ALL IC BFM 2002) protocol.

Diagnostic criteria for ALL were: over 25% of blasts in the bone marrow and positive immunophenotypic and cytogenetic findings. Immunophenotypic characteristics of individual cells were determined by FACSCalibur multiparameter flow cytometry (Becton Dickinson, USA) using a Paint-A-Gate Software (Becton Dickinson, USA). Bone marrow aspirate samples were evaluated using ethylenediaminetetraacetic acid (EDTA). All samples were analyzed at the Institute for Mother and Child Health Care of Serbia "Dr Vukan Čupić".

The following clinical and laboratory variables were examined: gender, age at diagnosis, initial WBC count, peripheral blood blast percentage, bone marrow blast percentage, prednisone response on day 8 of treatment, immunophenotypic characteristics of leukemic blasts, and infiltration of the CNS. Relapse and lethal outcomes were analyzed as well.

Baseline hematological parameters were determined using a hematology analyzer Advia 2120 (Siemens Healthcare, Germany) on whole-blood samples with EDTA. A CNS infiltration was detected by cerebrospinal fluid (CSF) microscopy in a Fuchs-Rosenthal counting chamber.

The statistical analysis was carried out using the Statistical Package for the Social Sciences version 26.0 software. Prognostic factors were analyzed using the independent samples t-test, Chi-square test, and Fisher's exact test. The level of statistical significance was set at $p < 0.05$.

Written informed consent was obtained from all participants, i.e. their parents. The study was approved by the Ethics Committee of the Institute for Child and Youth Health Care of Vojvodina (No. 3591-13).

Results

A total of 53 patients with ALL were admitted to the Department of Hematology and Oncology of the Institute for Child and Youth Health Care of Vojvodina from May 2003 to November 2009. The mean age at diagnosis was 6.4 ± 7.8 years, and male children were predominant in the sample (56.6%). Gender had no impact on relapse ($p = 0.264$) or lethal outcome ($p = 0.890$).

The mean age of males and females was 5.9 ± 7.8 years and 5.9 ± 7.6 years, respectively. There was no statistically significant difference of age at diagnosis ($p = 0.407$). However, further age analysis revealed that patients under the age of one year were not at greater risk for relapse ($p = 0.130$) or lethal outcome ($p = 0.155$), while patients above ten years of age were not

Table 1. Impact of white blood cell count, peripheral blood blast percentage, and bone marrow blast percentage on the disease progression in children with acute lymphoblastic leukemia
Tabela 1. *Uticaj broja leukocita, procenta leukemijskih blasta u perifernoj krvi i koštanoj srži na tok bolesti kod dece sa akutnom limfoblastnom leukemijom*

Disease progression *Tok bolesti*	White blood cells *Leukociti* (10^9/L)	Leukemic blasts in peripheral blood *Leukemijski blasti u perifernoj krvi* (%)	Leukemic blasts in bone marrow *Leukemijski blasti u koštanoj srži* (%)
Relapse/*Relaps* (n=6)	28.1 ± 33.4	49.0 ± 58.8	85.3 ± 79.3
Without relapse *Bez relapsa* (n=47)	40.6 ± 65.2	48.9 ± 52.1	83.2 ± 88.1
p-value/*p-vrednost**	0.467	0.999	0.608
Survivors *Preživeli* (n=7)	37.4 ± 65.1	46.2 ± 52.4	82.9 ± 76.6
Non-survivors *Umrli* (n=46)	50.7 ± 40.6	67.6 ± 72.8	87.0 ± 61.4
p-value/*p-vrednost**	0.477	0.188	0.320

Legend: The values are represented as mean values ± standard deviation; *Independent samples t-test
*Legenda: Vrednosti su predstavljene kao srednja vrednost ± standardna devijacija; *Studentov t-test*

Table 2. Central nervous system status in pediatric acute lymphoblastic leukemia
Tabela 2. *Status centralnog nervnog sistema u pedijatrijskoj akutnoj limfoblastnoj leukemiji*

CNS status *CNS status*	Meaning/*Značenje*	Frequency/*Učestalost*		
		Female/*Ženski pol*	Male/*Muški pol*	Total/*Ukupno*
1	CSF without blasts/*CST bez blasta*	18 (78.3%)	27 (90.0%)	45 (84.9%)
2	Traumatic lumbar puncture *Traumatska lumbalna punkcija*	3 (13.0%)	3 (10.0%)	6 (11.3%)
3	CNS involvement/*CNS zahvaćenost*	2 (8.7%)	0	2 (3.8%)
	Total/*Ukupno*	23 (100%)	30 (100%)	53 (100%)

Legend: The values are represented as n (% within group); CNS – central nervous system; CSF – cerebrospinal fluid
Legenda: Vrednosti su predstavljene kao n (% u grupi); CNS – centralni nervni system; CST – cerebrospinalna tečnost

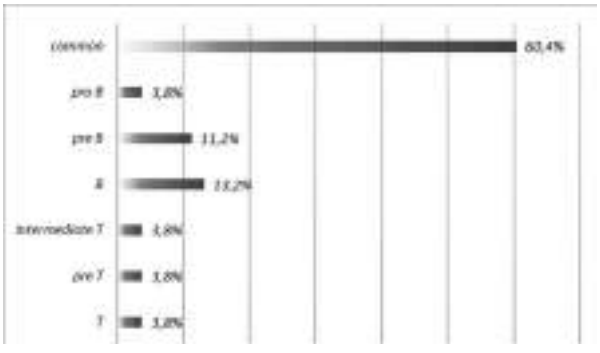
at greater risk for relapse (p = 0.402) but were at significantly greater risk for lethal outcome (p = 0.041).

Sixteen patients (30.2%) were classified in the SR group, twenty-one patients (39.6%) in the IR group, and sixteen patients (30.2%) in the HR group. None of the patients were at greater risk for relapse (p > 0.05). Patients in the standard and intermediate risk groups were at no greater risk for lethal outcome (p > 0.05), while the survival rate was significantly lower in patients in the HR group (p = 0.021).

Initial WBC count, peripheral blood blast percentage and bone marrow blast percentage were not significant for relapse or lethal outcome **(Table 1)**. However, it was determined that bone marrow blast percentage was higher in boys (p = 0.036).

Good prednisone response on day 8 of the treatment (< 1000 blasts/μl) was found in 42 patients (79.2%). Poor response (⩾ 1000 blasts/μl) was found in 11 patients (20.8%). Patients with poor prednisone response were not at greater risk for relapse (p = 0.069) or lethal outcome (p = 0.300).

Immunophenotypes are summarized in **Graph 1**. In total, 88.6% of patients had B-line ALL and 11.4% had T-line ALL. Comparison between the T and B subtypes revealed no statistically significant difference regarding relapse (p = 0.864) or lethal outcome (p = 0.071). To the contrary, comparison made between the mature B- and T-cell ALL and all the other ALL types showed that children with mature cell ALL were at greater risk for lethal outcome (p = 0.042).



Graph 1. ALL immunophenotypes and their percentage share in the sample
Grafikon 1. *Imunofenotipovi ALL i njihova procentualna zastupljenost u uzorku*
Legend/*Legenda:* ALL – acute lymphoblastic leukemia/*ALL – akutna limfoblastna leukemija*

The CNS status is shown in **Table 2**. Children with traumatic lumbar puncture and CNS involvement were at greater risk for relapse (p = 0.013), while CNS status had no impact on the lethal outcome (p = 0.283). There was no correlation between leukemia immunophenotype and CNS involvement (p = 0.219).

Relapsed ALL was found in 6 children. Two of them (33%) relapsed after finishing treatment (approximately after six months) and four of them (77%) relapsed during the treatment. Time to relapse was not significant for lethal outcome (p = 0.333). Lethal outcome was reported in 7 children (13.2%).

Discussion

Prognostic factors and risk stratification are critical for effective and efficient treatment of ALL. Based on prognostic factors, patients are classified into SR, IR and HR groups. These groups provide an insight into the probability of relapse and define the best treatment options. Patients in the HR group receive intensive care and treatment, while less intensive treatment is proposed to patients in the SR group. According to the current BFM protocol, children with IR can receive intensive or less intensive treatment based on ALL IC BFM 2002 randomization criteria. Subsequently, the disease outcomes are being compared [6, 11]. Despite intensive care and treatment, patients with HR have greater odds for poor outcome in comparison to patients with IR or SR [12], which was confirmed in our study.

The ALL IC BFM 2009 protocol is currently in use in our country. It has been used worldwide with a success rate up to 90% [13, 14]. In this study, we analyzed data from 2003 to 2009, when protocol ALL IC BFM 2002, the previous version of ALL IC BFM 2009 protocol, was in use.

Various prognostic factors have been used so far [15] and in our study we analyzed: gender, age at diagnosis, initial WBC count, peripheral blood blast percentage, bone marrow blast percentage, prednisone response on day 8 of treatment, immunophenotypic features of leukemic blasts, and CNS infiltration.

Formerly, boys had worse prognosis due to testicular relapse, which is nowadays far less common because of current ALL treatment. Today, boys have no greater odds for relapse or lethal outcome [7, 15], which is in correlation with our results.

The age peak in pediatric ALL is between two and five years [2, 16]. The mean age at diagnosis in our study was 6.4 ± 7.8 years, which is in line with epidemiological data of authors from other countries [2, 17]. Children aged between one and 10 years have a significantly better prognosis. The worst prognosis is reported in infants with ALL [18]. In our study, children older than 10 years were at greater risk of lethal outcome.

According to the European Group for the Immunological Characterization of Leukemias, B-II subtype (CD10+) was the most common ALL in our sample accounting for 60.4%, which is in correlation with 63% in up-to-date literature [7, 15]. In our patients, 88.6% of ALL were B-line, and 11.4% were T-line. De Sousa et al. reported 89.5% of B-line ALL and 10.5% of T-line ALL [2]. Among our patients, significantly more frequent lethal outcome was noted in mature cell ALL, which is in correlation with other studies [15]. Children with T-line ALL are at greater risk for poor outcome [19], which was not noted in our study.

Leukemic blasts in the CSF are found in 15 - 20% of patients [15]. Our results are in line with these findings with 15.1%. The CNS status 2 and 3 are connected with poor outcome. In our study, CNS status 3 was more common in relapsed patients.

According to the National Cancer Institute, initial WBC count lower than 50×10^9/L is in correlation with better outcome [15, 20], but that was not confirmed in our study. We consider this parameter significant, but it was not confirmed in our analysis, most probably due to the small sample.

Peripheral blood blast percentage and bone marrow blast percentage were analyzed prior to treatment and were not significant for relapse or lethal outcome. Nowadays, in modern hemato-oncology, minimal residual disease is a more accurate prognostic parameter [2, 4], but it was not quantified at our institute when the study was conducted.

Glucocorticoids are included in ALL treatment with other chemotherapeutic agents, since they have the ability to induce apoptosis of leukemic blasts [21, 22]. More than 1,000 blasts/μL after day 8 of treatment (period when only glucocorticoids are applied) is considered a bad prognostic marker [22]. This was not noted in our study, which can be explained by a small sample.

Relapsed ALL is an outgrowth of leukemia blasts after achieved remission, and it can be expected in 15 – 20% of patients. It occurs most commonly during the first two years following the initial treatment [6, 15], but relapsed ALL cases after more than 10 years after the initial treatment were reported as well [23]. In our study group, relapsed ALL was found in 11% of cases and lethal outcome in 13.2% and that is in correlation with aforementioned prognostic factors.

Conclusion

Therapy of childhood acute lymphoblastic leukemia should be based on the prognostic factors for each patient. Prognostic factors associated with poor outcome include age over 10 years, mature cell acute lymphoblastic leukemia and central nervous system involvement. The results of this study are in correlation with current literature.Viverrioretre reheben atastra ductum is.

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ANALYSIS OF OUTCOME PREDICTORS IN PATIENTS WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE

ANALIZA PREDIKTORA KLINIČKOG ISHODA KOD PACIJENATA SA SPONTANOM INTRACEREBRALNOM HEMORAGIJOM

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Summary

Introduction. Spontaneous intracerebral hemorrhage is not a monophasic event, but a condition characterized by hematoma expansion with mechanical damage to the surrounding tissue. The development of multiple complications is associated with a high mortality rate of 40%. In order to make therapeutic decisions, it is important to know what factors predict the outcome in these patients. The aim of this study was to evaluate outcome prediction scales in patients with spontaneous intracerebral hemorrhage according to functional outcome at 7 and 30 days after the onset. **Material and Methods**. A three-year retrospective study (2017 - 2019) included 116 patients treated at the Emergency Center, Clinical Center of Vojvodina, Novi Sad, Serbia. The collected data included the National Institutes of Health Stroke Scale, the original intracerebral hemorrhage score, the modified Graeb score and Glasgow coma scale. Demographic data, localization, shape and volume of hematomas, as well as occurrence of intraventricular hemorrhage were compared. **Results**. In the group of 116 patients, male gender was dominant (82%) as well as the age over 65 years (56%); Glasgow coma scale: 1.5 interquartile range = 1 - 2 points, National Institutes of Health Stroke Scale 24, interquartile range = 15 - 32, intracerebral hemorrhage score 3 - 4 (68.1%). Intraventricular hemorrhage was found in 82.3% and oval hematoma in 71.6% of patients. The mortality rate was highest in the first 7 days (41.4%). The 7-day and 30-day mortality was significantly associated with the intracerebral hemorrhage score (p=0.000) and the intracerebral hemorrhage volume (p=0.014). **Conclusion**. Elderly men with known vascular risk factors are prone to spontaneous intracerebral hemorrhage. The intracerebral hemorrhage score and hematoma volume may be the potential indicators of poor outcome in the first 7 days of spontaneous intracerebral hemorrhage.

Key words: Cerebral Hemorrhage; Treatment Outcome; Hematoma; Risk Factors; Predictive Value of Tests; Risk Assessment; Mortality

Sažetak

Uvod. Spontana intracerebralna hemoragija nije monofazni događaj već bolest za koju je karakteristična ekspanzija hematoma uz mehaničko oštećenje okolnog tkiva. Razvoj brojnih komplikacija udružen je sa visokom stopom smrtnosti, od 40%. Za donošenje odluka o terapijskom delovanju, važno je znati koji faktori predviđaju ishod kod ovih pacijenata. Cilj rada bila je procena pojedinih prediktivnih skala kod pacijenata sa spontanom intracerebralnom hemoragijom prema funkcionalnom ishodu nakon sedmog i 30. dana bolesti. **Materijal i metode.** Retrospektivno trogodišnje istraživanje (2017–2019. godine) uključilo je 116 pacijenata lečenih u Urgentnom centru Kliničkog centra Vojvodine, Novi Sad, Srbija. Prikupljeni podaci uključivali su *National Institutes of Health Stroke Scale*, originalni intracerebralni skor (*The original ICH Score*), modifikovanu *Graeb* skor (*The Modified Graeb Score-mGS*) i *Glazgov* koma skalu (*Glasgow Coma Scale-GCS*). Poredili su se demografski podaci, lokalizacija, oblik i volumen hematoma i pojava intraventrikularne hemoragije. **Rezultati.** U grupi od 116 pacijenata, dominirao je muški pol (82%) starosti preko 65 godina (56%). *Glasgow Coma Scale*: 1.5 interkvartilni raspon = 1-2 bodova, *National Institutes of Health Stroke Scale* 24, interkvartilni raspon 15–32, intracerebralni hemoragični skor 3-4 (68,1%). Kod 82,3% zabeležena je intraventrikularna hemoragija, a ovoidni oblik hematoma kod 71,6% pacijenata. Letalitet je bio najveći u prvih sedam dana (41,4%). Sedmodnevni i 30-dnevni mortalitet imali su značajnu udruženost sa intracerebralnim hemoragičnim skorom (p = 0,000) i volumenom (p = 0,014). **Zaključak.** Stariji muškarci sa poznatim vaskularnim faktorima rizika imaju veću sklonost ka spontanoj intracerebralnoj hemoragiji. Određivanje skora intracerebralne hemoragije i volumena hematoma mogu biti potencijalni pokazatelji lošijeg ishoda u prvih sedam dana spontanog intracerebralnog krvarenja.

Ključne reči: cerebralna hemoragija; ishod lečenja; hematom; faktori rizika; prediktivna vrednost testova; procena rizika; mortalitet

Introduction

Non-traumatic spontaneous intracerebral hemorrhage (SICH) accounts for about 10 – 15% of all strokes and has a high mortality rate of approximately 40% after 30 days of the onset [1–4]. Hypertension is the most important risk factor for SICH, especially in elderly people [3]. The most common localizations for intracerebral hemorrhage (ICH) are in the putamen (35 – 50%), lobar regions (30%), thalamus (10 – 15%), pons (5

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Abbreviations

SICH – spontaneous intracerebral hemorrhage
ICH – intracerebral hemorrhage
IVH – intraventricular hemorrhage
CT – computed tomography
NIHSS – National Institutes of Health Stroke Scale
GCS – Glasgow coma scale
mGraeb – modified Graeb

– 12%), caudate nucleus (7%) and cerebellum (5%). Intraventricular hemorrhage (IVH) is a common complication of ICH that results in death in 32 – 43% of cases and it is an independent predictor of poor outcome [4–6]. The ICH is not a monophasic event, but a condition characterized by hematoma expansion as a consequence of continuous bleeding from the primary source with mechanical damage to the surrounding tissue. The volume and shape of hematoma increase the risk for hematoma growth, which is a predictor of poor outcome and mortality [4–8].

In order to make treatment decisions and to establish the prognosis, it is important to know the outcome prediction factors. Several predictive models [9–15] have been developed and evaluated, but in practical work the ICH scale is the most commonly used. In this research, we used several predictive scales to analyze the outcome in SICH.

Material and Methods

In the period from January 2017 to December 2019, a retrospective study included 116 SICH patients hospitalized at the Emergency Department of the University Clinical Center of Vojvodina in Novi Sad, Serbia.

Inclusion criteria included adult patients (≥ 18 years); patients with spontaneous ICH of nontraumatic origin detected on computed tomography (CT) or angiography; patients with previous ICH or stroke. Exclusion criteria included secondary ICH (aneurysms, vascular malformations, cerebral primary and/or secondary tumor, previous trauma, subarachnoid hemorrhage, subdural hematoma, coagulation disorders) and hemorrhagic transformation in patients with acute cerebral ischemia. An informed written consent was required from the patients or their surrogates.

Demographic data, comorbidities, and risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, previous stroke, or ICH) were analyzed. We used the following predictive scales: basal National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma scale (GCS), ICH score, and modified Graeb scale (mGraeb) score.

The NIHSS score is commonly used in patients presenting with acute stroke (either ischemic or hemorrhagic). It consists of 15 items and a total score of 42 points. A score of 0 indicates no clinically relevant neurological abnormality.

The GCS is used to rate the best eye opening response, the best verbal response, and the best motor response. The final GCS score or grade is the sum of these numbers.

The ICH score (0–6) is the sum of individual points assigned to five different variables: GCS score 3–4 (2 points) or 5–12 (1 point); age ≥ 80 years (1 point); infratentorial origin (1 point); ICH volume ≥ 30 mL (1 point); and IVH (1 point) [10].

The second predictive score, mGraeb score, is based on the fourth ventricle (maximum score 4), third (maximum score 4), right and left lateral ventricles (maximum score 4 for each), right and left occipital horns (maximum score 2 for each), and the right and left temporal horns (maximum score 2 for each). An additional score of +1 is given to each compartment if it is expanded beyond normal anatomic limits attributable to clot. The maximum possible score is 32, in which every compartment is filled with blood and expanded. A score of 0 means no intraventricular blood [7, 16].

Non-enhanced CT images of the brain were used to confirm the location of hematoma (supratentorial or infratentorial), a regular hematoma shape, including a roundish or oval hematoma with smooth margin, irregular hematoma shape, including a pleomorphic contour of hematoma, separated hematomas and multicentric hematomas, dimensions and volumes of hematoma and blood penetration into the ventricular system.

The ICH hematoma volume was measured on the initial head CT scan with the use of the ABC/2 method [1]

$V = A \times B \times C \times 1/2$

"V" represents the volume of the hematoma; "A" is the greatest diameter on the largest hemorrhage slice, "B" is the diameter perpendicular to "A", and "C" is the approximate number of axial slices with hemorrhage multiplied by the slice thickness [1, 16, 17]. The presence or absence of IVH was also noted on the initial head CT.

None of the patients underwent surgical intervention.

Statistical package for social sciences IBM 22.0 was used for statistical processing purposes. Data processing started with a descriptive statistical analysis for all variables. In order to determine the association between the scoring systems and the outcome, Pearson's linear correlations were used. To show the statistical significance of the correlations, that is, to show the statistical significance of possible predictor variables (ICH score, mGraeb score, age) and dependent variables (length of stay and outcome) the Student's t-test was used. Multivariate Mann-Whitney U test was used to determine the existence of a statistically significant difference depending on the localization of the hematoma, as well as its size. For easier presentation of results, only the main effects of the variables are presented in the discussion. A "p" value lower than 0.05 was considered statistically significant.

The study design was approved by the Ethics Committee of the Clinical Center of Vojvodina (No: 00-1088/2019).

Table 1. Demographic and clinical characteristics of patients
Tabela 1. *Demografske i kliničke karakteristike pacijenata*

Characteristics/*Karakteristike*	N/*B* (%)
1. Gender/*Pol*	
Male/*Muški*	96 (83%)
Female/*Ženski*	20 (17%)
2. Age/*Starost* ±SD/AS	±13.24/64.41
≤ 50	17 (14.65%)
51 – 64	34 (29.31%)
≥ 65	65 (56.03%)
3. Risk factors/*Faktori rizika*	
Hypertension/*Hipertenzija*	100 (86.2%)
Dyslipidemia/*Dislipidemija*	11 (9.5%)
Diabetes/*Dijabetes*	53 (45.7%)
Atrial fibrillation/*Atrijalna fibrilacija*	22 (19%)
Previous intracerebral hemorrhage/*Prethodna intracerebralna hemoragija*	5 (4.3%)
Previous ischemic stroke/*Prethodni ishemijski moždani udar*	20 (17.2%)
4. Comorbidities/*Komorbiditeti*	
Yes/*Da*	116 (100%)
No/*Ne*	
5. Glasgow Coma Scale (GCS)/*Glazgovska skala kome*	
13 - 15	7 (6%)
9 - 12	51 (44%)
≤ 8	58 (50%)
Median (IQR)	Median 1.5 IQR = 1 - 2
6. Basal NIHSS/*Bazalni NIHSS (median (IQR), ± SD/AM*	Median 24, IQR 15 - 32 ± 10.95/22.98
7. Hospitalization time/*Dužina hospitalizacije, median (IQR), ± SD/AM*	Median 4, IQR 2 - 11 ± 12.28/9.20
8. Mortality/*Mortalitet*	
In the first 24 h/*U toku prva 24 sata*	26 (22.4%)
7 days/*7 dana*	48 (41.4%)
30 days/*30 dana*	13 (11.2%)
90 days/*90 dana*	15 (13%)
Surviving patients/*Preživeli pacijenti*	14 (12%)

Legend: N - number of patients; SD - standard deviation; AM - arithmetic mean IQR - interquartile range; NIHSS - National Institutes of Health Stroke Scale; GCS - Glasgow coma scale
Legenda: B – broj pacijenata; SD – standardna devijacija; AM – aritmetička sredina; IQR – interkvartilni raspon; NIHSS - skala za *moždani udar Nacionalnog instituta* za *zdravlje; GCS – Glazgovska skala kome*

Results

All sociodemographic and clinical characteristics of 116 patients are shown in **Table 1.** In patients with SICH, male gender was dominant (83%) as well as the age over 65 years (41.37%), while the diagnosis was less frequent in slightly younger patients aged from 50 to 64 years (29.31%). Arterial hypertension was registered in 100% of patients, diabetes mellitus in 45.7%, atrial fibrillation in 19%, and dyslipidemia in 9.5% of patients. Of the total number of patients, 17.2% had experienced a previous stroke, and 4.3% had a rehemorrhage.

Table 2 presents the neuroradiological characteristics of hematoma scores obtained by applying the tested scales.

Neuroradiological techniques, like CT, were used to identify the localization of the hematoma; supratentorial localization was found in 82.2% and infratentorial in 17.2% of patients. The most common hematoma localizations were the lobar region (47.2%), followed by basal ganglia (21.6%), thalamus region (14.7%), cerebellum (8.7%) and the brain stem (7.8%). The SICH was slightly more frequent in the right hemisphere (56.1%). The intraventricular extension of hemorrhage was found in 82.8% of patients. Of the total number of patients, in 78.45% the mGraeb score ranged from 1 to 21, while in 5.7% of patients it was over 21. The most common shape of hematoma was oval (71.6%), while pleomorphic (10.3%) and multicentric (7.8%) were less present. Large volume hematomas, over 30 ml, ac-

Table 2. Radiological characteristics and scoring system of intracerebral hematomas
Tabela 2. *Radiološke karakteristike i bodovni sistem intracerebralnih hematoma*

Characteristics/*Karakteristike*	N/*B* (%)
1. Localization/*Lokalizacija*	
Supratentorial/*Supratentorijalno*	96 (82.8%)
Infratentorial/*Infratentorijalno*	20 (17.2%)
Lobar región/*Lobarna regija*	55 (47.4%)
Basal ganglia/*Bazalne ganglije*	25 (21.6%)
Thalamus region/*Talamusna regija*	17 (14.7%)
Cerebelum/*Cerebelum*	10 (8.7%)
Brainstem/*Moždano stablo*	9 (7.8%)
2. Side of intracerebral hemorrhage/*Strana intracerebralnog krvarenja*	
Right hemisphere/*Desna hemisfera*	65 (56.1%)
Left hemisphere/*Leva hemisfera*	51 (44%)
3. Intraventricular hemorrhage/*Intraventrikularno krvarenje*	
Yes/*Da*	96 (82.8%)
No/*Ne*	20 (17.2%)
4. Hematoma shape/*Oblik hematoma*	
Round/*Okrugli*	5 (4.3%)
Oval/*Ovalni*	83 (71.6%)
Separate/*Razuđeni*	7 (6.0%)
Pleomorphic/*Pleomorfni*	12 (10.3%)
Multicentric/*Multicentrični*	9 (7.8%)
5. ICH volume/*ICH zapremina (ml)*	
< 30	52 (44.83%)
≥ 30	64 (52.17%)
6. mGraeb score/*Modifikovani Graeb skor*	
0	19 (16.38%)
1 - 20	91 (78.45%)
≥ 21	6 (5.17%)
7. ICH score/*ICH skor*	
0 - 2	30 (25.9%)
3 - 4	79 (68.1%)
5 - 6	7 (6.0%)

Legend**:** N - number of patients; ICH - intracerebral hemorrhage/*Legenda: B – broj pacijenata; ICH – intracerebralno krvarenje*

Table 3. Comparison of predictors of functional outcome of patients in relation to 7-day and 30-day survival
Tabela 3. *Poređenje prediktora funkcionalnog ishoda kod pacijenata u odnosu na 7-dnevno i 30-dnevno preživljavanje*

Variables/*Varijable*	Total/*Ukupno* N/*B* = 116 Median (IQR) *Srednji IQR*	30 days/*30 dana* N/*B* = 35 Median (IQR) *Srednji IQR*	7 days/*7 dana* N/*B* = 81 Median (IQR) *Srednji IQR*	p/*p*
Hematoma localization/*Lokalizacija hematoma*	1 (1 - 1)	2 (1 - 3)	4 (3 - 4)	.815
Hematoma shape/*Oblik hematoma*	2 (2 - 2)	2 (2 - 2)	2 (2 - 2)	.774
Hemisphere/*Hemisfere*	1 (1 - 2)	1.5 (1 - 2)	1 (1 - 2)	.995
Localization/*Lokalizacija*	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)	.882
ICH score/*ICH skor*	3 (3 - 4)	2 (2 - 3.5)	4 (3 - 4)	**.000**
mGraeb score/*Modifikovani Greab skor*	9.5 (2.75 - 16)	8 (1 - 13)	11.0 (3 - 16.5)	.176
ICH volume/*ICH zapremina*	34 (10.06 -75.27)	15.54 (4.44 -61.32	42.62 (15.5 -80.8)	**.014**

Legend: N - number of patients; ICH - intracerebral hemorrhage; IQR - interquartal range; p - statistical significance
Legenda: B – broj pacijenata; ICH – intracerebralno krvarenje; IQR – interkvartalni raspon; p – statistička značajnost

counted for more than 50%. The ICH score calculation is of great importance for assessing the functional outcome. The ICH scores from 3 to 4 were recorded in 68.1% of patients, from 0 to 2 in 25.9%, and scores from 5 to 6 in 6% of patients.

Of all the examined variables, the ICH score and ICH volume were the most significant in the assessment of the functional outcome in the first 7 and 30 days **(Table 3)**.

Using the Mann-Whitney U test for all variables, hematoma volume and ICH score were separated by their statistical significance in the functional outcome: ICH volume had a median interquartile range (IQR) of 34 (10,06 - 75,27), while in deceased patients this value was 42.62 (15.5 - 80.8) after 7 days, and 15.54 (4.44 - 61.32) after 30 days.

The median ICH score, as one of the leading scoring systems in patients with SICH, was 3 (3 – 4), the recorded median IQR in the deceased was 4 (3 – 4) in the first 7 days, provided that the scores in the deceased during 30 days were 2 (2 – 3.5). These data suggest that ICH score and ICH volume may be potential indicators of poorer outcome in the first 7 days of SICH.

Discussion

Our results show that SICH primarily affects the elderly population and it is most common in men over the age of 65 years. Hypertension, followed by diabetes mellitus and atrial fibrillation are the main risk factors for SICH [18–20].

One of the unfavorable prognostic factors is hematoma expansion, which may be affected by its shape. Compared to regular hematoma shape, the irregular shape has been related to a higher risk of hematoma growth [21], which is a predictor of poor outcome [22]. In our study, oval shaped hematomas were most common, which was not a significant predictor of an adverse outcome associated with irregular shape with heterogeneous density [23]. Other factors, such as hematoma volume, have significantly more adverse effects. More than half of our patients had a hematoma volume over 30 ml with consequently significant poor prognostic impact on the early outcome of SICH. Other authors have similar conclusions: higher volume and size of hematomas on admission significantly correlate with early mortality, in the first 30 days [24–26]. Furthermore, advanced age increases the risk of ICH, which is associated with vascular changes that occur with aging, as well as hypertension [27].

Although ICH score is widely used as a predictive tool for mortality at 30 days after hemorrhagic stroke, Hemphill at al. claim that ICH score "should not be used as a singular indicator of prognosis". Therefore, the authors of this study perceived ICH score as a possible indicator of unfavorable outcome of SICH [4].

In our study, the ICH score ranged from 3 to 4 in more than two-thirds of patients, especially in those with high mortality in the first 7 days of the disease. In the group with 30-day mortality, the ICH score was twice lower, which confirms that some other factors (maybe prognostic types) affect late mortality. Hemphill et al. [10] also concluded that the use of the ICH score is simple and practical, and that it can very well predict the risk of mortality from the moment of patient admission to the hospital. In their study, each increase in ICH scores significantly correlated with a progressive increase in 30-day mortality [10]. The ICH score ≤ 2 is thought to predict 30-day mortality rate of patients with sensitivity and specificity of 63% and 87%, respectively [28].

The presence and severity of IVH is measured by mGraeb score. The process in which ICH passes into the ventricular system is dynamic and difficult to predict, especially during the first few hours of SICH. Secondary IVH, as a complication of SICH, occurs in $\approx$ 40% of patients, where the following rule applies: the larger the ICH hematoma, the more likely IVH is to occur [29]. More than 80% of our patients had IVH, but this does not define the mGraeb score as one of the significant predictors of survival in the first 7 and 30 days of the disease. While some research suggests that IVH extension severity, measured as a continuous variable by the mGraeb scale, is associated with poor outcome in SICH [7, 30, 31], others show that lower IVH severity (Graeb scores 1 - 4) has similar outcome like in patients without IVH [32, 33], which can apply to our study. Finding the precise volumetric scale for measuring IVH severity and predicting poor outcome following ICH, points to the necessity of defining radiological, clinical and therapeutic procedures in SICH [34].

Although in most cases patients were treated immediately after acute SICH, this study confirmed a higher lethal outcome in 2/3 of patients during the first 7 days, while the number of adverse outcomes increases to a total of 74% in 30 days, if the time interval is observed.

An increased NIHSS score on admission has an unfavorable impact on ICH outcomes [35]. A NIHSS score greater than 20 usually indicates severe paralysis with impaired consciousness. In our study, basal NIHSS score was very high (median 24) and half of the patients had low GCS. Although we did not investigate the association of NIHSS with mortality (GCS is included in ICH score), this data only confirms the already known devastating characteristic of SICH.

The limited therapeutic modalities for patients with SICH may be associated with increased mortality rates in the early and late period of the disease. These modalities should be based on roadmaps that may provide a chance for recovery: conservative treatment focused on acute reduction and control of blood pressure with a reduction in systolic blood pressure to 130 – 150 mmHg may play a role in reducing ICH [36]; consideration of surgical hematoma evacuation, decompressive hemicraniectomy, or external ventricular drain, diminish the effect of elevated intracranial pressure; ultra-early hemostatic therapy has been shown to reduce ICH growth in 2 studies, using recombinant activated factor VII administered within 4 hours of the onset [23, 37]. It remains to be determined whether recombinant activated factor VII may be useful in a

particular subset of patients with ICH, whether or not they are taking oral anticoagulant therapy. Currently, its benefits remain unproven [4].

The major limitation of this study is being retrospective in nature so it has limited analysis, mutual comparison, and influence on the outcome of other predictive scales. Also, most patients had a control CT in the first 24 – 48 h, which were not used in the analysis. This limited the monitoring of the influence of radiological findings on the possible outcome of SICH. We assume that larger sample size, linking hematoma growth with mortality in a defined period of time, and influence of other clinical and radiological signs on functional outcome of SICH, could partially help in trying to answer the question which predictive scale is the most accurate. Until then, "the ICH score is primarily used as a clinical grading scale and communication tool. It is not meant to provide prognostic information, and should not be used as a primary means to predict the outcomes of patients with ICH" [14].

Conclusion

Elderly men with known vascular risk factors are more prone to spontaneous intracerebral hemorrhage. Calculation of the intracerebral hemorrhage score and hematoma volume is a quick and easy way to assess the possible clinical outcome in the first 7 and 30 days of the disease. Despite several existing predictive outcome models for intracerebral hemorrhage, a standard clinical assessment scale does not exist. However, using the above scales may provide a more effective, standardized, and integrated therapeutic approach to patients with spontaneous intracerebral hemorrhage.

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ANALYSIS OF THE CIRCADIAN RHYTHM, SLEEP AND REST IN THE WORKING POPULATION

ANALIZA CIRKADIJALNOG RITMA, SNA I ODMORA RADNO AKTIVNE POPULACIJE

Andrea MIRKOVIĆ[1] and Nikola SAVIĆ[2, 3]

Summary

Introduction. Circadian rhythm, sleep and rest are of great importance for the proper functioning of the body. They have an impact on numerous organ functions and human health in general. The aim of this study was to analyze the circadian rhythm, sleep and rest associated with health in the working population. **Material and Methods.** The research was designed as a cross-sectional study. A questionnaire was created as a research instrument for the working population who used the services of the Eye Clinic "Etiko". The study included a total of 110 respondents. Participation in the study was voluntary and anonymous. **Results.** It was found that there are statistically significant differences between the frequency of use of digital devices and sleep quality among the respondents. A large number of respondents (41.2%) who use digital devices every day before bedtime rated their quality of sleep as poor. Most of the respondents who work night shifts rated their sleep as unsatisfactory. **Conclusion.** Analysis of circadian rhythm, sleep and rest is extremely important for the evaluation of the overall health potential of the working population.

Key words: Circadian Rhythm; Sleep; Rest; Work; Sleep Quality; Quality of Life; Surveys and Questionnaires; Shift Work Schedule; Digital Technology

Sažetak

Uvod. Cirkadijalni ritam, san i odmor izuzetno su važni za pravilno funkcionisanje našeg organizma. Imaju uticaj na brojne funkcije organa i kompletno zdravlje individue. Cilj rada bio je analiza cirkadijalnog ritma, sna i odmora u vezi sa zdravljem, u populaciji radno aktivnog stanovništva. **Materijal i metode.** Istraživanje je sprovedeno u obliku studije preseka. Kao instrument istraživanja napravljen je upitnik za radno aktivno stanovništvo, koje je koristilo zdravstvene usluge očne ambulante Etiko. Istraživanje je obuhvatilo uzorak od 110 ispitanika. Učešće u istraživanju bilo je dobrovoljno i anonimno. **Rezultati.** Utvrđeno je da postoje statistički značajne razlike između učestalosti korišćenja digitalnih uređaja i kvaliteta sna ispitanika. Veliki broj ispitanika (41,2%) koji koriste digitalne uređaje svakodnevno pred spavanje, ocenilo je kvalitet svog sna kao loš. Najveći broj ispitanika, koji radi noćne smene, ocenilo je svoj san kao nezadovoljavajući. **Zaključak.** Analiza cirkadijalnog ritma, sna i odmora, od izuzetnog je značaja za evaluaciju ukupnog zdravstvenog potencijala radno aktivne populacije.

Ključne reči: cirkadijalni ritam; spavanje; odmor; rad; kvalitet sna; kvalitet života; ankete i upitnici; rad u smenama; digitalni uređaji

Introduction

Sleep is of fundamental importance for the functioning of the human body. It affects our psychological abilities, social relationships, and health status. Sleep disorders are a group of conditions that affect the ability to sleep regularly, thus causing significant damage to the social and professional functions of the person affected by these disorders [1–3]. Sleep disorders are a broad category of disorders that involve all types of dysfunctions that include sleep, difficulty falling asleep at night, poor sleep quality, waking up too early, circadian rhythm disorders, and many others. Studies have shown that melatonin synchronizes circadian rhythms and improves the onset, duration and quality of sleep, participates in oxidation, circadian rhythm maintenance, and regulates neuronal survival [1–11]. In children, blue light exposure has been shown to affect sleep, causing sleep problems and sleep disorders [1–9]. Atypical work schedules are causing reduced sleep leading to drowsiness, fatigue, decreased cognitive performance and health problems in people who work night shifts [12]. Melatonin secretion is highest in the middle of the night, between 2 – 4 ante meridiem (A. M. - before noon) during the rapid eye movement (REM) phase [4, 5]. Normal sleep patterns are subject to changes during aging, they include changes in sleep patterns and waking up at night. The modern way of life is associated with increased exposure to artificial light and shifting the light spectrum towards an artificial light source containing a strong blue component, reduced exposure to daylight, late meals, reduced sleep, potential shift work, exchanging day and night, and frequent intercontinental zone changes. Exposure to blue light during the day is important for suppressing the secretion of melatonin, which plays a key role in the circadian rhythm. Chronic exposure to low-intensity blue light just before bedtime can have serious implications for sleep quality and the circadian phase [2–5]. In modern society, many people, including students, suffer to some degree from chronological

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Abbreviations
REM – rapid eye movement

disorders, because the accumulated lack of sleep affects social interactions [13]. The vast majority of them are not even aware of it. The American Academy of Sleep and Meditation also pointed out and specified conditions that are affected by wakefulness and sleep disorders during the twenty-four-hour cycle. According to their research, about 25% of the population has an inadequate circadian rhythm, which could have epidemic proportions in modern society if the diagnostic guidelines were used accurately. Shift work also affects the circadian rhythm [9]. Approximately 20% of shift workers in the western world suffer from some sleep disorder. Night shift workers remain awake and active during the period when their psychophysiological functions are set to inactivity. Due to the changed ratio of the cycle of wakefulness/sleep, feeding, noise, circadian rhythm synchronization disorders with external conditions occur: metabolic diseases (obesity and diabetes), depression, bipolar and seasonal affective diseases, cardiovascular diseases, thrombosis or cancer, as well as modulation of C-reactive protein (CRP). A mild but chronic form of this disorder can be far more common than official figures really show.

The aim of this research was to examine the sleep habits of the working population, their blue light exposure before bedtime, as well as how they assess their quality of sleep.

Material and Methods

The research was designed as a cross-sectional study. A questionnaire was created as a research instrument for the working population to assess their quality of sleep, circadian rhythm, and rest. The questionnaire had two parts: the first part examined the socio-demographic characteristics of the respondents and the second part was in the form of an assessment scale. The research included a total of 110 respondents who used the services of the

Tabele 1. Sociodemographic characteristics of the respondents
Tabela 1. *Sociodemografske karakteristike ispitanika*

Variables/*Varijable*	Number/*Broj*	%
Gender/*Pol*		
Male/*Muški*	41	37.3%
Female/*Ženski*	69	62.7%
Age/*Starost*		
> 25	4	3.6%
25 - 30	9	8.2%
30 - 35	16	14.5%
35 - 40	36	32.7%
40 - 45	35	31.8%
45 - 50	6	5.5%
< 50	4	3.6%
Education level/*Nivo obrazovanja*		
Primary school/*Osnovna škola*	2	1.8%
High school/*Srednja škola*	21	19.1%
College/*Fakultet*	50	45.5%
MSc/*Magistratura*	29	26.4%
PhD/*Doktorat*	8	7.3%
Place of living/*Mesto stanovanja*		
Rural environment/*Seoska sredina*	27	24.5%
Urban environment/*Gradska sredina*	83	75.5%
Shift work/*Rad u smenama*		
Yes/*Da*	55	50%
No/*Ne*	44	40%
Sometimes/*Nekada*	11	10%
Night shift/*Noćne smene*		
Yes/*Da*	23	20.9%
No/*Ne*	87	79.1%
Night shifts per month/*Noćne smene u toku meseca*		
0	87	71.9%
< 4	13	11.8%
> 4	7	6.4%
Only night shifts/*Samo noćne smene*	3	2.7%

Tabele 2. Analysis of circadian rhythm, sleep and rest in the working population
Tabela 2. *Analiza cirkadijalnog ritma, sna i odmora kod radno aktivnog stanovništva*

Quality of sleep/*Kvalitet spavanja*							
Variables *Varijable*	Bad *Loš*	Unsatisfactory *Nezadovoljavajući*	Satisfactory *Zadovoljavajući*	Good *Dobar*	Perfect *Odličan*	N *Broj*	p/*p*
Use of digital devices before bedtime/*Korišćenje digitalnih uređaja pred spavanje*							
Often/*Često*	6	4	5	3	8	26	0.006
Rarely/*Retko*	11	6	6	5	4	32	
Daly/*Svakodnevno*	21	16	13	1	0	51	
No/*Ne*	0	0	1	0	0	1	
Night shifts/*Noćne smene*							
Yes/*Da*	14	6	2	0	1	23	0.018
No/*Ne*	24	20	23	9	11	87	
Bedtime/*Vreme odlaska na spavanje*							
> 22 h	2	5	2	0	0	9	0.058
22 - 23 h	2	5	4	1	2	14	
23 - 00 h	10	7	1	4	5	27	
< 00 h	24	9	18	4	5	60	
Sleeping habits/*Navike spavanja*							
Sleeping in the bedroom *Spava u spavaćoj sobi*	27	24	21	8	6	86	0.28
Falls asleep in the living room *Zaspi u dnevnoj sobi*	11	2	4	1	6	24	
Place of living and sleep quality/*Mesto stanovanja i kvalitet spavanja*							
Rural environment/*Seoska sredina*	8	7	6	3	3	27	0.068
Urban environment/*Gradska sredina*	30	19	19	6	9	83	
Mood on waking/*Raspoloženje pri buđenju*							
Rested/*Odmoran*	4	2	6	4	5	21	0.000
Grumpy/*Mrzovoljan*	11	16	7	2	0	36	
Tired/*Umoran*	22	7	11	1	0	41	
Ready for the daily tasks *Spreman za dnevne obaveze*	1	1	1	2	7	12	

Eye Clinic "Etiko" in the period from September to October 2021. Participation in the study was voluntary and anonymous. The research was approved by the competent authorities of the institution. Prior to the start of the research, the respondents received all the necessary information about the study orally and in writing. Respondents were given instructions regarding the proper completion of the questionnaire. The researchers collected the data in person. Statistical data processing included methods of descriptive and inferential statistics and data were tested by χ^2 test. The data were analyzed using the Statistical package for social sciences for Windows. The obtained results are shown in tables and graphs.

Results

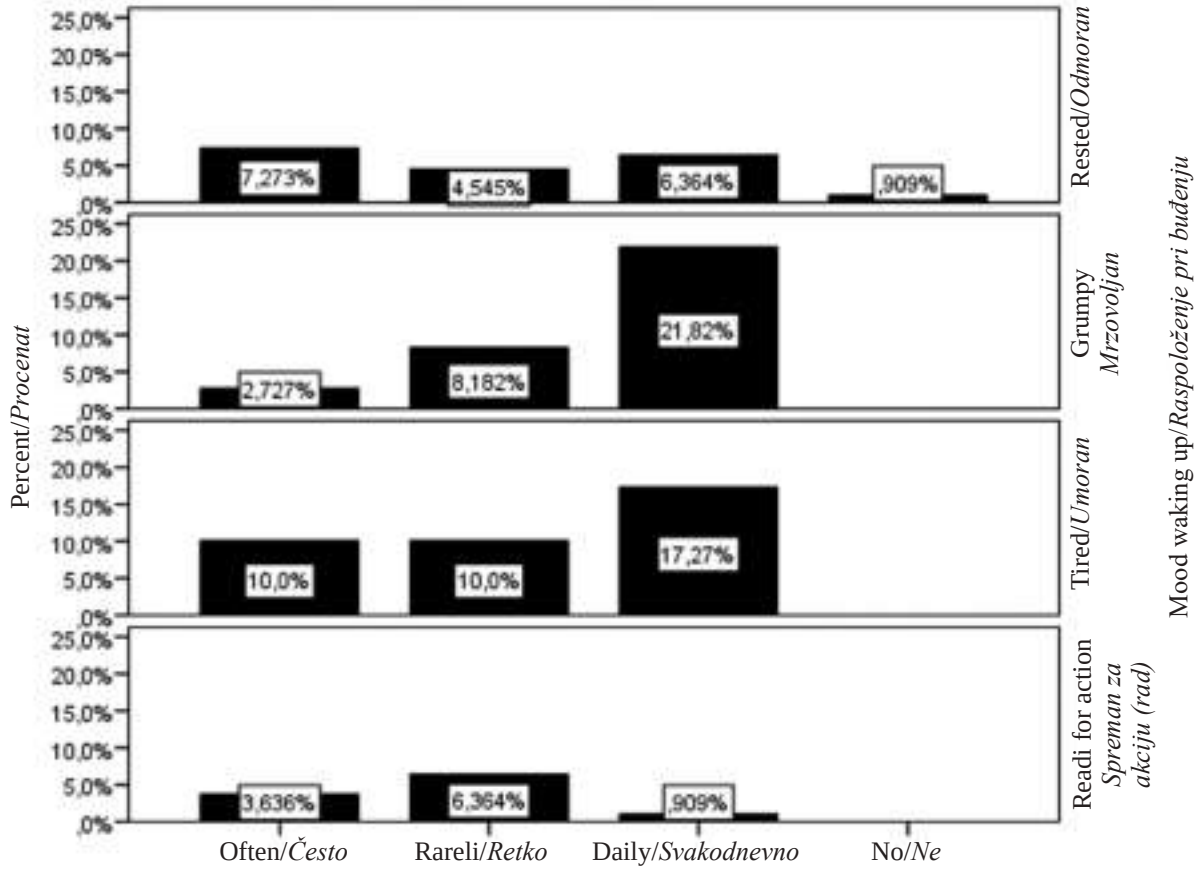
The most important sociodemographic characteristics of the respondents are given in **Table 1**. The following part of the results shows the analysis of circadian rhythm, sleep and rest in the working population.

The results in **Table 2** show the self-reported sleep quality of the respondents in relation to the given variables.

Distribution of mood when waking up and using digital devices before going to bed is shown in **Graph 1.**

Discussion

It was found that there are statistically significant differences between the frequency of use of digital devices and quality of sleep among the respondents. Statistically significant differences were found in the variable related to using digital devices on daily basis, i.e. as many as 41.2% of the respondents used digital devices every day before bedtime. They rated their quality of sleep as poor, and 27.5% rated it as unsatisfactory. Similar results were found by Good et al., who studied sleep in the United States military personnel; their research showed that incandescent lighting reduces sleep quality compared to natural daylight, thus reducing the amount of melatonin released during the REM phase and that exposure to strong light during the night encourages alertness [11]. Stothard et al., studied circadian rhythms and the natural change of the day and night cycle and found that increased exposure to artificial light at night leads to late circadian cycles and sleep disorders that have far-reaching consequences on the



Graph 1. Mood on waking in relation to the use of digital devices before bedtime
Grafikon 1. *Distribucija raspoloženja pri buđenju i upotreba digitalnih uređaja pred odalazak na spavanje*

human mental and physical health [14]. A study conducted by Le Bougeois and colleagues in Colorado examined the digital media use in adolescents and found harmful effects of digital devices on healthy sleep patterns, manifesting with delayed sleep time and reduced sleep duration in adolescents [15]. Philips and colleagues researched sleep habits and academic performance among student population; they found irregular sleep patterns, delayed circadian rhythms, and lower academic achievement due to exposure to night light [16].

Statistically significant differences were observed in the variables of night shift and quality of sleep. Persons who reported working night shifts rated the quality of their sleep as poor or unsatisfactory. A total of 69.9% of respondents who work night shifts characterized their sleep as bad, which is almost twice as high as in the control group of respondents working no night shifts, since only 31% of them rated their quality sleep as bad. Similar results are found in a number of studies investigating sleep disorders in shift workers [11, 17–18]. Touitou and colleagues from the Fondation Ophtalmologique A. Rothschild, Unité de Chronobiologie in France, claim that workers who work night shifts have 2 to 4 hours less sleep on daily basis, which results in sleep deprivation in the long run. A study by Gansesan et al. on shift work, sleep and performance in health workers found that sleep was most limited during consecutive night shifts and that alertness and performance remained most impaired during this time due to lack of circadian adaptation. They found that in shift workers, who work early day shifts, especially immediately after night shifts, may have similar patterns of limited sleep and rest rhythm [18]. The time for sleep also significantly affects the quality of sleep; statistically significant differences were found in the variable going to sleep after midnight since as many as 40.7% of respondents who go to bed after midnight rated their quality of sleep as poor, which was confirmed by previous studies [11–18]. Examining the sleep habits, we found no significant differences in the quality of sleep between the group that sleeps only in the bedroom and those who sleep in the living room, although our assumption was that respondents who fall asleep in the living room will assess the quality of their sleep as bad or unsatisfactory. We started from the hypothesis that respondents living in rural areas have better sleep quality than respondents living in the city, but the results showed that there are no statistically significant differences in these two categories in terms of sleep

quality, so we assume that the reason is the availability of digital devices in rural areas. The last variable we tested was mood on waking in relation to sleep quality. Respondents who wake up tired in the morning rated their quality of sleep as bad and unsatisfactory and we were interested if the use of digital devices before going to bed affected the mood on waking. The results showed statistically significant differences in this variable since as many as 47.6% of respondents who used digital devices every day before going to bed were grumpy in the morning, while 37.25% of them stated that they were tired in the morning, which is similar to the results of other studies [13, 18–20].

Conclusion

Exposure to electronic devices just before going to bed correlates with poor sleep quality and leads to circadian rhythm disorders and negatively affects mood on waking. Night shifts disrupt the quality of sleep and circadian rhythm. This suggests that employed people need more extensive information and education on the negative effects of disrupted circadian rhythm on their health as well as preventive activities that would improve the quality of sleep in the working population.

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CASE REPORTS
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Case report
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CEREBRAL VENOUS SINUS THROMBOSIS ASSOCIATED WITH OLIGOSYMPTOMATIC COVID-19 INFECTION – A CASE REPORT

TROMBOZA MOŽDANIH VENSKIH SINUSA POVEZANA SA OLIGOSIMPTOMATSKOM COVID–19 INFEKCIJOM – PRIKAZ SLUČAJA

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Summary

Introduction. Severe acute respiratory syndrome coronavirus 2 infection-induced coagulopathy may cause various thrombotic complications, such as cerebral venous sinus thrombosis, a less common type of stroke with a variable clinical presentation and high mortality rate. The objective of this paper was to identify clinical, laboratory and radiological characteristics, risk factors, therapeutic modalities, and outcome of a young patient with cerebral venous sinus thrombosis associated with oligosymptomatic coronavirus disease 2019 infection. **Case Report.** We present a case of a 32-year-old woman suffering from a stroke due to cerebral venous sinus thrombosis associated with a mild form of coronavirus disease 2019 infection. The patient was without a history of previous diseases and risk factors for cerebral venous sinus thrombosis. Two weeks before the cerebrovascular incident, the patient presented with oligosymptomatic coronavirus disease 2019 infection associated with headache. Laboratory findings were characterized by two conditions: hypercoagulability and systemic inflammation. Bilateral thalamic and right frontal hemorrhagic venous infarctions with superior sagittal and straight sinus thrombosis and thrombosis of the vein of Galen were established by magnetic resonance imaging of the head. The main therapeutic approaches included anticoagulant therapy, therapeutic protocol for coronavirus disease 2019 infection, seizure control therapy and intracranial hypertension management. The treatment outcome was good, with minimal residual symptoms. **Conclusion.** Physicians should always consider the high risk of cerebral venous sinus thrombosis with nonspecific neurological symptoms in patients with mild coronavirus disease 2019 infection in order to provide early diagnosis, the most effective individually tailored treatment, and to prevent complications.

Key words: Sinus Thrombosis, Intracranial; Venous Thrombosis; COVID-19; Severe Acute Respiratory Syndrome; Risk Factors; Diagnosis; Signs and Symptoms; Stroke; Blood Coagulation Disorders

Sažetak

Uvod. Koagulopatija indukovana infekcijom koronavirusom 2, sa teškim akutnim respiratornim sindromom, može dovesti do različitih trombotskih komplikacija kao što je tromboza moždanih venskih sinusa, redak tip moždanog udara sa varijabilnom kliničkom prezentacijom i visokom stopom mortaliteta. Cilj rada bio je identifikovati kliničku, laboratorijsku i radiološku prezentaciju, faktore rizika, terapijske modalitete i ishod lečenja kod mlade pacijentkinje obolele od tromboze moždanih venskih sinusa povezane sa oligosimptomatskom COVID-19 infekcijom. **Prikaz slučaja.** Prikaz slučaja 32-godišnje žene obolele od moždanog udara usled tromboze moždanih venskih sinusa, udruženog sa blagom formom infekcije COVID-19. Pacijentinja je bila bez značajnih prethodnih oboljenja i bez faktora rizika za trombozu moždanih venskih sinusa. Dve nedelje od cerebrovaskularnog incidenta prethodila je oligosimptomatska klinička slika infekcije COVID-19 praćena glavoboljom. Laboratorijski nalazi bili su karakteristični za dva stanja: hiperkoagulabilno i stanje sistemske inflamacije. Magnetnom rezonancijom glave utvrđeni su bitalamički i desni frontalni hemoragični venski infarkti sa trombozom gornjeg sagitalnog i ravnog sinusa, kao i Galenove vene. Osnovni terapijski pristup u lečenju predstavljale su antikoagulantna terapija u terapijskim dozama, terapijski protokol lečenja infekcije COVID-19, antikonvulzivna terapija i terapija povećanog intrakranijalnog pritiska. Ishod lečenja bio je dobar, sa minimalnim rezudualnim simptomima. **Zaključak.** Lekari bi uvek trebalo da uzmu u obzir mogućnost pojave tromboze moždanih venskih sinusa sa nespecifičnim neurološkim simptomima kod pacijenata i sa blagom infekcijom COVID-19 kako bi se omogućila rana dijagnoza oboljenja, primena najefikasnijeg individualno prilagođenog lečenja i sprečile komplikacije bolesti.

Ključne reči: intrakranijalna tromboza venskih sinusa; venska tromboza; covid-19; teški akutni respiratorni sindrom; faktori rizika; dijagnoza; znaci i simptomi; moždani udar; koagulopatije

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Abbreviations

ICP	– intracranial pressure
SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
CVST	– cerebral venous sinus thrombosis
COVID-19	– coronavirus disease 2019
MRI	– magnetic resonance imaging
LMWH	– low molecular-weight heparin

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease (< 1%) that is caused by partial or complete occlusion of dural venous sinuses and/or cerebral veins. It is mostly found in young female adults (< 50 years old) [1]. The predisposing factors for CVST are numerous, but CVST associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a less known entity with no identifiable risk factors [2]. The coronavius infection induces hypercoagulation with elevated D-dimer, fibrinogen level, fibrin/fibrinogen degradation products, antiphospholipid antibodies and thrombocytopenia, which increases the risk of thrombus formation within dural venous sinuses and/or cerebral veins [2]. The clinical presentation varies, depending on the affected venous sinus and/or cerebral veins, presence of raised intracranial pressure (ICP) or extensive parenchymal damage. Management of CVST is based on early diagnosis with detection of thrombotic process, along with urgent conservative and endovascular treatment [3, 4]. Up to 80% of patients have a good outcome with complete recovery. However, the outcome of a small proportion of patients (~13%) is poor (death or severe disability) [1, 2].

Case Report

A 32-year-old woman with no significant comorbidities and no major risk factors for CVST was admitted to our emergency department with sudden episode of new onset seizures, decreased level of consciousness and focal neurologic deficit (left hemiparesis). The symptoms were subacute (> 48 hours to 30 days) while CVST occurred 14 days after clinical presentation of coronavirus disease 2019 (COVID-19) symptoms. Later, the patient reported that prior to admission she had a mild cough with low grade fever and mild headaches for over 2 weeks. The headaches were described as diffuse and progressive. On admission, her body temperature was 37.3 °C, blood pressure 135/80 mmHg, heart rate 73/min, respiratory rate 20/min, oxygen saturation 98%, and her body mass index was 20.2. Initial neurological examination revealed generalized tonic-clonic seizures, decreased level of consciousness, visual disturbance (altered field of vision), focal neurologic deficit (left hemiparesis) and 7th cranial nerve palsy **(Table 1)**. Clinical presentation of COVID-19 infection at the time of admission was classified as mild according to the World Health Organization guidelines [5].

Magnetic resonance imaging (MRI) of the brain showed bilateral thalamic and right frontal hemorrhagic venous infarctions with superior sagittal and straight sinus thrombosis and thrombosis of the vein of Galen **(Figure 1)**.

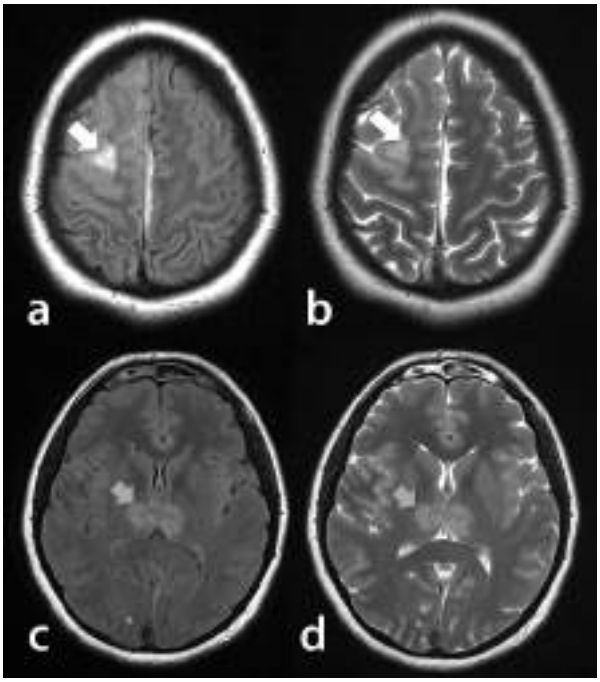

Figure 1. Magnetic resonance imaging of the brain: Axial FLAIR (a) and T2W (b) images showing subcortical hyperintense right frontal lesion (yellow arrow) corresponding to venous infarction. Axial FLAIR (c) and T2W (c) images presenting bilateral thalamic infarction (red arrow) and thrombosis of superior sagittal sinus (blue arrow)
Slika 1. *Magnetna rezonancija mozga: Aksijalni FLAIR (a) i T2W (b) slike koje prikazuju subkortikalnu hiperintenzivnu desnu frontalnu leziju (žuta strelica) koja odgovara venskom infarktu. Aksijalni FLAIR (c) i T2W (c) slike koje prikazuju bilateralni talamički infarkt (crvena strelica) i trombozu gornjeg sagitalnog sinusa (plava strelica)*

There were multifocal ground-glass opacities throughout the right lung on chest computed tomography images.

The reverse-transcriptase-polymerase-chain-reaction assay was positive for COVID-19. Inflammatory biomarkers such as C-reactive protein, erythrocyte sedimentation rate, serum ferritin and lactate dehydrogenase were moderately elevated. D-dimer values were significantly elevated. Values of the coagulation studies: activated partial thromboplastin time, prothrombin time, international normalized ratio and platelets were within normal limits **(Table 1)**.

The basic therapeutic approach in the treatment of CVST is shown in **Table 1**. In the further course of hospitalization, the patient's general condition has improved, she was hemodynamically stable and respiratory sufficient. The evaluation of the neurological status showed significant improvement and the patient was discharged on day 17. The treatment outcome was good, with minimal residual symptoms (Modified Rankin Scale for Neurologic Disability = 1).

Table 1. Demographic and clinical characteristics and laboratory findings
Tabela 1. *Demografske i kliničke karakteristike i laboratorijski nalazi*

Patient characteristics/*Karakteristike pacijenta*	
Demography/*Demografija*	
Sex/*Pol*	Female/*Žensko*
Age (years)/*Starost (godine*)	32
Body mass index/*Indeks telesne mase*	20.2
Comorbidities/*Komorbiditeti*	No/*Ne*
Risk factors for CVST/*Faktori rizika za CVST*	No/*Ne*
Severity of COVID-19 infection *Težina infekcije COVID-19*	Mild/*Blaga*
Clinical presentation *Klinička prezentacija*	Generalized tonic-clonic seizures Consciousness disorders Visual disturbance Focal neurologic deficit (left hemiparesis) 7th cranial nerve palsy *Generalizovani toničko-klonički napadi* *Poremećaj svesti* *Poremećaj vida* *Fokalni neurološki deficit (levostrana hemipareza)* *Paraliza VII kranijalnog živca*
Localization of CVST (MRI) *Lokalizacija CVST (MRI)*	Superior sagittal and straight sinuses, vein of Galen *Gornji sagitalni sinus, ravni sinus, Galenova vena*
Brain lesion (MRI) *Lezija mozga (MRI)*	Bilateral thalamic and right frontal hemorrhagic venous infarctions/*Bilateralni talamički i desni frontalni hemoragični venski infarkt*
Chest computed tomography *Kompjuterska tomografija grudnog koša*	Pulmonary ground glass opacities (right lung) *Zamućenja tipa "brušenog stakla" (desno plućno krilo)*
Laboratory findings/*Laboratorijski nalazi*	
White blood cell count/*Broj belih krvnih zrnaca*	6.9
Erythrocyte sedimentation rate (mm/hr) *Sedimentacija eritrocita* (mm/hr)	37
C-reactive protein (mg/L)/*C-reaktivni protein (mg/L)*	48.8
Interleukin-6/*Interleukin-6*	20.9
Procalcitonin (ng/mL)/*Prokalcitonin (ng/mL)*	0.02
Lactate dehydrogenase, serum (U/L) *Laktat dehidrogenaza, serum (U/L)*	291
Ferritin, serum (ng/mL)/*Feritin, serum (ng/mL)*	172
D-dimer assay, quantitative (ng/L) *Analiza D-dimera, kvantitativno (ng/L)*	2850
International normalized ratio - before anticoagulant therapy/*Internacionalni normalizovani odnos - pre antikoagulantne terapije*	1.20
Activated partial thromboplastin time (s) *Aktivirano parcijalno tromboplastinsko vreme (s)*	29.4
Platelets/*Trombociti*	305
Thrombin time assay (s)/*Analiza trombinskog vremena (s)*	21.8
Fibrinogen (mg/dl)*Fibrinogen (mg/dl)*	434
Alanine Aminotransferase Test (IU/L) *Alanin aminotransferaza test (IU/L)*	61
Aspartate Aminotransferase Test (IU/L) *Test aspartat aminotransferaze (IU/L)*	42
Treatment/*Lečenje*	
Anticoagulant therapy *Antikoagulantna terapija*	Low molecular-weight heparin *Heparini niske molekularne težine*

Treatment of COVID-19 infection *Lečenje infekcije COVID-19*	World Health Organization: COVID-19 Clinical Management: Living guidance/*Svetska zdravstvena organizacija: Klinički menadžment COVID-19: Praktični vodič*
Control of seizures/*Kontrola epileptičnih napada*	Antiepileptic drugs/*Antiepileptički lekovi*
Intracranial hypertension management *Lečenje intrakranijalne hipertenzije*	Osmotic therapy (mannitol), Hyperventilation (PCO_2 30–35 mmHg), Elevating the head of the bed *Osmotska terapija (manitol), hiperventilacija (PCO_2 30-35 mmHg), Podizanje uzglavlja kreveta*
Outcome (Modified Rankin Scale for Neurologic Disability)/*Ishod (Modifikovana Rankinova skala za neurološki invaliditet)*	mRS = 1

Legend/*Legenda*: CVST - cerebral venous sinus thrombosis/*CVST - Tromboza moždanih venskih sinusa;* MRI – magnetic resonance imaging/*MRI – magnetna rezonacija*

Discussion

COVID-19-induced CVST is 30 to 60 times more frequent compared to non-COVID-19 population [6]. The CSVT is more common in women than in men (83.3%) [7]. It occurs predominantly in young population without common risk factors for CVST [1].

Clinical presentation of CVST is nonspecific. It is based on localization/number of affected brain sinuses and veins, collateral venous network and brain parenchymal damage. The onset of symptoms is acute to subacute in about 80% of patients with CVST. Severity of COVID-19 infection is not closely related to the severity of the clinical presentation of CVST [8].

Superior sagittal sinus and transverse sinus are most commonly affected by the thrombotic process. Multiple vessel thrombosis is very common [2]. "Deep" venous system thrombosis has poor prognosis and high mortality [9]. The COVID-19 is an underlying cause of a systemic inflammatory reaction, confirmed by data on high levels of inflammatory biomarkers. Extremely elevated D-dimer is associated with a systemic prothrombotic state [10].

Treatment of CVST should be aimed at controlling the thrombotic process using anticoagulant therapy/endovascular procedures, treatment of the underlying cause (COVID-19 infection) and identified risk factors, seizure control therapy and treatment of intracranial hypertension. Low molecular-weight heparins (LMWH) have shown better effectiveness compared to unfractionated heparins in the prevention and progression of the thrombotic process with a lower risk of bleeding complications [11, 12]. After initial treatment with LMWH, long-term administration of oral anticoagulant therapy should be used. Management of elevated ICP includes osmotic therapy (mannitol), hyperventilation (PCO2 30–35 mmHg) and head elevation [9].

Indications for endovascular treatment (endovascular thrombolysis or mechanical thrombectomy) are progression of the thrombotic process and clinical progression despite the use of anticoagulant therapy [2, 9]. Antiepileptics are used to control seizures and should not be used for prophylactic purposes [13].

The mortality rate (20%) is significantly higher than in non-COVID-19 patients with CVST (2 – 8%). Predictive factors of poor prognosis include older age (> 50 years old), male sex, coma, mental status disorder, hemorrhage on admission computed tomography scan, status epilepticus, deep CVST thrombosis, involvement of multiple venous sinuses and severe to critical form of COVID-19 infection. Most patients have a good prognosis (Modified Rankin Scale for Neurologic Disability of 0–1), but they usually have consequences (depression, anxiety) that affect their work ability [8].

Conclusion

Coronavirus disease 2019 bears a high risk for the development of thrombotic complications, including cerebral venous system. Physicians should consider the high risk of cerebral venous sinus thrombosis in patients with mild coronavirus disease 2019 infection with nonspecific neurological symptoms in order to provide early diagnosis, the most effective individually tailored treatment, and to prevent complications.

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Case report
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ROOT CANAL RETREATMENT AND REPAIR OF IATROGENIC PERFORATION − A CASE REPORT

ENDODONTSKI RETRETMAN I SANACIJA JATROGENE PERFORACIJE KANALA KORENA ZUBA – PRIKAZ SLUČAJA

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Summary

Introduction. Root perforations may occur following endodontic treatment, thus compromising the root integrity and treatment outcome. **Case Report.** A patient presented with a root canal perforation following an earlier treatment of the upper left lateral incisor (tooth 22). Once the diagnosis of a symptomatic periapical periodontitis was established, a decision was made to retreat the root canal using mineral trioxide aggregate and perform apicoectomy. The procedure was performed in three sessions and two follow-up visits, after 12 and 18 months, respectively. At the last follow-up, bone neoformation was observed in the periapical region of the treated tooth. **Conclusion.** Successful outcome in this case depended on appropriate diagnosis, root canal and surgical site disinfection, as well as sealing of the root canal perforation to prevent recontamination.

Key words: Root Canal Therapy; Retreatment; Endodontics; Apicoectomy; Iatrogenic Disease; Root Canal Filling Materials; Treatment Outcome

Sažetak

Uvod. U toku endodontskog tretmana može doći do perforacije kanala korena, a samim tim i negativnog uticaja na integritet korena i ishod lečenja. **Prikaz slučaja.** Pacijent je upućen radi sanacije perforacije kanala korena gorenjeg levog lateralnog sekutića (zuba 22), koja je nastala prilikom prethodnog tretmana. Kada je postavljena dijagnoza simptomatskog apikalnog parodontitisa, doneta je odluka o endodontskom retretmanu, nakon kog će uslediti apikotomija uz zaptivanje perforacije mineral-trioksid agregatom. Celokupan tretman je obavljen u tri posete i kontrolisan dva puta (nakon 12 i 18 meseci). Na poslednjoj kontroli uočeno je ponovno formiranje kosti u periapikalnoj regiji tretiranog zuba. **Zaključak.** Postignut uspeh u ovom slučaju zavisio je od adekvatno postavljene dijagnoze, dezinfekcije kanala korena i hirurškog polja kao i zaptivanja perforacije kanala korena radi sprečavanja rekontaminacije.

Ključne reči: terapija kanala korena zuba; retretman; endodoncija; apikotomija; jatrogena oboljenja; materijali za punjenje kanala korena zuba; ishod lečenja

Introduction

According to the findings of cross-sectional studies conducted in different countries, more than 30% of all root-filled teeth are associated with apical periodontitis (AP) or "postoperative disease," indicating a great need for retreatment of the affected teeth [1]. Accidental root perforations, which may have serious adverse implications, occur in approximately 2 – 12% of endodontically treated teeth. Root perforation is an artificial communication between the root canal system and the supporting tissues of the tooth or oral cavity that decreases the likelihood of successful endodontic treatment outcome, and often leads to tooth loss [2]. Perforations may occur due to pathological processes, such as root resorption and dental caries, or they are iatrogenic complications found during or after root canal therapy [3]. Root perforations are commonly treated by sealing them with a wide range of materials, such as amalgam, composite, zinc oxide eugenol, biodentine (tricalcium silicate cement), or mineral trioxide aggregate (MTA). At present, biodentine and MTA are most commonly used, since they provide the best results for perforation repair [4].

Biodentine, like MTA, belongs to the group of calcium silicate-based cements with high biocompatibility and bioactivity, as well as improved mechanical properties and shorter setting time compared to calcium silicate. As a result, this material has a wide range of applications, including closure of iatrogenic perforations, direct pulp capping, endodontic therapy of teeth with incomplete root growth, and retrofilling after apicoectomy [5]. The MTA is a calcium silicate-based cement, originally designed for retrofilling of root canals, as well as for direct pulp capping and iatrogenic perforation closure. In many extant studies, oral tissue reacted positively to cement bridges placed directly above the filling, exhibiting cementogenesis properties [6]. Available evidence indicates that, when in direct contact with fibroblasts, cementoblasts, periosteal ligament, and osteoblasts, MTA is more biocompatible and less toxic than other materials.

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Abbreviations
MTA – mineral trioxide aggregate
AP – apical periodontitis
CBCT – cone beam computed tomography

However, its main drawbacks, such as relatively long setting time, poor handling, and tooth discoloration potential, have attracted criticism [7]. These negative aspects notwithstanding, the aim of this follow-up case report is to present a successful use of MTA in the treatment of iatrogenic perforation.

Case Report

A 22-year-old female patient presented at the Department of Dental Medicine of the Faculty of Medicine, University of Novi Sad, Serbia, complaining of pain in the maxillary left lateral incisor (tooth 22). The patient's medical history revealed that she was in good health and had no systemic diseases. However, she reported having a surgical procedure on the affected tooth four years before. Subsequent clinical examination confirmed a positive response to percussion and digital palpation in the periapical region of tooth 22 with no sinus tract. Periapical radiographic examination revealed a radiolucent lesion around the periapical region of tooth 22, presenting features of AP. Since there were signs of root perforation due to previous treatment, cone beam computed tomography (CBCT) was performed to make an accurate diagnosis of the lesion and its relationship with the adjacent teeth, and to confirm the presence of root canal perforation on the cervical third of the root. The final diagnosis was symptomatic AP, necessitating root canal retreatment, followed by endodontic surgery (root-end resection) and perforation sealing. Prior to commencing the treatment, the patient was instructed to take antibiotics for three days (amoxicillin caps. 500 mg, three times a day).

After administration of local anesthesia (2% lidocaine with epinephrine 1:100 000) (Galenika a.d., Belgrade, R. Serbia), the tooth was isolated with a rubber dam, the restorative material was removed and the access cavity was prepared. The cement, along with gutta-percha, was removed from the canal. The instrumentation was continued using hand files and applying the step-back technique, whereby 1% sodium hypochlorite (NaOCl), 17% ethylenediaminetetraacetic acid (i-EDTA Solution) (i-dental, Šiauliai, Lithuania), saline solution and 2% chlorhexidine digluconate (GLUCO-CHeX) (CERKAMED, Stalowa Wola, Poland) were used as irrigants, in this particular order. Due to persistent apical leakage, a mixture of calcium hydroxide and 2% chlorhexidine was placed into the canal, and the tooth was temporarily restored with i-PRO N (i-dental, Šiauliai, Lithuania). On the next visit 10 days later, the tooth was isolated, the temporary restoration was removed, and the canal was thoroughly irrigated with saline solution, 1% NaOCl, 17% i-EDTA Solution, saline solution and 2% GLUCO-CHeX. The canal was gently dried with paper points and obturated with gutta-percha (DiaDent, Seoul, South Korea) and AH Plus sealer (Denstply DeTrey, Konstanz, Germany) using lateral compaction method.

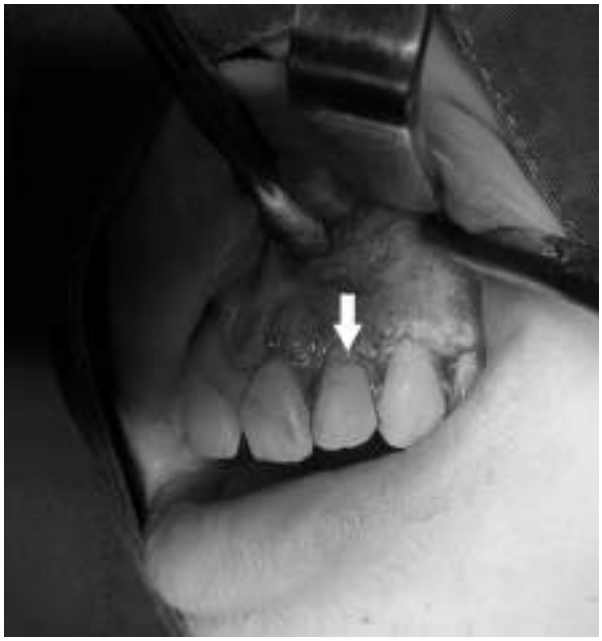

Figure 1. Visible perforation site
Slika 1. *Vidljivo mesto perforacije*

Two days later, apicoectomy was performed under local anesthesia (2% lidocaine with epinephrine 1:100,000) whereby intraoral access to the lesion was achieved via intrasulcular incision of the buccal region from tooth 11 to tooth 24. After flap detachment, the perforation was clearly visible **(Figure 1)** and a minimum osteotomy was performed to obtain a surgery window using a surgical steel drill no. 06 (Kom-

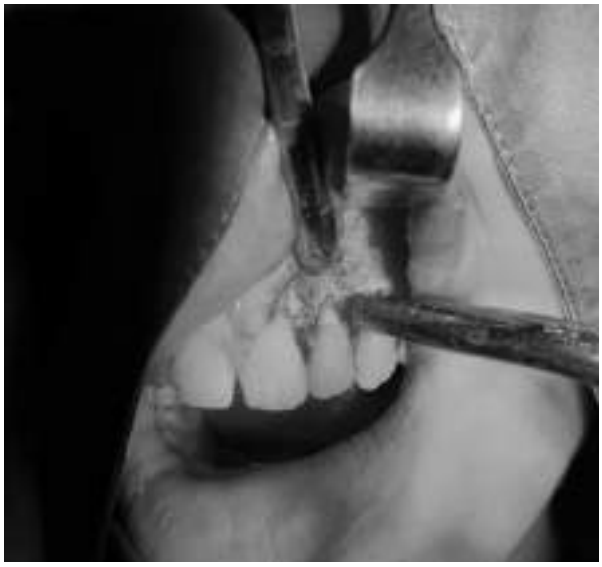

Figure 2. Perforation site sealed with MTA
Slika 2. *Zatvaranje perforacije sa mineral-trioksid agregatom*

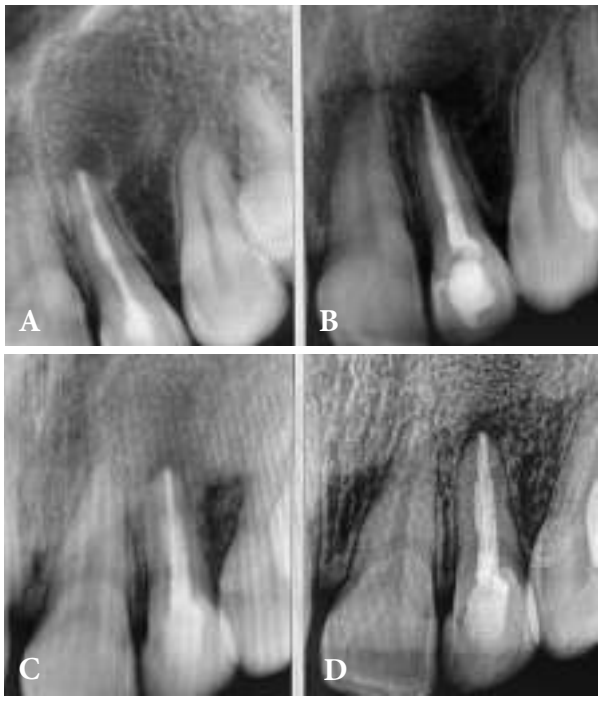

Figure 3. a: Initial periapical radiography; b: Postoperative periapical radiography; c: Follow-up periapical radiography after 12 months; d: Follow-up periapical radiography after 18 months

Slika 3. *a) Inicijalna periapikalna radiografija; b) Postoperativna periapikalna radiografija; c) Kontrolna periapikalna radiografija nakon 12 meseci; d) Kontrolna periapikalna radiografija nakon 18 meseci*

et Dental Gebr. Brasseler GmbH & Co., Lemgo, Germany) with intensive sterile saline solution irrigation. The apical third of the root was removed using fissure drill (NPOOO SISTEMA, Minsk, Belarus) and the perforation site was sealed with MTA (Tehnodent, Severnyi, Russia) (**Figure 2**). Once the flap was repositioned, the surgical site was closed by intrasulcular suturing with 3-0 silk thread (ETHICON, AgnTho's AB, Lidingö, Sweden). A postoperative radiograph was taken immediately after suturing. The suture was removed seven days later, and the patient progressed well postoperatively without any sequelae. Radiographic examination performed at the 12-month follow-up revealed further healing and the patient confirmed that the tooth had remained asymptomatic. Upon clinical examination, the tooth was pain-free and unresponsive to percussion and palpation. At the 18-month follow-up, adequate clinical function was confirmed and radiographic findings showed bone neoformation in the periapical region of tooth 22 (**Figure 3**).

Discussion

According to Lopes and Siqueira, the success of endodontic treatment is verified by the absence of a periapical lesion after an appropriate follow-up period [8]. Therefore, the prior treatment of our patient failed to achieve the expected result, as evidenced radiographically by the presence of a periapical lesion four years after the treatment and clinically by pain upon percussion and palpation [9]. In such cases, correct diagnosis has a direct impact on the treatment plan and outcome. In this case, a CBCT scan was indicated, as it provides a three-dimensional mapping of the lesion and its relationship with adjacent teeth and anatomical structures. The periapical and panoramic radiography is less accurate, and may not provide sufficient data for apicoectomy [10]. This case also met all the criteria for surgical intervention, and the need for periapical surgery was only confirmed after a detailed analysis of the patient's medical history and clinical and radiographic findings [11]. Whether teeth with root perforations can be successfully treated depends on the severity of the initial damage to the periodontal tissues, the size of the perforation, the location of the perforation in relation to the gingival sulcus, the time span between injury and repair, the adequacy of the perforation seal, the sterility of the perforation, and the biocompatibility of the material used to repair the perforation [12]. Authors of several studies in this field have concluded that MTA provides effective sealing of root perforations so it can be considered a suitable material for this purpose, as it improves the likelihood of successful outcomes in teeth with perforations that would otherwise be compromised [13–16].

Conclusion

Mineral trioxide aggregate is a material with excellent properties that provides good marginal sealing and promotes osteoblast activity. A successful outcome in this case depended on appropriate diagnosis, root canal and surgical site disinfection, as well as sealing of the root canal perforation to prevent recontamination.

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RUPTURE OF THE UNSCARRED UTERUS DURING INDUCED TERMINATION OF PREGNANCY IN THE SECOND TRIMESTER − A CASE REPORT

RUPTURA NEOŽILJNOG UTERUSA TOKOM INDUKOVANOG PREKIDA TRUDNOĆE U DRUGOM TRIMESTRU − PRIKAZ SLUČAJA

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Summary

Introduction. Uterine rupture is a rare complication of induced termination of pregnancy in the second trimester. We report a case of a patient with a rupture of the unscarred uterus during a prostaglandin-induced abortion in the second trimester of pregnancy. **Case Report**. A 26-year-old pregnant woman was admitted to the Clinic of Gynecology and Obstetrics in the 22nd week of gestation of her fourth pregnancy due to complete absence of amniotic fluid. The patient denied previous surgeries and other diseases. Due to a poor prognosis for the fetus, the Ethics Committee approved the termination of pregnancy. The induction of abortion was started by applying two dinoprostone gels intracervically and continued by using carboprost tromethamine intramuscularly. The patient aborted after 38 hours from the start of induction. During instrumental revision of the uterine cavity, a rupture of the right side of the uterus was suspected. Ultrasound examination showed a parametrial hematoma. Laparotomy was indicated due to suspected uterine rupture. The intraoperative findings showed a hematoma located in the right parametrium and a complete rupture of the posterior wall of the uterus extending from the right vaginal fornix to the right uterine horn. A total abdominal hysterectomy with preservation of both ovaries was performed. **Conclusion.** Since ruptures of the unscarred uterus are rare, almost at the chance level, it is important to always keep them in mind as a potential complication of induced termination of pregnancy in the second trimester.

Key words: Uterine Rupture; Abortion, Induced; Pregnancy Trimester, Second; Oxytocin; Prostaglandins; Risk Factors; Hysterectomy; Salpingectomy; Signs and Symptoms; Ultrasonography

Sažetak

Uvod. Ruptura uterusa je retka komplikacija indukovanog prekida trudnoće u drugom trimestru. Ovo je prikaz slučaja pacijentkinje kod koje se desila ruptura neožiljnog uterusa tokom prostaglandinima indukovanog abortusa u drugom trimestru trudnoće. **Prikaz slučaja**. Pacijentkinja starosti 26 godina je primljena na Kliniku za ginekologiju i akušertsvo u 22. nedelji četvrte trudnoće zbog odsustva plodove vode. Pacijentkinja je imala tri uredna vaginalna porođaja; negira prethodne operacije i druge bolesti. S obzirom na lošu prognozu po fetus, Etički komitet odobrava prekid trudnoće. Indukcija pobačaja je započeta aplikacijom dva gela dinoprostona intracervikalno, a potom nastavljena upotrebom karboprost trometamina intramuskularno. Pacijentkinja je pobacila nakon 38 sati od početka indukcije. Prilikom pokušaja instrumentalne revizije kavuma uterusa, postavljena je sumnja na rupturu uterusa desno. Ultrazvučno se verifikuje hematom parametrijuma. S obzirom na suspektnu rupturu uterusa, indikuje se laparotomija. Intraoperativno se nailazi na hematom parametrijuma desno i kompletnu rupturu zadnjeg zida uterusa koja se prostire od forniksa vagine do desnog roga uterusa. Načinjena je totalna abdominalna histerektomija sa konzervacijom ovarijuma obostrano. **Zaključak**. S obzirom da je ruptura neožiljnog uterusa retka, praktično na nivou akcidenta, važno ju je uvek imati na umu kao potencijalnu komplikaciju indukovanog prekida trudnoće u drugom trimestru.

Ključne reči: ruptura uterusa; indukovani abortus; trudnoća, drugi trimestar; oksitocin; prostaglandini; faktori rizika; histerektomija; salpingotomija; znaci i simptomi; ultrasonografija

Introduction

Uterine rupture is a rare complication of induced termination of pregnancy in the second trimester with an overall incidence of 1.1% [1], while in the intact uterus the incidence is about 0.2% [2]. We report a case of a patient with a rupture of the unscarred uterus during a dinoprostone and carboprost tromethamine induced abortion and absence of the usual risk factors. The complications of uterine rupture may be life-threatening including maternal hemorrhage, blood transfusion, bladder injury, hysterectomy and maternal death. A delayed diagnosis is associated with poor outcome [3, 4].

Case Report

A 26-year-old pregnant woman was admitted to the Clinic of Gynecology and Obstetrics of the University Clinical Center of Vojvodina due to com-

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Abbreviations
WBC – white blood cell

plete absence of amniotic fluid in the 22nd week of gestation of her fourth pregnancy. Previously, the patient had 3 vaginal deliveries and no history of uterine surgery. On admission, laboratory test results were within the reference values, except for the white blood cell (WBC) count (17.24 x 10^9/l). The urinalysis showed an asymptomatic bacteriuria while the cervical smear was positive for Enterococcus spp. Parenteral antibiotic therapy (first generation of cephalosporins) was initiated. Fetal ultrasound showed normal heart rate and complete absence of amniotic fluid with consequent pulmonary hypoplasia. After clinical and ultrasound evaluation of the patient's condition, the risks of continuation of pregnancy were presented to the patient, so she submitted a request for pregnancy termination to the Ethics Committee of the Clinic of Gynecology and Obstetrics. The Ethics Committee approved the request due to possibility that the child could present with severe physical and mental disabilities which could not have been ruled out. Due to the indication, induction of abortion was started by applying two Prepidil® (dinoprostone) gels intracervically. The patient developed contractions and the fetal membranes ruptured; six hours after application of gel, abortion induction was continued using Prostin 15M® 250 mcg/ml (carboprost tromethamine) intramuscularly at an interval of 2 hours. On several occasions, a Buscopan® (hioscin-bytilbromid) was administered intravenously, Bensedin® (diazepam) intramuscularly and also Fentanyl® (fentanyl) and Flormidal® (midasolam) for analgesia with adequate hydration. Since abortion did not occur after the administration of eight ampoules of carboprost tromethamine, it was decided to stop the induced abortion. Ultrasound examination verified the presence of fetus in the uterus, intact walls of the uterus and absence of free fluid in the Douglas space. Abdominal palpation showed calm tone of the uterus without contractions and the abdomen was without peritoneal irritation and defense of the abdominal muscles. Orvagyl® (metronidazole) solution was also included in the therapy, intravenously, since there was an increase in infection parameters: WBC - 22.07x10^9/l, C-reactive protein - 27.2 mg/L. Except signs of anemia, other laboratory markers were in physiological range. The patient aborted 38 hours from the start of the prostaglandin induced abortion. After abortion, the infusion with 20IU of Oxytocin was initiated and an ampoule of Methylergonovine was administrated intravenously. Instrumental removal of the placenta was performed and about 200 ml of liquid blood and coagula were evacuated from the uterine cavity. During instrumental revision of the uterine cavity, a rupture of the right side of the uterus was suspected. Ultrasound examination showed that the uterus was in normal involution with a minimal amount of residual content in the cavity; in the uterine area of the right parametria, a hematoma with a diameter 50 x 80 mm was observed, but without free fluid in the abdomen **(Figure 1)**. During the intervention, the patient was hemodynamically stable. Laparotomy was indicated due to a suspicion of uterine rupture. The intraoperative finding was: hematoma about 90 x 70 mm in diameter located in the right parametria, which was also invading the wall of right side of the uterus. There was a complete rupture of the posterior uterine wall, from the right vaginal fornix along the entire length to the cornual part of the uterus and the enlarged, livid right fallopian tube. The other organs of the abdominal cavity were normal **(Figure 2)**. Because of the active bleeding from the uterine artery, progressive growth of the hematoma and complete uterine rupture, total abdominal hysterectomy and bilateral salpingectomy with preservation of both ovaries was performed. The estimated blood loss was about 1300 ml. In the early postoperative period, the patient received a transfusion of 3 units of resuspended erythrocytes (925 ml) and 2 units of fresh frozen plasma (395 ml). Dual

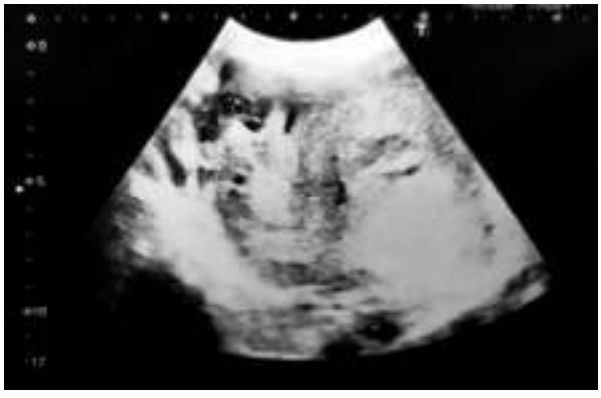

Figure 1. Transabdominal ultrasound of the pelvis showing hematoma of the right parametria
Slika 1. *Transabdominalni ultrazvuk karlice koji pokazuje hematom desnog parametrijuma*

Figure 2. Uterine rupture – intraoperative finding
Slika 2. *Ruptura uterusa – intraoperativni nalaz*

antibiotic therapy (third generation of cephalosporins and Metronidazole) was continued. Further postoperative course was without major complications. Control laboratory findings were normal with the presence of anemia. Definitive pathophysiological examination showed decidualization of the endometrium, permeated by blood and dense inflammatory infiltrate of lymphocytes, plasma cells and neutrophilic granulocytes, which also permeated the myometrium that also contained enlarged blood vessels filled with numerous blood clots. This finding showed that there were signs of subclinical infection of the uterine tissue. The patient was discharged on the fourth postoperative day in good general condition, hemodynamically stable and afebrile.

Discussion

Unscarred uterine rupture during termination of pregnancy in the 2nd trimester is extremely rare, because the main risk factors are previous cesarean delivery or other uterine surgical procedures. That is the reason why it is unusual and unexpected for unscarred uterus to rupture. The main risk factors for rupture of unscarred uterus are multiparity, prolonged and obstructed labor or abortion, and short interval between pregnancies. Most authors suggest that induction of abortion or labor with oxytocin and prostaglandin analogs may trigger uterine rupture. Some studies showed that uterine congenital anomalies, history of uterine curettage, and obstetrical maneuvers could be the reasons for uterine rupture [3, 5, 6]. Weakened myometrium caused by multiple gestations and strong influence of prostaglandin F2-alpha and prostaglandin E2 analogs could be the reason of uterine rupture in our patient. We also presume that subclinical infection could be the contributing factor. Furthermore, pathological insertion of placenta could also be the reason of unexpected uterine rupture [7]. In our case, the placenta was inserted on the anterior wall of the uterus, and rupture was found on the posterior wall, so abnormal placentation could be excluded as a potential cause. The clinical picture of uterine rupture is usually noisy and typical signs are severe pelvic pain, a tearing sensation, bleeding and unstable hemodynamic state progressing to shock [8]. Our patient presented with completely unsuspicious clinical picture. She was hemodynamically stable with signs of mild abdominal pain and a minor bleeding from the uterus, which looked like a normal course of induced abortion. Poor clinical signs in our patient are explained by the fact that the broad ligament remained intact, and together with myometrium played a compressive role, preventing the expansion of the hematoma and its diffusion into the abdominal cavity. Since the clinical picture was misleading, the ultrasound examination played an important role in the diagnostic process. Surgical treatment of uterine rupture in a healthy uterus should be conservative, especially in young women who want to become pregnant again (includes suture of the rupture). If conservative treatment seems impossible, due to the extent of the lesions, a hysterectomy with ovarian conservation is necessary [8].

Conclusion

Since ruptures of the unscarred uterus are rare, almost at the level of chance, it is important to always keep them in mind as a potential complication of induced termination of pregnancy in the second trimester. It is necessary to perform a control ultrasound after the abortion in order to avoid life-threatening complications, since the rupture itself is difficult to predict and prevent. Also, cautious use of dinoprostone and carboprost tromethamine during induction of abortion and raising physician awareness of their potential side effects is of utmost importance.

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CUTANEOUS METASTASIS AS THE FIRST MANIFESTATION OF NEUROENDOCRINE NEOPLASM OF THE LUNG – A CASE REPORT

KOŽNE METASTAZE KAO PRVI ZNAK NEUROENDOKRINE NEOPLAZME PLUĆA – PRIKAZ SLUČAJA

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Summary

Introduction. Neuroendocrine neoplasms are rare heterogeneous malignancies that may occur in almost any organ in the body. These neoplasms are associated with a wide range of clinical and pathophysiological manifestations. **Case Report.** A 67-year-old female patient, non-smoker with a history of rheumatoid arthritis and osteoporosis, visited her general practitioner complaining of back pain, heart palpitations, and change in stool consistency. Physical examination revealed multiple subcutaneous nodules in the neck and chest area that were painful to touch. Due to suspected hyperthyroidism, she was referred to an endocrinologist. The ultrasound of the thyroid gland showed multiple cysts in the right lobe and a nodule in the left lobe of the thyroid gland. Laboratory tests showed elevated calcitonin and carbohydrate antigen levels. Based on the assumption that medullary thyroid carcinoma was the most likely diagnosis, she was referred to the Nuclear Medicine Department of the Oncology Institute of Vojvodina. A fine-needle aspiration biopsy of the left thyroid nodule was done and thyroid malignancy was excluded. By histopathological analysis of the enlarged right chest lymph node and a skin lump on the left loin, a lung cancer with neuroendocrine morphology with positive neuroendocrine markers was diagnosed. Computed tomography revealed a tumor infiltrating the left hilum with metastases. **Conclusion.** Skin metastases of neuroendocrine neoplasms are rare and may occur in any part of the human body. They may develop before the primary tumor is recognized and are associated with disseminated malignancy. Diagnosis and treatment are important to control the disease and improve the quality of life of patients.

Key words: Lung Neoplasms; Neoplasm Metastasis; Carcinoma, Neuroendocrine; Skin Neoplasms; Tomography, X-Ray Computed; Biomarkers, Tumor; Hyperthyroidism; Diagnosis, Differential; Biopsy, Fine-Needle

Sažetak

Uvod. Neuroendokrine neoplazme predstavljaju retku, heterogenu grupu malignoteta i mogu se pojaviti u skoro svakom organu u telu. Ove neoplazme su povezane sa širokim spektrom kliničkog i patofiziološkog ispoljavanja. **Prikaz slučaja.** Žena starosti 67 godina, nepušač, sa istorijom reumatoidnog artritisa i osteoporoze, javlja se doktoru opšte medicine zbog bolova u ledima, palpitacija i promene u konzistenciji stolice. Fizikalnim pregledom se pronalaze brojni potkožni čvorići u predelu vrata i grudnog koša koji su bili bolni na dodir. Zbog sumnje na hipertiroidizam, upućena je endokrinologu. Ultrazvukom štitaste žlezde viđene su brojne ciste u desnom režnju i čvor u levom režnju. Laboratorijski testovi su utvrdili povišene vrednosti kalcitonina i karbohidratnog antigena. Zbog sumnje na postojanje medularnog karcinoma štitaste žlezde, poslata je u Centar za nuklearnu medicinu u Institut za onkologiju Vojvodine. Punkcijom čvora u levom režnju, isključen je malignitet štitaste žlezde. Patohistološkom analizom uvećanog limfnog čvora desne polovine grudnog koša i kožnog čvora na levoj slabini dijagnostikovan je karcinom pluća sa neuroendokrinom morfologijom i pozitivnim tumorskim markerima. Kompjuterskom tomografijom otkrivena je tumorska infiltracija u levom hilusu sa metastazama. **Zaključak.** Kožne metastaze neuroendokrinih neoplazmi su retke i mogu se pojaviti na bilo kom delu ljudskog tela. Mogu se javiti pre nego što se primarni tumor prepozna i povezane su sa proširenjem maligne bolesti. Dijagnoza i lečenje su važni zbog kontrole bolesti i poboljšanja kvaliteta života bolesnika.

Ključne reči: neoplazme pluća; metastaze; neuroendokrini karcinomi; neoplazme kože; CT; tumorski biomarkeri; hipertireoidizam; diferencijalna dijagnoza; aspiraciona biopsija tankom iglom

Introduction

Neuroendocrine neoplasms (NENs) are rare, heterogeneous malignancies that may occur in almost any organ in the body, most commonly originating from cells with a neuroendocrine phenotype in the gastrointestinal tract, lungs, and pancreas [1]. They share the secretion of neuroendocrine biomarkers into the systemic circulation such as synaptophysin, chromogranin A, serotonin and its metabolites, insulin, glucagon, gastrin, and special histological features of neuroendocrine tumors (NETs) including proliferation, organoid nesting, palisading, rosettes and trabecular growth pattern. There are two different

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Abbreviations

NENs	– neuroendocrine neoplasms
NETs	– neuroendocrine tumors
CRP	– C-reactive protein
LDH	– lactate dehydrogenase
TSH	– thyroid stimulating hormone
CT	– computed tomography
SRS	– somatostatin receptor scintigraphy
^{177}Lu-DOTATATE	– lutetium-177 tetra-azacyclododecanetetra-acetic acid (DOTA) tyrosine-containing somatostatin analog Tyr3- Octreotate (TATE)
ACTH	– adrenocorticotropic hormone
PRRT	– peptide receptor radiotargeted therapy

groups of NENs: well-differentiated and low proliferating NENs called NETs, and poorly differentiated and highly proliferating NENs called small- or large-cell neuroendocrine carcinomas [2]. These neoplasms are associated with a wide range of clinical and pathophysiological manifestations. The aim of this case report was to describe the diagnosis and incidental finding of a NET of the lung based on cutaneous metastasis.

Case Report

A 67-year-old female patient, non-smoker with a history of rheumatoid arthritis and osteoporosis, visited her general practitioner complaining of back pain, heart palpitations, and change in stool consistency. She was exposed to pesticides in the workplace and had no relevant family history. Physical examination revealed multiple neck and chest subcutaneous lesions. Morphologically, the lesions were skin-colored nodules and varied in size, from a few millimeters to a few centimeters, the largest one on the right loin, about 4 cm in size. Based on clinical palpation, nodules were painful to touch, especially in the area of sternum and ribs, without exudation or bleeding. There were no other abnormal findings on physical examination.

Due to suspected hyperthyroidism, she was referred to an endocrinologist. The ultrasound of the thyroid gland showed multiple cysts in the right lobe and a nodule in the left lobe of the thyroid gland. Laboratory tests showed an elevated calcitonin level of 88,3 pg/ml (normal range < 6,4 pg/ml) and carbohydrate antigen 19-9 level of 88,37 (normal range < 27 kIU/l). Based on the assumption that medullary thyroid carcinoma was the most likely diagnosis, she was referred to the Nuclear Medicine Department of the Oncology Institute of Vojvodina. The laboratory tests revealed elevated levels of C-reactive protein (CRP) 17.27 mg/l (normal range 0 – 5 mg/l), lactate dehydrogenase (LDH) 278 U/L (normal range 135 - 225 U/L), procalcitonin 17 ng/ml (normal range < 0.05 ng/ml), thyroid stimulating hormone (TSH) 5.33 μgIU/mL (normal range 0.27 – 4.2 μgIU/mL), antithyroglobulin antibody 154 IU/mL (normal range 0 – 115 IU/mL), antithyroid peroxidase 59 IU/mL (normal range, 0 – 34 IU/mL). The results of other hematological, biochemical laboratory tests and carcinoembryonic antigen were within normal ranges. Due to elevated TSH levels, Euthyrox 50 μg was initiated. The thyroid ultrasound showed hypoechogenic nodules on both lobes, measuring up to 0.73 cm in the left lobe. A fine-needle aspiration biopsy was performed and cytological findings revealed blood cells, colloids, macrophages and rare thyrocytes (Bethesda I classification). Cytological examination of the skin nodule on the left loin showed atypical cells with fine chromatin and moderate eosinophilic granular cytoplasm. Histopathological analysis of the enlarged lymph node of the right half of the chest revealed groups of atypical cells in the dermis arranged in small nests and trabecular pattern, which showed positivity to Synaptophysin, CD56 and Chromogranin. The proliferative rate was high: Ki67 index of 30%, while the number of mitoses was above 20 per 10 high power fields **(Figure 1)**. The computed tomography (CT) showed: a tumor infiltrating the left hilum measuring 6 x 8 x 10 cm, infiltrating all hilum structures, without clear demarcation in relation to the esophagus and aortic arch; infiltration of the pleura and lung parenchyma on the left, nodular and micronodular changes on the right side; pericardial effusion; mediastinal lymphadenomegaly; bilateral subcutaneous nodules; osteolytic rib (rib 9 on the right and rib 7 on the left side) and lumbar spine metastases **(Figure 2)**.

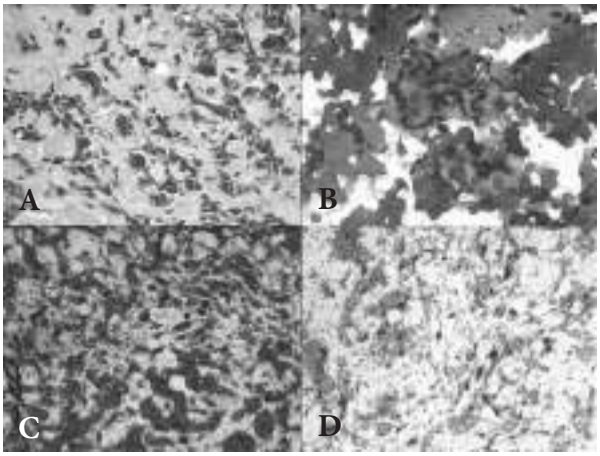

Figure 1. Lymph node puncture: atypical cells of the hyperchromatic nucleus and scarce cytoplasm, MGG x 400 (A); Biopsy of skin changes: groups of tumor cells, H&E x 400 (B); Positivity of tumor cells to synaptophysin, x 200 (C); Ki67 proliferative index, x 200 (D)
Slika 1. *Punktat limfnog čvora: atipične ćelije hiperhromatičnog jedra i oskudne citoplazme, MGG x 400 (A); Bioptat promene na koži: grupe tumorskih ćelija, H&E x 400 (B); Pozitivnost tumorskih ćelija na Synaptophysin, x 200 (C); Ki67 proliferativni indeks, x 200 (D)*
Legend: MGG - May Grunwald-Giemsa stain; H&E - hematoxylin and eosin staining
Legenda: MGG - May Grunwald-Giemsa bojenje; H&E – hematoksilin-eozin bojenje

During the follow-up period, the patient received VI cycles of first-line chemotherapy according to the platinum/etoposide regimen and a single dose spinal radiotherapy (VT12-VL2). She also received pain therapy. The CT was repeated and revealed a pleural effusion on the left side with inhomogeneous con-

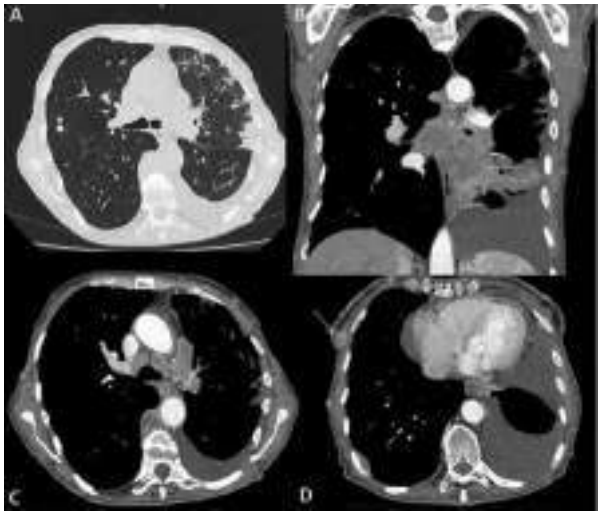

Figure 2. CT scan of the chest shows tumor infiltration of the left hilum with infiltration of all structures of the hilum and lung parenchyma on the left (A); Nodular and micronodular changes of the right lung (B); Pericardial effusion and subcutaneous nodular lesions bilaterally (white arrow) (C and D)
Slika 2. *CT nalaz grudnog koša opisuje tumorsku inflitraciju levog hilusa sa infiltracijom svih strukturs hilusa i plućnog parenhima levo (A); Nodularne i mikronodularne promene desnog plućnog krila (B); perikardni izliv i subkutane nodularne lezije obostrano (bela strelica) (C i D)*
Legend**:** CT – Computed tomography
*Legenda**:** CT – Kompjuterska tomografija*

solidation of the lung parenchyma above, which was inseparable from the distal segment of the esophagus. Right subpleural basal nodular changes up to 0.9 cm, pericardial effusion, and a left pericardial soft tissue mass up to 2.4 cm were found, as well as diffuse oval foci in the subcutaneous regions of the chest, breast, abdomen and pelvis up to 3.1 cm, a soft tissue mass on the lower pole of the left kidney, pathological lymph nodes in the pelvis up to 1.2 cm, and bone metastases (VT9 - 12, VL2 - 4, iliac bones, left ischial bone, sacrum and left femur). Somatostatin receptor scintigraphy (SRS) with 111In-labeled octreotide was proposed and confirmed lesions in the left lung and mediastinum. Because of low expression of somatostatin receptor (grade 1), she was not a candidate for lutetium-177 tetra-azacyclododecanetetraacetic acid (DOTA) tyrosine-containing somatostatin analog Tyr3-octreotate (TATE) (177-Lu-DOTATATE) therapy and was referred to another institution for further treatment **(Figure 3)**. The patient passed away one year after the diagnosis. A written informed consent for publishing clinical data for this study was obtained from the patient during treatment.

Discussion

The NENs are a heterogeneous family of neoplasms that arise from neuroendocrine cells. They most commonly occur in the gastrointestinal tract (48%), lung (25%), and pancreas (9%), but may also

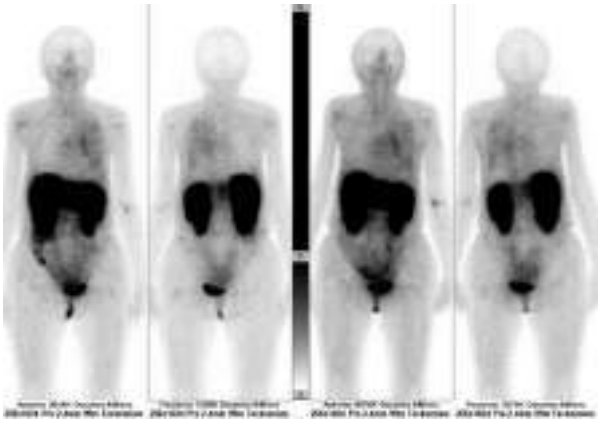

Figure 3. SRS with 111In-labeled octreotide confirmed the presence of a lesion in the left lung and mediastinum with low expression of somatostatin receptor (grade 1)
Slika 3. *SRS sa oktreotidom obeleženim 111In je potvrdila leziju u levom plućnom krilu i medijastinumu sa niskom ekspresijom somatostatinskih receptora (gradus 1)*
Legend: SRS – Somatostatin receptor scintigraphy
Legenda: SRS – Scintigrafija somatostatinskih receptora

develop in other organs including the breast, prostate, thymus and skin [3]. The NENs of the lung arise from Kulchitsky cells that are normally present in the bronchial mucosa and share the common morphologic features of neuroendocrine tumors including round, ovoid or spindle-shaped cells with a high nucleus to cytoplasm ratio, high mitotic rates, and are commonly necrotic. The NENs have traditionally been considered uncommon. The incidence of the lung NENs is 0.2 to 2 cases per 100,000 and represents 30% of well-differentiated NETs and 1 – 2% of all lung cancers [4]. The risk factors associated with NENs are: age (people aged 45 to 55 years), gender (NENs are more common in women than in men), race/ethnicity (these tumors are more common in white people than in other racial and ethnic groups), family history (family members of persons with NENs are at higher risk), and multiple endocrine neoplasia type 1 [5]. The clinicopathological characteristics of NENs include grade, differentiation and stage. Histological grade reflects the biological aggressiveness of the neoplasm based on Ki67 index (a nuclear protein involved with cell proliferation) and the mitotic rate. The World Health Organization classifies NENs into low- and intermediate-grade lung tumors (grades 1 and 2) called typical carcinoid and atypical carcinoid, respectively; high-grade lung tumors (grade 3) are called small cell lung cancers or large cell neuroendocrine carcinomas [6, 7]. The differentiation refers to how closely the neoplastic cells resemble the originating tissue. Low grade tumors (grades 1 and 2) are well-differentiated, whereas high grade tumors (grade 3) are poorly differentiated [8]. The NENs are considered to be early stage (completely resectable) or advanced stage (locally advanced and unresectable or metastatic) [9]. They may spread to almost all organs, but the frequent sites are hilar lymph nodes, liver, adrenal glands, bones, and brain. The incidence

of skin metastases from lung cancer varies between 1 – 12% of cases and clinically cannot be distinguished from skin metastases originating from other organs [10]. The most common sites of skin metastases from lung cancer are the chest, abdomen, head and neck. Clinically, skin metastases occur as round or oval nodules, mobile or fixed, firm, skin-colored (sometimes red, dark red or black). They may appear as solitary or grouped papules, plaque-like, zosteriform, erysipelas-like or as cicatricle alopecia on the scalp, chest, back and eyelid. The nodules are usually painless, but in our case the nodules were painful, especially to touch. The occurrence of cutaneous metastases from lung cancer may represent the first manifestation of carcinoma, but coincide with a progression of the neoplastic disease [11]. The differential diagnosis of a cutaneous NET includes both primary and secondary tumors, melanoma, primary extraskeletal Ewing's sarcoma, primitive neuroectodermal tumor and cutaneous metastasis from the breast, lung, stomach, colon, upper aerodigestive-tract, uterus, and kidney carcinoma [12]. The diagnosis of lung NENs is based on a combination of clinical symptoms, laboratory findings and imaging, but it may be an incidental finding. Functioning NENs cause clinical symptoms of secreted hormones, and both functioning and nonfunctioning tend to present late with nonspecific symptoms that are attributed to differential diagnosis. The symptoms of lung NENs are chronic cough, chest pain, dyspnea, hemoptysis, fever, unilateral wheezing, and recurrent infections [13]. Lung NENs may be a source of ectopic adrenocorticotropic hormone (ACTH) production and may be diagnosed as unexplained Cushing syndrome [14]. Sometimes, lung NENs cause a condition called carcinoid syndrome. Carcinoid syndrome is characterized by profound flushing, palpation, diarrhea, and it appears when secreting hormones from NENs reach systemic circulation. The term "carcinoid tumor" is no longer recommended, because most of the NENs do not cause a carcinoid syndrome [15]. For patients presenting with functioning lung NENs, biochemical testing should be considered based on clinical symptoms. Serum levels of serotonin, histamine, tachykinin, prostaglandins, and ACTH, should be established [16]. Chromogranin A is a diagnostic biomarker of choice for NENs. False positive results may appear in severe arterial hypertension, treatment with proton-pump inhibitors, renal insufficiency and adenocarcinoma [17]. The LDH levels may be increased in disorders like myocardial infarction, liver disease, hypothyroidism and infectious diseases; it can also be a potential biomarker of metastasis [18]. Elevated CRP levels are associated with subsequently increased lung cancer risk, suggesting an etiologic role for chronic pulmonary inflammation in lung carcinogenesis [19]. Procalcitonin is produced in response to inflammation and it has an important role in diagnosis and prognosis of sepsis. Serum calcitonin concentrations may be elevated due to chronic renal failure, pernicious anemia, hepatic cirrhosis, various medications, extra-thyroid neoplasms, false-positive calcitonin assay laboratory results, lower respiratory tract infections, smoking, chronic inflammatory conditions of the lung, and in any condition with increased gastrin or calcium such as hyperparathyroidism or Zollinger-Ellison syndrome [20]. Elevated level of procalcitonin and calcitonin may be found in some malignant diseases such as thyroid medullary carcinoma and small cell lung cancer [21]. Diagnostic and treatment planning is individualized and based on tumor factors such as site, stage, grade, differentiation and symptoms, as well as patient factors such as age and comorbidities. Nuclear medicine methods have been shown to play a relevant role in the evaluation of NETs and help in predicting the response to peptide receptor radiotargeted therapy (PRRT). Somatostatin analogue preparations, octreotide long-acting repeatable and lanreotide are used in somatostatin receptor scintigraphy (SRS) and in therapy, initially in patients with secretory symptoms. Adverse effects of this therapy include diarrhea, nausea, vomiting, abdominal pain, hyperglycemia, and cholelithiasis [22]. Although somatostatin analogue preparations have shown high diagnostic accuracy for whole-body imaging, there are some limitations in the evaluation of organs with high physiologic uptake and in the detection of small lesions [23, 24]. In our case, SRS revealed a tumor in the left lung and mediastinum, but it was Krenning score 1. Krenning score assesses the applicability of PRRT, such as ^{177}Lu-DOTATATE, usually in scores greater than 2, so this patient was not a candidate for PRRT [25]. Biopsy of skin lesions is an important component in making the diagnosis of lung cancer with cutaneous metastasis. Imaging methods, such as chest radiography and CT, are used to identify the primary site of carcinoma [26]. Treatment of solitary skin metastasis includes surgery combined with either or both chemotherapy and radiotherapy. Patients with resectable skin lesions have better survival than those with multiple, non-resectable sites [27]. When the metastases are multiple, chemotherapy is used as the initial treatment. Due to the aggressive nature of lung cancer with cutaneous metastasis, both chemotherapy and radiation therapy may be effective only as palliative treatment [28].

Conclusion

Skin metastases of neuroendocrine neoplasms are unusual and may appear on any area of skin. They may develop before the primary tumor is recognized and are associated with disseminated malignancy. Because of heterogeneous clinical symptoms, the diagnosis may be delayed.

At the time of presentation, skin metastases are an indicator of poor prognosis and early evaluation is essential. Diagnostic and treatment options are rapidly developing, so many patients may have a well-controlled disease and better quality of life.

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Case report
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OVARIAN INFLAMMATORY MYOFIBROBLASTIC TUMOR – A CASE REPORT

INFLAMATORNI MIOFIBROBLASTNI TUMOR JAJNIKA – PRIKAZ SLUČAJA

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Summary

Introduction. Inflammatory myofibroblastic tumor is a mesenchymal neoplasm with an aggressive potential and a tendency for recurrence. It is known to occur in a variety of locations, including the female genital tract. The objective of this study was to provide an overview of the clinical, histopathological, immunohistochemical and molecular features of the inflammatory myofibroblastic tumor, emphasizing potential diagnostic pitfalls in the female genital tract. **Case Report.** The diagnosis of an inflammatory myofibroblastic tumor of the right ovary with extension to the right parametrium and peritoneal adipose tissue was made in a 74-year-old patient after a detailed laboratory testing, computed tomography and histopathological examination. **Conclusion.** This case report presents an unusual experience of specialists in everyday practice, with a successful combination of skills in gynecological surgery and pathology. Inflammatory myofibroblastic tumor is a diagnostic challenge that needs to be considered in the differential diagnosis of tumors of both the ovary and the entire female genital tract.

Key words: Ovarian Neoplasms; Genital Neoplasms, Female; Myofibroblasts; Diagnosis, Differential; Tomography, X-Ray Computed; Immunohistochemistry; Morphological and Microscopic Findings; Gynecologic Surgical Procedures

Sažetak

Uvod. Inflamatorni miofibroblastni tumor je mezenhimalna neoplazma sa agresivnim potencijalom i težnjom za nastankom recidiva. Poznato je da može nastati na različitim lokacijama, uključujući ženski genitalni trakt. Cilj prikaza slučaja bio je da se obezbedi prikaz kliničkih, patohistoloških, imunohistohemijskih i molekularnih osobina inflamatornog miofibroblastnog tumora, sa naglašavanjem diferencijalno-dijagnostičkih izazova u ženskom genitalnom traktu. **Prikaz slučaja.** Dijagnoza inflamatornog miofibroblastnog tumora desnog jajnika sa ekstenzijom u desne parametrijume i peritonealno masno tkivo postavljena je kod pacijentkinje stare 74 godine, nakon detaljnih laboratorijskih pretraga, kompjuterizovane tomografije i patohistološke analize. **Zaključak.** Članak predstavlja neobično iskustvo specijalista u svakodnevnoj praksi, sa uspešnim kombinovanjem veština ginekološke hirurgije i patologije. Inflamatorni miofibroblastni tumor predstavlja dijagnostički izazov koji je neophodno razmotriti prilikom diferencijalne dijagnostike tumora kako jajnika, tako i celokupnog ženskog genitalnog trakta.

Ključne reči: neoplazme jajnika; neoplazme genitalnih organa žene; miofibroblasti; diferencijalna dijagnoza; CT; imunohistohemija; morfološki i histohemijski nalazi; ginekološke hirurške procedure

Introduction

Although it may suggest a malignancy at first sight and is challenging to diagnose, inflammatory myofibroblastic tumor (IMT) has a low to intermediate malignant potential, in spite of its benign origin, and it has been defined as a rare neoplasm with controversial pathogenesis and diversity of histopathological findings. A multiplicity of nomenclature for this tumor [1], potential growth in a wide range of organs [2–4], and possible histopathological overlapping with other mesenchymal tumors [2–5], makes this lesion a potential source of diagnostic errors. To our knowledge, this is one of the rare cases of IMT presenting as an adnexal mass in a female adult and spreading beyond the uterus to other intraperitoneal organs.

Case Report

A 74-year-old female visited our outpatient clinic for regular gynecological examination. Laboratory tests, endovaginal ultrasonography, and multislice computed tomography (MSCT) revealed some abnormalities and the results are shown in **Table 1**. A preoperative diagnosis of right ovarian tumor was made. Intraoperatively, the right ovarian mass was noted to be densely adherent to and infiltrating the uterus fixed in the pouch of Douglas, right ovary, intestinal bands, descendent sigmoid colon and rec-

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Abbreviations
IMT – inflammatory myofibroblastic tumor
FISH – fluorescence in situ hybridization
ALK – anaplastic lymphoma kinase

tum, making it difficult to safely identify the dissection plane. On gross examination, the irregularly shaped uterus was adherent to the left ovary, right ovarian mass and intestinal resectate. The uterine body and the right ovarian mass were adherent to the adjacent fibrous tissue and the serosal surface of the intestine. There were multiple yellowish-white solid areas up to 1.6 cm extending into the myometrial insertion of the right ovary. Mostly unrecognizable right ovary consisted of 4 cm fallopian tube and the ill-defined tumor mass measured 5.5 x 5.5 x 5 cm, white with interspersed yellowish areas, firm to fleshy and soft consistency. Serial sectioning showed heterogeneous appearance with areas of necrosis and foci of hemorrhage **(Figure 1)**.

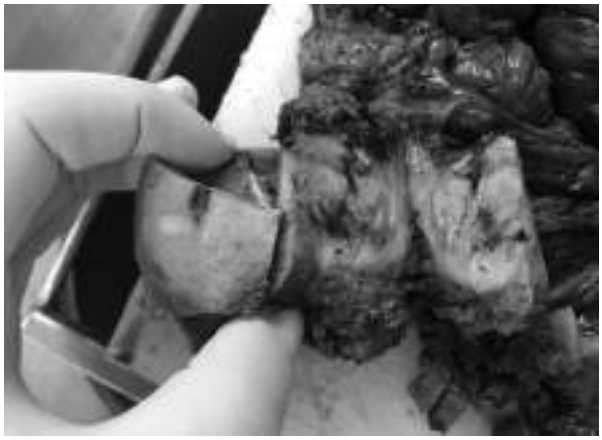

Figure 1. Heterogeneous appearance of the tumor, with areas of necrosis and foci of hemorrhage
Slika 1. *Heterogeni izgled tumora, sa područjima nekroze i fokusima krvarenja*

Microscopic examination showed diffuse proliferation of myofibroblast and fibroblast spindle cells, as well as radial and round cells with moderately abundant eosinophilic cytoplasm, vesicular nuclei (bland chromatin pattern) and focally prominent nucleoli **(Figures 2a and 2b)**. Focal aggregates of round multinucleated cells with peripheral nuclei (Touton giant cells) were seen. Tumor cells were arranged in different patterns: dense fascicular architecture; hypercellular areas of spindle and round cells intermixed with fibromyxoid stroma; and focal areas of abundant stroma with hyalinized collagen fibers and scattered individual spindle cells. No nuclear pleomorphism, atypical mitosis or significant mitotic activity was noted. Along with the myofibroblasts, there was a severe inflammatory reaction, mainly including lymphocytes and plasmocytes, as well as polymorphs. Highly vascularized tumor tissue with focal microabscesses showed no tumor cell infiltration of blood vessel walls **(Figure 2c)**. Tumor tissue microscopically infiltrated the wall of fallopian tube and adjacent fibroadipose tissue, along with the intestinal wall **(Figure 2d)**. The tissue specimen was smooth muscle actin (SMA): positive, CD45: positive, epithelial membrane antigen (EMA): partially positive,

Table 1. Abnormal results of laboratory tests, endovaginal ultrasonography and computed tomography
Tabela 1. *Abnormalni rezultati laboratorijskih pretraga, endovaginalne ultrasonografije i kompjuterizovane tomografije*

Hemoglobin/*Hemoglobin*	119 g/L
Neutrophilia/*Neutrofili*	79.1%
Sedimentation rate/*Sedimentacija*	91 mm/h
C-reactive protein/*C-reaktivni protein*	79.5 mg/L
Urine testing/*Urinokultura*	Negative/*Negativna*
Cancer antigen 125/*Tumor-marker 125*	71.4 U/ml
ROMA index/*ROMA indeks*	43.4%
PAP smear/*PAPA bris*	Negative/*N*egativan
Exploratory curettage *Eksplorativna kiretaža – patohistološki nalaz*	Complex endometrial hyperplasia *Kompleksna hiperplazija endometrijuma*
Endovaginal ultrasonography *Endovaginalna ultrasonografija*	Complex, irregular, hypoechoic, cystic pelvic mass suspected to be a neoplasm; endometrium measured 12 mm/*Kompleksna, nepravilna, hipoehogena, cistična karlična masa; postoji sumnja na neoplazmu; endometrijum veličine 12 mm*
Multislice CT scan of the abdomen and pelvis with oral and intravenous contrast *Multidetektorska kompjuterizovana tomografija abdomena i male karlice sa oralnim i intravenskim kontrastrom*	Large, right inhomogeneous adnexal mass measured 80 x 65 x 65 mm, with no clear display of ovary and fallopian tube/*Velika, desnostrana nehomogena adneksalna masa dimenzija 80 x 65 x 65 mm, bez jasnog prikaza jajnika i jajovoda*

Legend: ROMA - Risk of Ovarian Malignancy Algorithm; PAP - Papanicolaou test; CT - computed tomography
Legenda: ROMA – Algoritam za rizik od maligniteta jajnika; PAPA – Papanikolau test; CT – kompjuterizovana tomografija

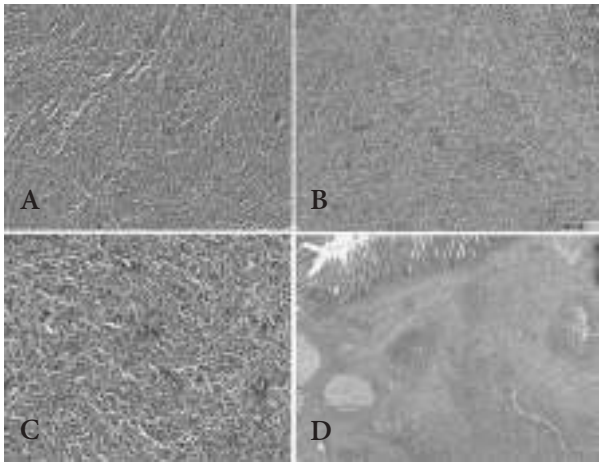

Figure 2. Microscopic appearance of IMT: (a) HE, x 20; (b); HE, x 20; (c) HE, x 20; (d) HE, x 2.5
Slika 2. *Histološki izgled inflamatornog miofibriblastnog tumora: (a) HE, x 20; (b); HE, x 20; (c) HE, x 20; (d) HE, x 2.5*

CD99: positive, D2-40: positive, CD31: positive, CD34: negative, vimentin: positive, CD68: positive, CD1A: positive, S100: negative, h-Caldesmon: negative, Ki-67: 15% positive, anaplastic lymphoma kinase (ALK): negative **(Figure 3)**. As the ALK staining (DAKO, Glostrup, Denmark) was negative, ALK fluorescence in situ hybridization (FISH) was performed on 5-µm-thick unstained formalin-fixed, paraffin-embedded (FFPE) whole sections, after reviewing hematoxylin and eosin (H&E) section to select regions that contained most tumor cells. The ALK chromosomal rearrangement was absent.

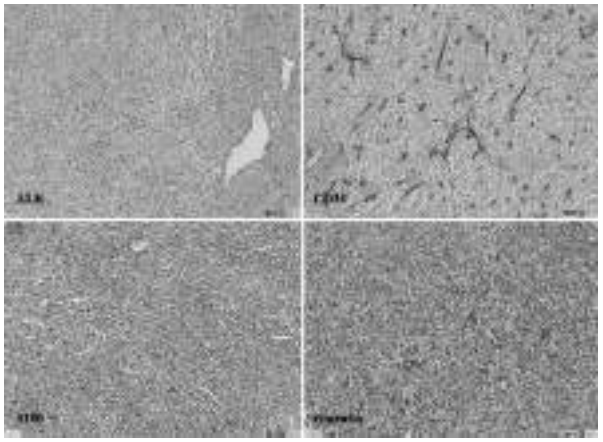

Figure 3. Immunohistochemical analysis showing: (a) anaplastic lymphoma kinase negativity, HE, x 10; (b) CD34 negativity, HE, x 10; (c) S100 negativity, HE, x10; (d) vimentin positivity, HE, x 10
Slika 3. *Imunohistohemijska analiza pokazuje: (a) anaplastična limfom kinaza - negativna, HE, x 10; (b) CD34 negativnost, HE, x 10; (c) S100 negativnost, HE, x 10; (d) vimentin pozitivnost, HE, x 10*

Discussion

A search through the PubMed using the key words "ovary" and "inflammatory myofibroblastic tumor" (2005 – 2019), revealed 2 reports involving 2 patients with primary IMTs of the ovary, one of them in a child [6, 7]. Current studies have reported that the tumor generally occurs in the age range of 6 – 73. The peak age incidence is in the first 4 decades [4], but our patient was an exception.

Histopathological diagnosis depends on identification of myofibroblastic cells and an underlying chronic inflammatory infiltrate, positive vimentin /SMA/calponin staining, and S-100 negative staining [8]. The IMTs often express ALK chromosomal rearrangement that results in abnormal activation of the kinase domain and expression of ALK protein. The ALK-1 gene rearrangement is helpful but not necessary, and the lack of its expression does not rule this diagnosis out. Also, immunostaining with anti-ALK antibodies is often necessary, because IMT and chronic inflammatory lesions can be confused with each other. The reason for the possible confusion is the fact that myofibroblasts are induced in the processes of granulation and inflammation [5–9].

In the area of immunohistochemical and molecular features of IMT, this study has some diagnostic limitations. The largest prospective series of IMT treatment cases suggests that ALK-1 antibody (CD246) from DAKO cannot detect all ALK fusion forms [9]. In addition, the cut-off FISH value of 15% positive tumor cells may lead to a false-negative result in IMTs with borderline percentages of positive cells. The abnormal ALK immunohistochemical expression and/or ALK rearrangement is detected in 88 – 100% of IMT cases of the uterus, but the small sample size of ovarian IMTs limits larger studies discussing this dilemma. Due to the conducted studies, the nonexistent ALK expression/rearrangement should not be exclusive for the diagnosis of IMT [7, 9]. Even though there are alternative non-ALK mechanisms of kinase activation, such as ROS1, RET, PDGFRB and NTRK3 related fusions [8], their use was not practical.

Pathologic differential diagnosis of IMT in the female genital tract can be challenging, as it shows a strong resemblance to smooth muscle tumors. Finding lymphoplasmacytic infiltrate in myxoid areas or nodular fasciitis could help distinguish IMT from leiomyoma or a smooth muscle tumor of unknown malignant potential. Differentiating IMT from leiomyosarcoma rests on aggressive biological behavior of leiomyosarcoma (high mitotic rate, atypical mitotic figures, nuclear atypia, coagulative necrosis) [2–6]. In addition, ALK negative tumors (endometrial and extragastrointestinal stromal tumors) may be in the differential diagnosis, since in our case the IMT was ALK negative [5–8].

Conclusion

Surgical approach to the disease varies based on the patient's age, pathological diagnosis and the extent

of the disease and goes from minor procedures to total hysterectomy and bilateral salpingo-oophorectomy. Intra- or extraperitoneal tumors tend to invade adjacent structures, disabling therapeutic procedures, and are therefore responsible for potential aggressive course of the disease.

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Case report
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A VARIANT OF ZINNER SYNDROME PRESENTING WITH TERMINAL HEMATURIA – A CASE REPORT

VARIJANTA CINEROVOG SINDROMA PREZENTOVANA KAO TERMINALNA HEMATURIJA – PRIKAZ SLUČAJA

Maja STANKOV[1, 2], Marijana BASTA NIKOLIĆ[1, 2], Sonja LUKAČ[1, 2], Ivan AĐIĆ[1, 3] and Jovo BOGDANOVIĆ[1, 4]

Summary

Introduction. Zinner syndrome is a rare congenital malformation characterized by ipsilateral renal agenesis or hypoplasia, seminal vesicle cysts, and ejaculatory duct obstruction. Patients are usually asymptomatic or develop unspecific symptoms. **Case Report.** We present a case of a 22-year-old male patient who presented with painless terminal hematuria. The patient denied trauma or other urinary tract symptoms. Magnetic resonance imaging of the abdomen and pelvis revealed a right renal hypoplasia, a tortuous dilated right ureter draining into polycystic right seminal vesicle, and a dilated ejaculatory duct. **Conclusion.** The size of the seminal vesicle cyst and symptoms affect the treatment. Asymptomatic cysts may be treated conservatively, while cysts that cause symptoms are often an indication for surgical treatment, due to the possibility of infertility caused by the obstruction of the ejaculatory canal. Magnetic resonance imaging has high-resolution properties providing excellent presentation of anatomical relationships and pathology which is extremely important in case of the need for surgical treatment.

Key words: Hematuria; Kidney Diseases; Cysts; Seminal Vesicles; Ejaculatory Ducts; Syndrome; Magnetic Resonance Imaging; Congenital Abnormalities; Infertility, Male; Urogenital Abnormalities

Sažetak

Uvod. Cinerov sindrom predstavlja retku kongenitalnu anomaliju koju karakterišu ispilateralna renalna agenezija ili hipoplazija, cista semene vezikule i opstrukcija ejakulatornog kanala. Pacijenti najčešće nemaju simptome ili imaju nespecifične simptome. **Prikaz slučaja.** Prikazujemo slučaj pacijenta starosti 22 godine koji se javio zbog tegoba u vidu bezbolne terminalne hematurije. Pacijent je negirao traumu i druge tegobe u vezi sa urinarnim traktom. Magnetnorezonantnim pregledom abdomena i karlice uočena je hipoplazija desnog bubrega, tortuozni desni ureter koji se uliva u cistično izmenjenu istostranu semenu vezikulu i dilatiran ejakulatorni kanal. **Zaključak.** Veličina ciste semene vezikule i simptomi utiču na način lečenja. Asimptomatske ciste se mogu lečiti konzervativno, dok su ciste koje prouzrokuju simptome često indikacija za operativno lečenje zbog mogućnosti infertiliteta usled opstrukcije ejakulaturonog kanala. Magnetna rezonancija omogućava odličan prikaz anatomskih odnosa i patologije, što je izuzetno važno u slučaju potrebe za operativnim lečenjem.

Ključne reči: hematurija; bolesti bubrega; ciste; semene vezikule; ejakulatorni kanali; sindrom; magnetna rezonanca; kongenitalne anomalije; muški infertilitet; urogenitalne anomalije

Introduction

Congenital pelvic cysts and ipsilateral renal hypoplasia or agenesis are rare malformations with an incidence of 0.0046%. The connection between upper urinary tract and seminal vesicle aberrations is found in the mutual embryological origins of the ureteric bud and seminal vesicles from the mesonephric or Wolffian duct. At 4 weeks of gestation the distal segment of the Wolffian duct gives rise to the ureteric bud. Delayed absorption of the distal end of the bud can result in ectopic insertion of the ipsilateral ureter into the bladder neck, urethra, ejaculatory duct or seminal vesicle. The ectopic ureter insertion may lead to both upper and lower urinary tract malformations [1–4].

Case Report

We report a case of a 22-year-old male patient who presented with painless terminal hematuria. The patient had no other urinary tract symptoms or trauma and he had already known about the right kidney hypoplasia. The physical examination and laboratory findings were unremarkable.

Abdominal and pelvic magnetic resonance imaging (MRI) and magnetic resonance (MR) urography were performed. Abdominal MRI showed right renal hypoplasia with compensatory hypertrophy of the left kidney. The tortuous dilated right ureter measured a distal diameter of 10 mm **(Figure 1)**. Pelvic MRI showed a cystic lesion of 62 x 37 mm located in the region of the right seminal vesicle. The lesion was hyperintense on T1-weighted (W) images, suggestive of hemorrhage or

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Abbreviations
MRI – magnetic resonance imaging
MR – magnetic resonance

Figure 1. MR urography shows a dilated right ureter draining into the cystic right seminal vesicle (arrow) and hypoplastic right kidney (dashed arrow)
Slika 1. *Magnetnorezonantna urografija - dilatiran desni ureter koji se uliva u cistično izmenjenu desnu semenu vezikulu (strelica) i hipoplastični desni bubreg (isprekidana strelica)*

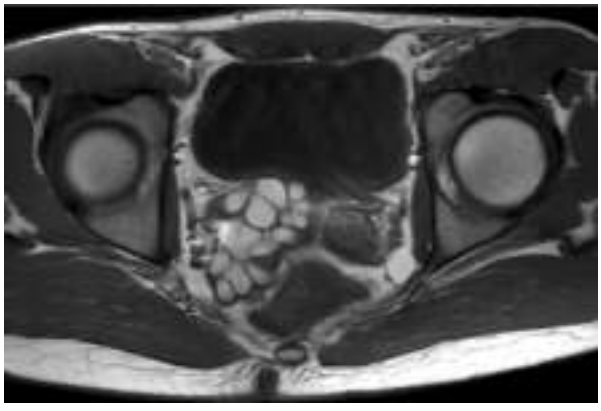

Figure 2. Axial T1-W shows the right seminal vesicle cysts
Slika 2. *T1W aksijalni presek - cistično izmenjena desna semena vezikula*

increased protein content **(Figure 2)**. The sagittal T2-W image showed a dilated (4 x 7 x 11 mm) ejaculatory duct **(Figure 3)**.

Discussion

A triad of unilateral renal agenesis, ipsilateral seminal vesicle cysts, and ejaculatory duct obstruction

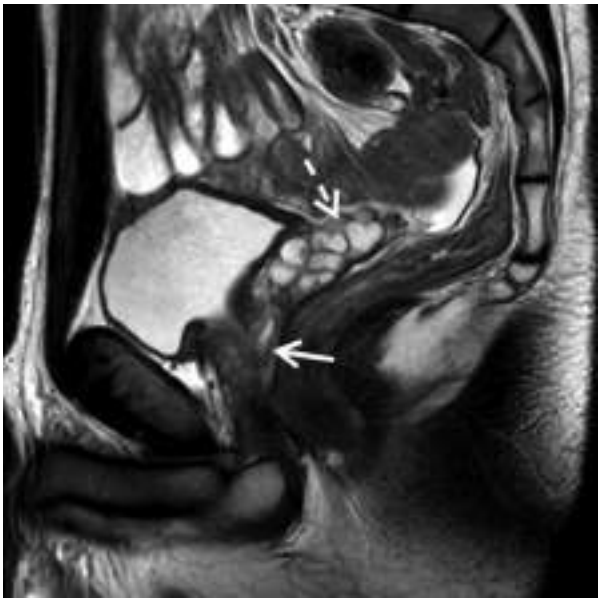

Figure 3. Sagittal T2-W shows the dilated ejaculatory duct (arrow) and the right seminal vesicle cysts (dashed arrow)
Slika 3. *T2W sagitalni presek - Dilatiran ejakulatorni kanal (strelica) i cistično izmenjena semena vezikula (isprekidana strelica)*

is associated with Zinner syndrome, one of the rarest congenital anomalies exclusively found in male patients. It is caused by malformation of the distal part of the mesonephric duct [1–5]. In the literature, renal hypoplasia is also related to this syndrome [3, 5, 6] and the affected kidney is often non-functional [7].

Patients are usually asymptomatic or develop unspecific symptoms. Symptoms usually occur in the 2nd to 4th decade, the period of highest reproductive activity. According to the literature, the size of seminal vesicle cyst correlates with the onset of symptoms. Cysts larger than 5 cm may cause symptoms due to the mass effect, bladder irritation, cyst distention or ejaculatory duct obstruction. Symptoms include voiding problems, perineal or scrotal pain or discomfort, epididymitis and painful ejaculation [3, 8].

The differential diagnosis covers a wide spectrum of pelvic cystic lesions such as Mullerian duct cyst, prostatic cyst, and ureterocele [2, 3, 9].

The treatment depends on the cyst size and symptoms of the patient. Asymptomatic cysts can be treated conservatively. Symptoms caused by a seminal vesicle cyst and the obstruction of the ejaculatory duct which result in infertility may be indications for surgery [3].

Conclusion

Magnetic resonance imaging is the diagnostic modality of choice due to its high-resolution properties providing excellent presentation of anatomical relationships and pathology. Therefore, complete urogenital imaging is important for accurate diagnosis and selection of patients for surgery.

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U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

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.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

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

∗ Kompjuterska datoteka

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

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

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.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

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

∗ *A computer file*

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

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.