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CORRELATION BETWEEN AUTOMATED ASSESSMENT OF SENILE CATARACT DENSITY AND THE APPLIED ULTRASOUND ENERGY DURING PHACOEMULSIFICATION

KORELACIJA IZMEĐU AUTOMATIZOVANE PROCENE GUSTINE SENILNE KATARAKTE I ULOŽENE ULTRAZVUČNE ENERGIJE TOKOM FAKOEMULZIFIKACIJE

Dušan TUCAKOVIĆ[1], Sava BARIŠIĆ[1], Vladimir ČANADANOVIĆ[1, 2], Sofija DAVIDOVIĆ[1, 2], Aleksandar MILJKOVIĆ[1, 2] and Stefan BRUNET[1, 2]

Summary

Introduction. Cataract density is highly important factor when choosing a surgical method and setting the parameters of a phacoemulsification device. Diagnostic devices enable automated assessment of lens opacification degree. **Material and Methods**. Study included 30 patients operated on for senile cataracts at the Clinic of Eye Diseases of the University Clinical Center of Vojvodina. After determining the preoperative best corrected visual acuity, cataract density was assessed using the Pentacam Nucleus Staging scale of the Scheimpflug imaging system, Pentacam AXL Wave (Oculus, Wetzlar, Germany). The evaluation of the applied ultrasound energy during phacoemulsification was quantified and expressed in the form of Cumulative Dissipated Energy index of the Centurion Vision System (Alcon, Irvine, USA) eye microsurgery device. The obtained results are expressed in the form of mean values, and their connection is presented in the form of correlation. **Results.** Statistically significant positive correlation was found between the cataract density expressed with use of the Pentacam Nucleus Staging scale and the applied ultrasound energy during surgery, expressed in the form of Cumulative Dissipated Energy index (r=0.37, p=0.04). No statistically significant correlation was found between preoperative best corrected visual acuity and cataract density expressed with the Pentacam Nucleus Staging scale (p>0.05) or between preoperative best corrected visual acuity and Cumulative Dissipated Energy index (p>0.05). **Conclusion.** The obtained data indicate a positive correlation (r=0.37, p=0.04) between the degree of lens opacification assessed by Pentacam Nucleus Staging scale and the required ultrasound energy applied during phacoemulsification expressed as Cumulative Dissipated Energy index.

Key words: Cataract; Phacoemulsification; Capsule Opacification; Ultrasonic Waves; Treatment Outcome

Sažetak

Uvod. Stepen gustine zamućenja sočiva veoma je važan faktor prilikom izbora hirurške metode i podešavanja parametara uređaja za fakoemulzifikaciju. Dijagnostički uređaji novije generacije omogućavaju automatizovanu procenu stepena gustine kataraktom zamućenog sočiva. **Materijal i metode.** U pitanju je prospektivna, nerandomizovana studija u kojoj je učestvovalo 30 konsekutivnih pacijenata operisanih zbog senilne katarakte na Klinci za očne bolesti Univerzitetskog kliničkog centra Vojvodine. Nakon određivanja preoperativne najbolje korigovane vidne oštrine, procena gustine katarakte izvršena je pomoću Pentacam Nucleus Staging scale Scheimpflug imaging system, *Pentacam AXL Wave, (Oculus, Wetzlar,* Nemačka). Procena uložene ultrazvučne energije tokom hirurškog zahvata kvantifikovana je i izražena u vidu indeksa ukupne uložene energije, *Centurion Vision System (Alcon, irivine, SAD)* uređaja za mikrohirurgiju oka. Dobijeni rezultati su izraženi u vidu srednjih vrednosti, a njihova povezanost je predstavljena u vidu korelacije. **Rezultati.** Dobijena je statistički značajna pozitivna korelacija između gustine katarakte izražene pomoću Pentacam Nucleus Staging scale i uložene ultrazvučne energije tokom fakoemulzifikacije izražena u formi indeksa ukupno uložene energije (r = 0,37, p = 0,04). Nije utvrđena statistički značajna korelacija između preoperativno izmerene najbolje korigovane vidne oštrine i gustine katarakte izražene pomoću *Pentacam Nucleus Staging scale* (p > 0,05), kao ni između preoperativno izmerene najbolje korigovane vidne oštrine i indeksa ukupno uložene energije tokom operacije (p > 0,05). **Zaključak.** Dobijeni podaci ukazuju na pozitivnu korelaciju (r = 0,37, p = 0,04) između stepena gustine katarakte izražena pomoću Pentacam Nucleus Staging scale i uložene ultrazvučne energije tokom fakoemulzifikacije izražene u formi indeksa ukupno uložene energije, što može biti od značaja pri odabiru optimalne hirurške metode.

Ključne reči: katarakta; fakoemulzifikacija; zamućenje kapsule sočiva; ultrazvučni talasi; ishod lečenja

Introduction

Cataract is one of the leading causes of blindness in the world, and is still considered a significant health problem within the population [1]. Cataract is defined as any reduced transparency of the natural intraocular lens, regardless of whether it affects visual acuity. The human lens is a transparent bi-

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Abbreviations

LOCS – Lens Opacities Classification System
PNS – Pentacam Nucleus Staging
CDE – Cumulative Dissipated Energy
BCVA – best corrected visual acuity
UCCV – University Clinical Center of Vojvodina

convex structure made of many closely connected fibers inside the capsule. Lens fibers are formed by the migration of lens epithelial cells from the periphery to the center of the lens and their dedifferentiation into lens fibers.

Due to its germinal and metabolic potential, the lens epithelium, together with the lens fibers, is very susceptible to oxidative stress, which is one of the most important causes of senile cataracts. In relation to the localization of opacities, cataracts are divided into cortical, nuclear and subcapsular [2–4]. Cataracts could be classified according to the patient age at the time of their occurrence, where, roughly speaking, there are senile cataracts in patients older than 65 years of age (age related), presenile cataracts in patients under 65 years of age, and childhood cataracts, as well as cataracts caused by other ocular conditions and systemic diseases [5]. Finally, we come to the classification of cataracts in relation to its 'maturity' or density. This classification has the greatest clinical significance due to its predictive role in the context of treatment.

In practice, subjective and objective methods are used to quantify cataract density. Subjective assessment according to the Lens Opacities Classification System III (LOCS III scale) is the most widespread and frequently used method [6, 7]. It is based on the comparison of reference photographs of cataracts taken on a slit lamp in mydriasis. Although it is a cheap and fast method, its subjectivity is the biggest drawback. Therefore, objective methods for this type of assessment have been developed over time [8].

The use of the Scheimpflug system for the eye anterior segment visualization, incorporated into the Pentacam AXL Wave device (Pentacam HR, Oculus incorporation, Wetzlar, Germany), is the method of choice in many centers dealing with the diagnosis and treatment of eye diseases [9]. The principle of this method is based on the use of a non-contact rotator camera, most often in medicated mydriasis, which records up to 50 images of the anterior segment of the eye in different meridians [10, 11]. The obtained data are analyzed with special software, and the degree of lens opacification density is expressed in the form of the Pentacam Nucleus Staging (PNS) scale with a range of 0 to 5 density units [12].

One of the most important parameters during the surgical treatment of cataracts using the phacoemulsification method is the amount of ultrasound energy applied. The harmful effect of intraoperatively applied ultrasound energy on corneal endothelial cells, which can directly affect the postoperative outcome of treatment, is well known [13]. Modern phacoemulsification devices quantify this value based on the degree of applied ultrasound energy and the duration of the operation, in the form of an index, such as the Cumulative Dissipated Energy (CDE) index within the Centurion Vision System (Alcon, Irvine, USA), which is used in our study [14].

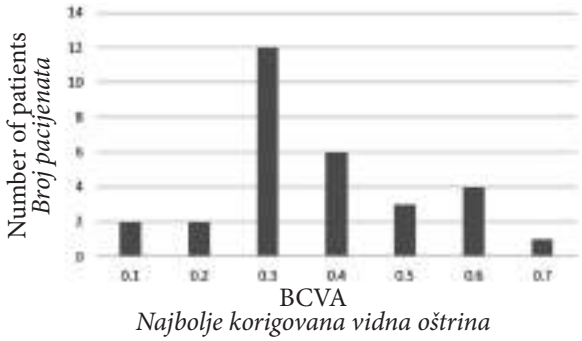
This study was created to determine the correlation between the preoperative best corrected visual acuity (BCVA), the automated lens-cataract density assessment scale, PNS and the total applied ultrasound energy index, CDE during the surgical treatment of cataract using the phacoemulsification method.

Material and Methods

The study we conducted was a non-randomized, prospective study. It included 30 consecutive patients that were operated for senile cataracts at the Clinic of Eye Diseases of the University Clinical Center of Vojvodina (UCCV) in the period from September to November 2021. Patients of both sexes, without associated eye diseases, with early senile cataract participated in the study. The exclusion factors for participation in the study included preoperative BCVA below 0.1, advanced corneal pathology, earlier eye surgeries and the occurrence of intra- and/or postoperative complications. Diabetes and chronic renal insufficiency were also exclusion factors for participation in the study as they are systemic diseases that can lead to the formation of cataracts. The best corrected visual acuity (BCVA) was determined with use of the Snellen optotype as part of the preoperative preparation for the patients. On the day of the operation, the patient's pupils were dilated with Phenylephrine 10% and Tropicamide 1% drops instilled three times consecutively with an interval of 15 minutes. Images of the anterior segment of the eye were taken with a Pentacam AXL Wave device (Pentacam HR, Oculus incorporation, Wetzlar, Germany) one hour after instillation of the last dose of drops, when maximum medicated mydriasis was achieved. We used the automatic recording mode.

All patients were surgically treated by the same surgeon using the Centurion Vision System phacoemulsification device (Alcon, Irvine, USA). The operations were performed under topical anesthesia, making self-healing incisions (central limbal incision at 12 o'clock and two paracentesis, temporally and nasally) with the stop-and-chop technique, and with the use of Sterile Irrigating Solution (BSS) and dispersive viscoelastic. All patients received a suitable soft hydrophobic acrylate intraocular lens (HOYA 254, HOYA Surgical optics, Frankfurt am Main, Germany) that was implanted before the end of the operation. All operations were completed without any intraoperative complications, and the patients were discharged home the same day in good general condition. The index of total CDE from the phacoemulsification machine was read and recorded at the end of each operation.

Statistical analysis of parametric and non-parametric indicators was made using MedCalc software (v.20.104, MedCalc Software Ltd). Arithmetic mean and standard deviation were used to describe the monitored parameters given that they all showed the tendency of normal distribution. Relation between the



Graph 1. Mean values of preoperative BCVA
Grafikon 1. *Srednje vrednosti preoperativno izmerene BCVA*

two characteristics was carried out using correlation analysis, by calculating the Pearson correlation coefficient (r). An appropriate level of statistical significance was set for all tests. All values of $p < 0.05$ indicated that there was a statistically significant difference between the observed results, with a risk of 5%.

Results

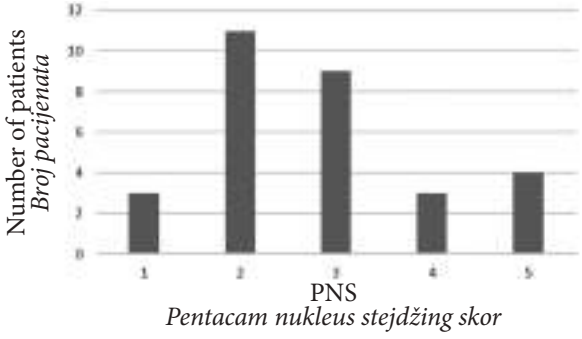
Our study included 30 consecutive patients operated on for senile cataract at the UCCV Clinic of Eye Diseases, aged 74 years in average (65-92 years), with a slight predominance of females (17/13).

The obtained mean values of preoperative BCVA were 0.37 (95% Ci; 0.31 - 0.42). The lowest recorded value was 0.10 and the highest 0.70 according to Snellen **(Graph 1).**

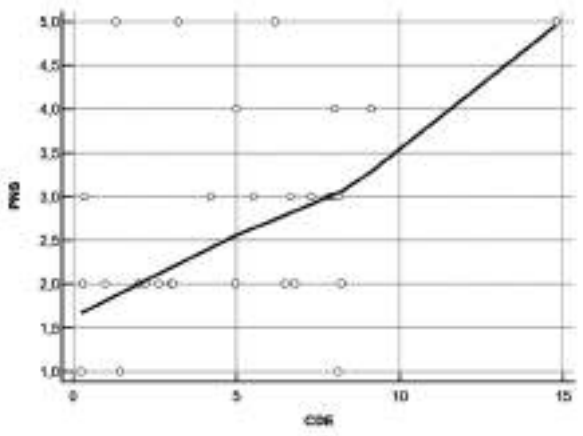
The Pentacam Nucleus Staging values averaged 2.80 or (95% CI; 2.35-3.24) and ranged from 1 to 5 **(Graph 2).**

The mean values obtained for CDE were 5.13 (95% Ci; 3.87 - 6.40). The lowest recorded value was 0.25, and the highest was 14.80.

No statistically significant correlation was found between CDE and BCVA, or between PNS and BCVA ($p>0.05$). On the other hand, a statistically significant positive correlation of mild to moderate degree ($r=0.37$, $p=0.04$) was found between PNS and CDE **(Graph 3).**



Graph 2. PNS mean values ranging from 1 to 5
Grafikon 2. *Srednje vrednosti Pentacam nukleus stejdžing skora u rasponu od 1 do 5*



Graph 3. Correlation between CDE and PNS
Grafikon 3. *Korelacija između uložene ultrazvučne energije i Pentacam nukleus stejdžing skora*

Discussion

Cataract surgery is one of the most frequently performed surgical procedures in medicine with increasing postoperative expectations. Preoperative preparation and precise execution of the procedure is therefore gaining more and more importance, which has led to an increasing number of published studies like this one [15].

The Pentacam Nucleus Staging value in our study is 2.80, which is almost in the middle of the scale. It is important to note that an automatic program was used in this case to quantify the whole lens density and that the patient sample was relatively small. During their research on 238 patients, Xu Ke et al. used a software option to assess the degree of cloudiness of individual lens segments with different section depths. It was observed that PNS values vary significantly depending on the observed lens segment. In the lens segments at a depth greater than 3 mm in over 90% of the cases, the obtained PNS values were almost identical regardless of the degree of the cataract. The reason for this is the reflection-based principle of operation of the Scheimpflug camera and the resulting limitations, due to which deeper lens segments may remain inadequately quantified in cases with predominantly anteriorly located opacities [16]. This indicates that the measurement should be directed to the front segments of the lens or to an earlier clinically determined segment of the lens.

The correlation that showed no statistical significance in our research is the relationship between BCVA and PNS. On the other hand, the research conducted by Beflíková et al. on a slightly larger sample ($n = 55$) obtained a statistically significant positive correlation between these two parameters ($r = 0.451$) [17]. The result we obtained can be explained by the clinical phenomenon that patients with pronounced dominantly nuclear opacities of the lens often have preserved high visual acuity with appropriate myopic correction. On the other hand, centrally localized initial opacities of the pos-

terior cortex of the lens can lead to a drastic drop in BCVA. For this reason, we believe it is necessary to give preference to the evaluation of lens opacification in relation to the visual acuity level when deciding on the operation.

The correlation between PNS and CDE has statistical significance and a positive trend. Such results are not surprising. Sandhya Jeria et al. have found a similar result comparing these two parameters. Nixon finds that preoperative parameter setting on the phacoemulsification device, based on the PNS score, has multiple significance. The operating time is shortened, and the ultrasound energy delivered to the eye is reduced to the required minimum [18].

Lim et al. compared the LOCS III system and the PNS scale for cataract assessment, and they have obtined a result that strongly supports the PNS scale as a better predictor of surgical outcome [19].

Conclusion

Comprehensive preoperative evaluation of cataract patients is one of the most important conditions for choosing and performing an optimal surgical procedure, as well as for achieving maximum postoperative goals. Our results that show statistically significant positive correlation (r=0.37, p=0.04) between the degree of lens opacification assessed by Pentacam Nucleus Staging scale and the amount of ultrasound energy invested during surgery expressed as Cumulative Dissipated Energy index, may have an improving effect on the surgical outcome. We believe that further research aimed at calculation of the Pentacam Nucleus Staging score, as well as increasing the availability of the device for its measurement will help in achieving the above mentioned goal. One of the main disadvantages and limiting factors is the price of the device, which reduces its overall availability and prevents wider usage.

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COMPLICATIONS OF PROXIMAL HUMERUS FRACTURES

KOMPLIKACIJE PRELOMA GORNJEG OKRAJKA RAMENICE

Božo TOPALOVIĆ[1], David STANIĆ[1] and Srđan NINKOVIĆ[1, 2]

Summary

Introduction. Proximal humerus fractures, resulting from direct or indirect trauma, pose a significant clinical challenge. The choice of surgical intervention is influenced by various factors including patient age, comorbidities, bone quality, activity level, fracture characteristics, and the surgeon's expertise. This study aims to assess the frequency and nature of complications arising from the surgical treatment of proximal humerus fractures. **Material and Methods.** In this retrospective analysis, 51 patients were included, with 22 males and 29 females. Two surgical techniques were employed: osteosynthesis using locking plates in 27 patients (average age 54.6 years) and intramedullary nailing in 24 patients (average age 58.4 years). The assessment of outcomes was conducted using the Constant Shoulder Score, and statistical analysis was performed using the Student's T-test. **Results**. Complications were observed in 12 patients (23.5%), comprising 7 males and 5 females. In the locking plate group, where 8 complications occurred, the mean Constant score was 77.44, while the intramedullary nail group, with 4 complications noted, had a mean Constant score of 70.25. No statistically significant difference was found in the incidence of complications based on gender or the type of surgical technique used. **Conclusion.** The study found a higher incidence of complications in male patients and those treated with locking plates, though these differences were not statistically significant. These findings emphasize the need for personalized surgical planning and highlight the complexity of managing proximal humerus fractures.

Key words: Humeral Fractures; Shoulder Fractures; Orthopedic Procedures; Fracture Fixation, Intramedullary; Fracture Fixation, Internal; Bone Plates; Postoperative Complications

Sažetak

Uvod. Prelomi proksimalnog humerusa, koji nastaju usled direktne ili indirektne traume, predstavljaju značajan klinički izazov. Izbor hirurške intervencije je pod uticajem različitih faktora uključujući starost pacijenata, komorbiditete, kvalitet kosti, nivo aktivnosti, karakteristike preloma i stručnost hirurga. Cilj ove studije bio je da se proceni učestalost i priroda komplikacija nakon hirurškog lečenja preloma proksimalnog humerusa. **Materijal i metode.** U ovu retrospektivnu analizu uključen je 51 pacijent, od kojih 22 muškaraca i 29 žena. Primenjene su dve hirurške tehnike: osteosinteza pomoću pločica na zaključavanje kod 27 pacijenata (prosečna starost 54,6 godina) i osteosinteza pomoću intramedularnog klina kod 24 pacijenta (prosečna starost 58,4 godine). Za procenu ishoda korišćen je *Constant* skor, a za statističku analizu primenjen je Studentov T-test. **Rezultati.** Komplikacije su uočene kod 12 pacijenata (23,5%), sa raspodelom od sedam muškaraca i pet žena. Prosečan *Constant* skor bio je 77,44 u grupi sa pločicama na zaključavanje, gde je zabeleženo osam komplikacija, i 70,25 u grupi sa intramedularnim klinom, sa četiri zabeležene komplikacije. Nije pronađena statistički značajna razlika u učestalosti komplikacija na osnovu pola ili vrste hirurške tehnike. **Zaključak.** Studija je pokazala veću učestalost komplikacija kod muškaraca i kod pacijenata lečenih pločicama na zaključavanje, iako ove razlike nisu bile statistički značajne. Ovi nalazi naglašavaju potrebu za individualizovanim hirurškim planiranjem i ističu složenost tretmana preloma proksimalnog humerusa.

Ključne reči: prelomi humerusa; prelomi ramena; ortopedske procedure; osteosinteza pomoću intramedularnog klina; osteosinteza pomoću zaključavajućih ploča; koštane pločice; postoperativne komplikacije

Introduction

Proximal humerus fractures result from either direct or indirect injury mechanisms. They frequently occur due to falls from a standing height, with road accidents being the second leading cause. Incidents involving electric shocks rarely contribute to such fractures [1]. Approximately 5% of all fractures are proximal humerus fractures [2]. Among individuals over 65 years of age, they rank third in frequency, following fractures of the distal radius and proximal femur [3]. The fracture rate shows exponential growth in the age groups 40-84 for women and 60-89 for men, and a ratio of women's fractures to men's being 2.3 to 1 [4]. The highest incidence is during the winter period, from November to March, and the lowest in September [5].

Codman [6] defined the four anatomical parts of the proximal humerus in 1934: head, lesser tuberosity, great tuberosity and shaft. Since then, many classifications of proximal humerus fractures have been introduced, with Neer's classification being the most often used [7]. Neer's classification categorizes proximal humerus fractures based on the number of dislocated segments.

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Abbreviations

CRPP – closed reduction and percutaneous pinning
ORIF – open reduction and internal fixation
HHR – humeral head replacement
IM – intramedullary

Treatment options for proximal humerus fractures are various, including conservative treatment, closed reduction and percutaneous fixation (CRPP), transosseous sutures, intramedullary pin fixation, open reduction and internal fixation (ORIF) and shoulder arthroplasty (HHR). Approximately 80% of fractures belong to the Neer 1 category and exhibit favorable functional outcomes with nonoperative treatment and early rehabilitation [8]. Vallier [9] notes that 3-part and 4-part fractures treated nonoperatively achieve satisfactory outcomes in only 10% of patients, so these types of fractures should be treated surgically in healthy, active individuals.

The choice of operative technique depends on the patient's age, comorbidities, bone quality, activity level, type of fracture, associated fractures, and the surgeon's technical ability.

Complications of proximal humerus fractures include post-traumatic shoulder stiffness and pain, avascular necrosis of the humeral head, nonunion fractures, fracture malunion, post-traumatic arthrosis, malposition of osteosynthetic material, superficial infection, deep infection, shoulder-hand syndrome, Sudeck's syndrome [10], rotator cuff injuries, vascular injuries, neurological injuries (injuries of the brachial plexus, axillary nerve, suprascapular nerve, radial nerve and musculocutaneus nerve), associated chest injuries, muscle calcifications, tendinitis of the shoulder muscles, osteoarthritis and subacromial impingement syndrome.

The objective of this study was to determine the percentage of complications associated with proximal humerus fractures, identify risk groups within age categories for the development of complications, indicate the most common mechanism of injury, determine the prevalence of each complication, determine the frequency of complications based on the type of treatment, and to explore whether there is a statistically significant difference in the frequency of complications based on gender.

Material and Methods

A retrospective study, conducted from June 2010 to August 2017, included 51 patients of both genders who had sustained proximal humerus fractures and underwent operative treatment. Participation in the study was voluntary, and the exclusion criteria comprised patients with open fractures, pathological fractures, or a history of previous shoulder surgery. Among the 51 patients analyzed, 22 were male (43.14%), and 29 were female (56.86%). The treatment modalities were divided between locking plate fixation in 27 patients (53%) and intramedullary nailing in 24 patients (47%). The average age of the cohort was 55.8 years. Specifically, patients treated with a locking plate had an average age of 54.6 years, while those who underwent intramedullary nailing had an average age of 58.4 years. The age range of the patients varied significantly, with the youngest being 28 years old and the oldest 77 years old.

Prior to sustaining their injuries, the patients' activity levels varied: 30 individuals (58.8%) were not engaged in any sports, 18 (35.3%) were recreational athletes, and 3 (5.9%) were professional athletes. The predominant mechanism of injury was a fall, accounting for 33 cases (64.7%). Traffic-related trauma caused injuries to 12 patients (23.5%), and 6 individuals (11.8%) sustained injuries during recreational activities. Information regarding diagnoses, injury dates, and surgical interventions was meticulously gathered from the patients' medical records. The outcomes of the treatments were evaluated during follow-up examinations.

The osteosyntheses in this study were performed using either the Stryker AxSOStm locking plate system or the Stryker T2 proximal humeral nailing system. Prophylactic measures included administering first-generation intravenous cephalosporins immediately before surgery, with antibiotic prophylaxis continuing for a total of 48 hours. All procedures were performed under general anesthesia, supplemented by regional block anesthesia, and were performed by the same surgeon.

Patients were positioned on a radiolucent table in a semi-sitting (beach-chair) position, with the headboard elevated at an angle of 35°-45°. The body alignment along the table edge facilitated the shoulder to cross over, ensuring a full range of motion of the operated arm during surgery.

For osteosynthesis using a locking plate, a deltopectoral approach was consistently employed. The surgical procedure began with a skin incision approximately 10 cm in length, starting 1 cm laterally from the coracoid process tip and extended proximally to the deltoid tuberosity. During this approach, careful attention was given to identify key neurovascular structures, particularly the axillary and musculocutaneous nerves. Fragment repositioning was carried out, and Kirschner pins were temporarily used if needed for stabilization. The locking plate was positioned, ensuring that its proximal end was located 5-10 mm lateral to the intertubercular sulcus and 15-20 mm distal to the greater tubercle's apex. Prior to screw insertion, the plate's placement was verified through X-ray imaging. After screw placement, the rotator cuff tendons were secured to the plate. A final X-ray confirmed the accurate positioning of the plate and screws, after which the wound was closed in layers.

In cases of intramedullary (IM) nailing, a minimally invasive anterolateral approach was employed. A 3 cm longitudinal incision was made anterolaterally from the acromion, with the deltoid muscle split along its fibers. The entry point for the nail was created just medial to the greater tubercle and 1.5 cm posterior to the bicipital groove. Following fracture repositioning and fixation, the incision was similarly closed in layers. To ensure the accuracy of fracture repositioning and the proper placement of the osteo-

synthetic material, radiographic confirmation was obtained using a mobile X-ray unit.

Postoperative care for all patients included immobilization of the upper arm at 45° abduction, the elbow at 90° flexion, and the forearm in a neutral position, lasting for a period ranging from 4 to 6 weeks. The duration of immobilization was individualized depending on the factors such as fracture type, patient age, success of repositioning, and stability of fixation. Passive movements in the elbow of the operated arm were initiated from the onset of immobilization. Starting from the second week, passive shoulder movements were introduced and continued until the immobilization was removed. Upon removal, physical therapy commenced to facilitate the regaining of full range of motion.

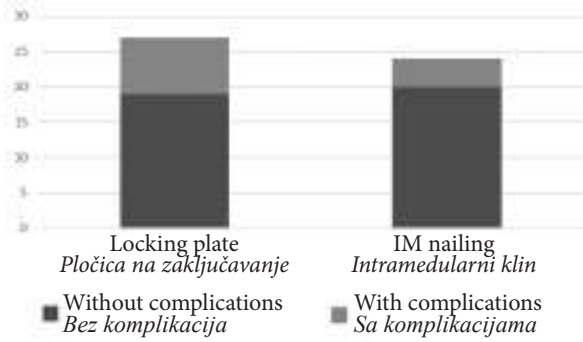
Follow-up assessments included postoperative X-rays taken on the 10th day after surgery, as well as at 3 and 6 weeks, and subsequently at 3 and 6 months. The average follow-up period extended over 4 years, ranging from 1 to 9 years. The well-established Constant score [11] was used to evaluate treatment outcomes. This scale allocates 35 points to subjective parameters, including pain (15 points) and quality of life (20 points), while the remaining 65 points are based on objective measurements of range of motion (40 points) and shoulder strength (25 points), resulting in a maximum score of 100 points.

All patients were overseen by the same surgeon who had performed their respective operations. Any development of complications was documented throughout follow-up visits. Statistical analysis of patient data with use of the Student's T-test was undertaken to identify correlations between different variables and the occurrence of complications.

Results

The study included 51 patients, and complications were observed in 12 participants (23.5%). Among the 22 male patients, 7 encountered complications, while 5 out of the 29 female patients also experienced complications. However, the difference in complication rates between genders was not statistically significant ($p > 0.05$).

Among the 27 patients who underwent osteosynthesis with a locking plate, 8 (29.6%) experienced complications. These complications included superficial infection in 2 patients (7.4%), osteonecrosis of the humeral head in 3 (11.1%), chronic pain in 4 (14.8%), and reduced range of motion in 6 (22.2%) patients. Within this subset, 3 patients could raise their arm above shoulder level, 2 up to shoulder level, and 1 had very limited mobility, below shoulder level. It is noteworthy that the patient with severely limited mobility had a history of forearm surgery 25 years prior, resulting in an elbow joint contracture.



Graph 1. Prevalence of complications depending on the operative technique
Grafikon 1. *Zastupljenost komplikacija zavisno od operativne tehnike*

In the group of 24 patients treated with intramedullary nailing, complications occurred in 4 patients (16.7%). This included chronic pain in all 4 patients, migration of osteosynthetic material in 3 (12.5%), and one of these three also had a reduced range of motion, managing 80° abduction and 50° flexion.

The frequency of complications between the two groups – those operated with locking plates and those with intramedullary nailing – showed no statistically significant difference ($p > 0.05$), as illustrated in **Graph 1**.

When evaluating treatment outcomes using the Constant score, the locking plate group had 33.3% of patients with excellent results, 22.2% with good results, 14.8% with satisfactory results, and 29.6% with poor results. In contrast, the intramedullary nail group had 29.2% of patients with excellent results, 16.7% with good results, 12.5% with satisfactory results, and 41.6% with poor results. The average Constant score [11] was 77.44 for the locking plate group and 70.25 for the intramedullary nail group. Once again, no statistically significant difference ($p>0.05$) was found in the Constant score between the two groups, as detailed in **Table 1.**

Table 1. Results of Constant score by group
Tabela 1. *Vrednost Constant skora po grupama*

	Locking plate/*Pločica na zaključavanje*	IM nail/*Intramedularni klin*	Total/*Ukupno*
Excellent/*Odličan*	9 (33.3%)	7 (29.2%)	16
Good/*Dobar*	6 (22.2%)	4 (16.7%)	10
Satisfying/*Zadovoljavajući*	4 (14.8%)	3 (12.5%)	7
Poor/*Lošš*	8 (29.6%)	10 (41.6%)	18
Average/*Prosečan*	77.44	70.25	74.06
Total/*Ukupno*	27	24	51

Discussion

Proximal humerus fractures are subject to surgical treatment in approximately 15.7% of cases [12]. The primary goal of these operative treatments is to secure stable fixation, enabling the prompt initiation of shoulder movement and early rehabilitation. Despite the increasing incidence of proximal humerus fractures, attributed to an aging population and a rise in osteoporosis cases, no single surgical technique has emerged as definitively superior. Consequently, advocating for a tailored approach for each patient is emphasized.

In our study, the average age of patients undergoing surgery with a locking plate was 54.6 years, compared to 58.4 years for those receiving intramedullary nailing. This finding is consistent with other research, where the average age for patients treated with a locking plate ranged from 59 to 71 years [13–16], and from 48 to 64.8 years for those treated with intramedullary nailing [13, 15, 17, 18]. Our study also noted a higher prevalence of proximal humerus fractures in women, with females constituting 57% of our patient group. This percentage is consistent with other studies, where female representation varied between 40% and 83% [14–17].

Regarding complications and outcomes, among the 27 patients in our study treated with a locking plate, 8 (29.6%) experienced complications. The average Constant score in this group was 77.44. This result is comparable to the findings of Ockert et al., who reported an average Constant score of 75.3, assessed 10 years post-operation with a locking plate, further corroborating our study's results [16].

Schliemann et al. recorded complications in 59% of patients treated with a locking plate, which is a higher percentage compared to our study [14]. It's important to note that their study exclusively involved participants over the age of 65. Lekic et al. observed complications in 33% of their patients [15], closely aligning with our results, while Ricchetti et al. reported a lower complication rate of 18.5% [19].

In contrast to Clavert et al., who found a 16.4% incidence of avascular necrosis of the humeral head in patients treated with a locking plate, our study observed this complication in 11.1% of cases [20]. Avascular necrosis is more common in comminuted fractures, and any dislocation can increase the risk of vascular supply damage to the humeral head. The pathophysiology behind this condition remains not fully understood, as osteonecrosis can occur even in minimally dislocated or non-dislocated fractures, and may not develop in cases where the head is deprived of blood supply [21]. Notably, even when osteonecrosis develops, patients may not experience significant issues if the greater tubercle is well-repositioned and healed, given that the shoulder joint does not bear body weight.

Sudkamp et al. reported a 19% rate of revision surgery following osteosynthesis with a locking plate [22], Ockert et al. noted 14% [16], and Schiliemann et al. observed 29.6% [14]. In our study, none of the patients required revision surgery. Indications for such surgeries in these studies included osteonecrosis, primary or secondary cutout, loss of fixation, and post-traumatic arthritis. Among these, we only encountered osteonecrosis in our study. However, patients with humeral head osteonecrosis often maintain satisfactory shoulder function and thus do not necessitate revision surgery.

Our research also included 24 patients treated with an intramedullary nail, where complications arose in 4 (16.7%) cases, and the average Constant score was 70.25. In a study by Linhart et al. among patients operated with an intramedullary nail, the mean value of the Constant score was 78.4, which is slightly higher than the mean value in our study, but not significantly [23]. Both our study and theirs fall into the „good" category of the Constant score. Similar to our findings, Boileau et al. [18] also did not have any patients requiring revision surgery. All fractures in their study healed, and patients regained sufficient range of motion for daily activities postoperatively. Their average Constant score was 69, aligning closely with our results.

The study conducted by Lekic et al. on patients treated with intramedullary nailing reported a 42% complication rate [14], while Agel et al. observed complications in 45% of their patients [17]. These figures are higher than those in our study. It is important to note that, in our research, any deviation from a complete return to pre-injury shoulder function was classified as a complication. However, complications do not always equate to poor outcomes or necessitate revision surgery. Particularly for elderly patients, a reduction in function may not be significantly problematic as long as they can perform daily activities without pain.

Our study found no statistically significant differences in outcomes or Constant scores between the locking plate and intramedullary nail groups, a finding echoed by Von Ruden et al. who reported Constant scores of 73 and 72 in these groups, respectively [24].

In our patient cohort, 29.6% of those treated with a locking plate experienced complications, compared to 16.7% in the intramedullary nail group. This difference was not statistically significant, aligning with the findings of Konrad et al., who also reported no significant difference in complication rates between these two groups (31% in the locking plate group and 21% in the intramedullary nail group) [13].

The overall benefit of operative treatment for proximal humerus fractures is substantial, with the complications observed in our study having minimal impact on patients' quality of life. Without operative intervention, these injuries could have led to severe disability. It is also noteworthy that the Constant score, while useful for assessing shoulder function, may not fully reflect a patient's quality of life. Many patients with a low Constant score still maintain satisfactory function and can perform daily activities. The distinction between objective and subjective assessments of shoulder hemiarthroplasty outcomes can be clarified by considering the impact of post-surgery range of motion on daily

activities. The majority of everyday tasks are accomplished at scapular level, involving 80 to 90 degrees of abduction and external rotation. In this range, functional outcomes are generally satisfactory for normal activities of daily living. However, activities requiring maximum abduction and flexion (180 degrees) represent a smaller portion, contributing to the variation in subjective evaluations, as they may not align with the overall functional success indicated by objective measures [25]. Furthermore, our study encompassed all types of fractures, including severe cases that would likely have resulted in significant disability if left untreated.

However, there are limitations to our study. These include a small sample size, the lack of subdivision of patients according to Neer's classification for individual evaluation, and its retrospective nature. Another limitation is the heterogeneity between the locking plate and intramedullary nail groups in terms of fracture type, patient gender, and age. Additionally, comparing our data with other studies [13–20, 22–24] is challenging due to variations in fracture types, patient demographics, follow-up duration, and study inclusion criteria.

Conclusion

Based on the analysis of the results from this study and a review of the literature, the following conclusions can be drawn:

– Proximal humerus fractures are predominantly observed in the elderly population.

– Although complications were observed more frequently in men, the difference was not statistically significant.

– Patients treated with osteosynthesis using a locking plate experienced more complications compared to those treated with intramedullary nailing, but this difference was not statistically significant.

– The Constant score was marginally higher in the group treated with a locking plate, but this difference did not reach statistical significance.

– It is important to note that the Constant score, while useful for assessing shoulder function, may not be the most accurate indicator of a patient's overall quality of life. This is because many patients with a lower Constant score still maintain satisfactory function and are able to perform daily activities without experiencing pain.

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BLOOD PRESSURE, LUNG FUNCTION AND MUSCULAR STRENGTH VALUES IN STUDENTS WITH JOINT HYPERMOBILITY

VREDNOSTI KRVNOG PRITISKA, PARAMETARA PLUĆNE FUNKCIJE I MIŠIĆNE JAČINE KOD STUDENATA SA HIPERMOBILNOŠĆU ZGLOBOVA

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Summary

Introduction. Elastin and collagen are the key components of bones, cartilage, tendons, skin, lungs and arterial walls. Weak connective tissue disorders and joint hypermobility are pathological conditions where the structure of collagen fibers is changed, resulting in a number of symptoms. The objective of this study was to determine the prevalence of weak connective tissue disorder in second- and third-year students of the Faculty of Medicine of the University of Novi Sad, and to compare muscle strength, pulmonary function and blood pressure between individuals with and without hypermobility. **Material and Methods.** The study included 100 students (50 females and 50 males) divided into two groups: Group 1 with weak connective tissue and Group 2 with normal connective tissue. The subjects were assessed according to the Beighton score and the Brighton criteria to diagnose hypermobility. Values of blood pressure, pulmonary function and muscle strength were also measured. **Results.** Analysis of anthropometric parameters and blood pressure values showed significant difference between the groups, including the body height (p=0.014) and body weight (p=0.021) values and systolic (p<0.001) and diastolic (p=0.004) blood pressure values. Dynamometric parameters and lung function values were significantly different between the groups, with vital capacity (p<0.001), forced vital capacity (p=0.05), forced expiratory volume in the 1st second (p=0.025). Lower values were noted in group 1. **Conclusion.** Weak connective tissue was found with high percentage of students of the Faculty of Medicine of the University of Novi Sad (67%). Blood pressure, lung function vales and dynamometric parameters were significantly lower in group 1.

Key words: Joint Instability; Blood Pressure; Spirometry; Muscle Strength; Connective Tissue

Sažetak

Uvod. Elastin i kolagen su ključne komponente kostiju, hrskavice, tetiva, kože, pluća i zidova krvnih sudova. Slabo vezivno tkivo i hipermobilnost zglobova predstavljaju patološka stanja kod kojih postoji izmenjena struktura kolagenih vlakana, što se manifestuje brojnim simptomima. Cilj istraživanja bio je da se utvrdi prevalencija slabog vezivnog tkiva kod studenata druge i treće godine Medicinskog fakulteta Univerziteta u Novom Sadu, kao i poređenje vrednosti mišićne jačine, parametara plućne funkcije i vrednosti krvnog pritiska kod osoba sa slabim vezivnim tkivom i bez njega. **Materijal i metode.** Istraživanje je obuhvatalo grupu od 100 studenata (50 ženskog i 50 muškog pola) koji su bili podeljeni u dve grupe: prva grupa osobe sa slabim vezivnim tkivom i druga grupa bez slabog vezivnog tkiva. Svim ispitanicima dijagnoza je postavljena pomoću *Beighton* skora i *Brighton* kriterijuma. Potom su merene vrednosti krvnog pritiska, parametri plućne funkcije i mišićne jačine. **Rezultati.** Analizirajući vrednosti antropometrijskih parametara i arterijskog krvnog pritiska između ispitivanih grupa uočeno je postojanje statistički značajne razlike. Razlike su evidentirane u pogledu telesne visine (p = 0,014), telesne mase (p = 0,021) kao i u pogledu vrednosti sistolnog (p < 0,001) i dijastolnog (p = 0,004) arterijskog krvnog pritiska. Takođe, postojanje statistički značajne razlike među grupama utvrđeno je i poređenjem vrednosti parametara plućne funkcije, vitalni kapacitet (p < 0,001), forisirani vitalni kapacitet (p = 0,05), forisirani ekspiratorini volumen u prvoj sekundi (p = 0,025) i dinamometrije. Niže vrednosti su prisutne u prvoj grupi. **Zaključak.** Slabo vezivno tkivo je zastupljeno u visokom procentu kod studenata Medicinskog fakulteta u Novom Sadu (67%). U prvoj grupi su evidentirane značajno niže vrednosti arterijskog krvnog pritiska, parametara plućne funkcije kao i dinamometrijskih parametara.

Ključne reči: hipermobilnost zglobova; krvni pritisak; spirometrija; dinamometrija; vezivno tkivo

Introduction

The concept of weak connective tissue was not in use until late 19th century and more significance was given to this term later [1, 2]. The hypermobility syndrome is defined as a condition with an increased degree of joint mobility, which exceeds the physiological limits [3]. This syndrome is characterized by the presence of musculoskeletal symptoms and symptoms by other organs that include connective tissue is their integral part, but systemic rheumatologic disease is not present [4, 5].

The connective tissue is a tissue of mesenchymal origin, and it is made of fibroblasts, matrix, collagen

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Abbreviations
BMI – body mass index
BW – body weight
BH – body height
VC – vital capacity
FVC – forced vital capacity
FEV1 – forced expiratory volume in the first second

and elastic fibers. The pathogenesis of weak connective tissue includes a change in the structure of collagen and elastin fibers, which is manifested through many symptoms [6, 7]. Joint hypermobility is characterized only by an increased degree of joint mobility that exceeds the physiological limits, but without the presence of symptoms by other organs [8], which is the main difference between joint hypermobility and the hypermobility syndrome [9, 10]. Joint hypermobility and hypermobility syndrome are hereditary disorders with the autosomal dominant pattern of inheritance and with polymorphic symptomatology [10, 11]. Differential diagnostics should distinguish this condition from other hereditary disorders of the connective tissue with low incidence such as Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, where severe clinical signs are present [12, 13].

Along with elastin, collagen is a key structural component of the bones, cartilage, tendon, skin, lungs and blood vessel walls. According to the literature, there is a correlation between some respiratory disorders and the weak connective tissue disorder. There has been an increase in the prevalence of asthma and atopy in persons with weak connective tissue [14]. Connective tissue allows for the connection of muscle fibers into an organized unit, thus forming the shape of muscles. Also, elastic and collagen fibers are integral part of all three proper muscle fascia and enable the transmission of force, which is developed due to contraction of muscle fibers, to the tendons [15]. These patients are often susceptible to injuries of ligaments [16, 17].

Different studies show the percentage distribution of week connective tissue syndrome in children and student population [18–21]. It was found that the percentage distribution of week connective tissue varies with age (decreasing with age), gender (the syndrome is more common in women), and ethnicity [22]. Furthermore, doing some sports, such as ballet or rhythmic gymnastics, can lead to hypermobility over time due to active training that involves stretching [23, 24].

The aim of this study was to determine the prevalence of week connective tissue in second- and third-year students at the Faculty of Medicine of the University of Novi Sad, and to compare the values of blood pressure, lung function parameters and muscle strength in students with and without weak connective tissue.

Material and Methods

The study was designed as prospective research. All participants were tested in a functional diagnostics laboratory before noon. The research consisted of four consecutive phases. The first phase included diagnosis, determination of prevalence and division of students into two groups. After establishing the prevalence of week connective tissue in 100 subjects, 20 patients were excluded from further examination due to hypertension (150/100 mmHg) and respiratory diseases. Group 1 included subjects with weak connective tissue (n=67) and the Group 2 was the control group (n=33). Anthropometric measurements and blood pressure values were taken in the second phase of the study. The values of pulmonary function parameters were measured in the third phase. Muscular strength was measured in the final, fourth phase of the study.

This research included 100 (50 females and 50 males) second- and third-year students of the Faculty of Medicine of the University of Novi Sad. Age and anthropometric parameters of the participants are presented in **Table 1.** All the students were healthy and not physically active. It was emphasized to them not to consume cigarettes, coffee or energy drinks before testing as it would affect the measured values of blood pressure. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Novi Sad (Novi Sad, Serbia; approval no. 01-39/234). Before the research, the concept of the study, risks and benefits of participation were explained to the participants in detail, both orally and in written, as well as what was expected of them, the methods and purpose of the examination, after which they signed the informed consent voluntarily.

The diagnosis was based on the Beighton score and the Brighton criteria. The Beighton score is a nine-point scale and requires the performance of five maneuvers, four passive bilateral and one active unilateral maneuver. It includes nine scoring points, where one point is assigned for the ability to perform each of the four maneuvers bilaterally and one more point for the flexibility of the spinal column beyond the physiological limits. Cutoff of ≥4 points was used for the diagnosis of week connective tissue and joint hypermobility [3].

Table 1. Age and anthropometric parameters
Tabela 1. *Godine života i antropometrijski parametri*

Parameters *Parametri*	Weak connective tissue *Slabo vezivno tkivo*	Control group *Kontrolna grupa*
Age (years)/*Godine života/*Mean ± SD/*Srednja vrednost* ± SD	20.59 ± 0.67	20.67 ± 0.9
Body height (cm)/*Telesna visina (cm)/*Mean ± SD/*Srednja vrednost* ± SD	171.2 ± 8.74	176.24 ± 8.81*
Body weight (kg)/*Telesna masa (kg)/*Mean ±SD/*Srednja vrednost* ± SD	65.62 ± 12.74	72.85 ± 14.41*
BMI (kg/m^2)/*Indeks telesne mase (kg/m^2)*/Mean ±SD/*Srednja vrednost* ± SD	22.38 ± 3.38	23.26 ± 3.14

*p<0.05

Table 2. Blood pressure values in both groups of subjects
Tabela 2. *Vrednosti krvnog pritiska kod obe grupe ispitanika*

Parameters *Parametri*	Systolic blood pressure (mmHg) *Sistolni krvni pritisak (mmHg)*	Diastolic blood pressure (mmHg) *Dijastolni krvni pritisak (mmHg)*
Weak connective tissue/*Slabo vezivno tkivo*	104.49 ± 11.38	66.12 ± 10.57
Control group/*Kontrolna grupa*	114.84 ± 14.8*	72.9 ± 8.64*

*p<0.05

We used the Brighton criteria, consisting of major and minor criteria, to determine the hypermobility syndrome, which is a set of symptoms and signs. The subjects needed to have: 1) two major; 2) one major and two minor; or 3) four minor criteria to be diagnosed with the hypermobility syndrome [5].

The body mass index (BMI) was calculated according to the following formula:

$$BMI=\frac{BW(kg)}{BH(m)^2}.$$

Body weight (BW) was measured using medical weighing scales with sliding weights with precision of 0.1 kg, while the body height (BH) was measured using a stadiometer with a precision of 0.1 cm. Arterial blood pressure was measured on the left hand with the subjects sitting, using the noninvasive auscultation method by the Riester device. The students had to sit for 5-10 minutes before measuring in order to obtain the best possible accuracy of the measurement.

Vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in the 1st second (FEV1) were measured with use of a spirometer (MIR Spirolab, Enraf-Nonius, Netherlands). The values of Tiffeneau index were calculated using the formula:

$$FEV1\%=\frac{FVC}{FEV1}\ x\ 100.$$

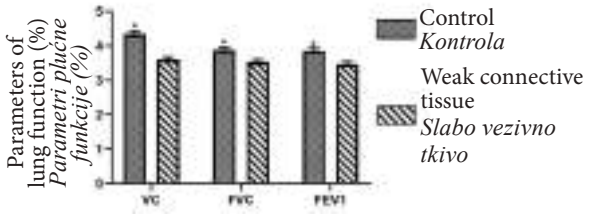
Using the Concept2Dyno (Concept2 Inc., Vermont, USA) isokinetic dynamometer with constant resistance and variable speed, we measured muscle strength in the examined groups. We tested the muscle strength of the leg extensors, flexors and arm extensors. The software system of the device calculated the achieved values of the average and maximum overloaded muscle strength when performing isolated contractions of certain muscle groups.

Mean value ± standard deviation (SD) was calculated for all experimental data. The obtained quantitative data were analyzed in order to determine the existence of statistically significant differences between the groups. Student's t-test was used for this purpose. Data were analyzed using the JASP 0.8.0.1 software. Statistically significant difference was set at $p \leq 0.05$.

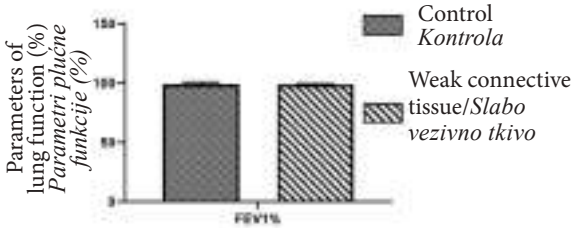
Results

In a group of 100 students (50 females and 50 males), after the diagnosis, 67% were found to be subjects with weak connective tissue.

Analysis of **Table 2** shows the mean values of systolic ($p < 0.001$) and diastolic ($p=0.004$) blood pressure among the examined groups. Lower values of these parameters were found in the group with weak connective tissue.



Graph 1. The means of VC, FVC, FEV1 in the examined groups
Grafikon 1. *Srednje vrednosti vitalnog kapaciteta, forsiranog vitalnog kapaciteta, forsiranog vitalnog kapaciteta u prvoj sekundi kod ispitivanih grupa*



Graph 2. The means of FEV1% in both groups of subjects
Grafikon 2. *Srednje vrednosti forsiranog vitalnog kapaciteta u prvoj sekundi u obe grupe ispitanika*

Comparison of the measured values of lung function parameters (VC, FVC, FEV1) showed a statistically significant difference between the examined groups **(Graph 1).**

Lower values were found in the group with weak connective tissue. The Tiffeneau index values were found not to be significantly different **(Graph 2).**

The mean values and the standard deviation of the dynamometric parameters of the two examined groups are presented in **Table 3**. Analysis of these parameters showed a statistically significant difference in the average and maximum values of muscle contraction strength of leg extensors, arm extensors and arm flexors between the groups. The control group had higher values of all dynamometric parameters.

Discussion

Variation in the prevalence of weak connective tissue and joint hypermobility is the subject of numerous studies [18, 20, 21]. Interest groups were mainly pediatric patients who were referred to different specialist examinations, and school-age children [25, 26]. The

Table 3. Comparison of dynamometric parameters between students with weak connective tissue and the control group
Tabela 3. *Poređenje vrednosti dinamometrijskih parametara između studenata sa slabim vezivnim tkivom i kontrolne grupe*

Parameters *Parametri*		Weak connective tissue *Slabo vezivno tkivo*	Control group *Kontrolna grupa*
Leg extensors *Ekstenzori noge*	Average value (kg)/*Prosečna vrednost (kg)*	95.16 ± 22.8	125.77 ± 36.25*
	Maximum value (kg)/*Maksimalna vrednost (kg)*	104.89 ± 26.06	136.55 ± 36.41*
Arm extensors *Ekstenzori ruke*	Average value (kg)/*Prosečna vrednost (kg)*	37.33 ± 16.25	52.39 ± 20.14*
	Maximum value (kg)/*Maksimalna vrednost (kg)*	40.79 ± 17.20	56.48 ± 20.59*
Arm flexors *Fleksori ruke*	Average value (kg)/*Prosečna vrednost (kg)*	39.90 ± 17.19	53.35 ± 18.99*
	Maximum value (kg)/*Maksimalna vrednost (kg)*	44.51 ± 18.16	59.19 ± 20.24*

*p<0.05

prevalence of weak connective tissue and joint hypermobility in these periods of life ranges from 8.87% to 34% [19–21, 27, 28]. There have been few studies where research was based on student population [29, 30], but none in Serbia.

In a study carried out by Al Jarallah et al. on a group of students in Kuwait with average age of 21 ± 2.2 years, prevalence of weak connective tissue was 22.3% [29], while prevalence was slightly higher (29.8%) among Iraqi students [30]. Contrary to the previous studies, prevalence of weak connective tissue in students of the Faculty of Medicine of the University of Novi Sad is 67%, which is extremely high. These results could be related to the multiethnic population in the territory of Vojvodina.

Type I and type III collagen take part in the structure of joint ligaments and connective tissue of blood vessel walls [31, 32]. Defects of these types of collagens are associated with abnormalities of connective tissue and vascular tissue in subjects with hypermobility [33]. Basically, it is possible to explain the presence of lower systolic and diastolic blood pressure values, which statistically significantly differ in people with the above diagnosis compared to healthy subjects. Engelbert et al. found the presence of lower systolic (100.2 ± 2.4) and diastolic (64.3 ± 1.7) blood pressure values in the pre-puberty group with hypermobility syndrome compared to the control group (110.1 ± 1; 71.6 ± 0.7). There have been no studies that compared the values of systolic and diastolic blood pressure in students with and without weak connective tissue [34].

The values of all measured pulmonary parameters in our study statistically significantly differ among the groups. There was no data so far about lung function parameters in people without respiratory illnesses and with a positive diagnosis of weak connective tissue. Lower values of lung function parameters in our research could be a consequence of a defect in connective tissue in students with the positive diagnosis. Namely, there is a change in the mechanical properties of the airways and the lung parenchyma, resulting in an increase in the airways expansibility and the tendency towards airways collapse, which explains the obtained results [14].

Reduced muscular strength of the upper limbs in adolescents with weak connective tissue was also found by Scheper et al. [35]. In terms of the values of muscle strength of the leg extensors in the students with weak connective tissue, our results comply with earlier studies on the isokinetic dynamometer [36, 37]. However, research by Jensen et al. [38] and Stewart & Burden [39] states that there was no statistically significant difference in muscle strength of leg extensors in subjects with weak connective tissue compared to the control group. In the same study, Stewart & Burden researched male athletes, whereas both sexes with no physical activity were included in our research. The fact that sport has an impact on the development of muscle strength is a possible explanation of these results. According to the literature, the state of hypermobility decreases with age [26, 30, 40], which is consistent with both our and the results of Jensen et al. Our subjects were 20.63 ± 0.77 years old, while subjects in Jensen et al. were older, about 40. The main factor contributing to the reduction of muscle strength is inactivity of the extremities caused by pain, as well as weakness of the ligaments, which is the base of joint instability [41].

Conclusion

Week connective tissue is present in a far greater percentage (67%) among a sample of 100 examined students of the Faculty of Medicine in Novi Sad than in other population groups. Lower values of systolic and diastolic blood pressure were recorded in the group of students with weak connective tissue. Pulmonary function parameters (vital capacity, forced vital capacity, forced expiratory volume in the 1st second) in students with weak connective tissue showed lower values than in the control group. Lower muscle strength of the upper and lower extremities was observed in the student population with weak connective tissue compared to the control group.

The results obtained in our research are important for raising the awareness about the effect of dosed physical activity on the development of muscle strength in persons with weak connective tissue to prevent complications that can have a significant impact on the quality of life.

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HOW VACUUM-ASSISTED TOMOSYNTHESIS-GUIDED BIOPSY FACILITATES THE DIAGNOSIS OF BREAST CHANGES

KAKO VAKUUM-ASISTIRANA BIOPSIJA VOĐENA TOMOSINTEZOM OLAKŠAVA DIJAGNOSTIKU PROMENA NA DOJKAMA

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Summary

Introduction. Breast cancer stands as the predominant form of cancer diagnosed in women worldwide. In the Republic of Serbia, breast cancer held the top position in 2020, accounting for 22.6% of all cancer cases. Early diagnosis of the disease can lead to favorable prognosis and high survival rates. National and opportunistic screening aim to conduct preventive mammography examinations in women aged 50-69, with vacuum-assisted biopsy guided by tomosynthesis being performed when necessary as a diagnostic procedure. **Material and Methods.** The vacuum-assisted tomosynthesis guided breast procedure typically takes half as the time of a stereotaxic biopsy. The procedure begins with planning the approach to the lesion, contingent up on its localization within the breast. **Results**. The first vacuum-assisted biopsy guided by tomosynthesis in Serbia was conducted at the Radiology Center of the Clinical Center of Vojvodina in December 2020, utilizing Selenia Hologic mammography unit. Between December 2020 and June 2023, a total of 161 tomosynthesis-guided VABs were performed in 160 patients, with one patient undergoing the procedure on both breasts. **Conclusion**. Most authors report using the vacuum sampling technique during the vacuum-assisted biopsy guided by tomosynthesis. Given the potential of complete removal of the lesion with this method, it is standard practice to place a marker at the biopsy site. The increasing incidence of breast cancer is observed globally, and it is attributed to advancements in standards of living and lifestyle changes.

Key words: Breast Neoplasms; Mammography; Biopsy, Needle; Image-Guided Biopsy; Imaging, Three-Dimensional; Early Diagnosis

Sažetak

Uvod. Karcinom dojke je vodeća lokalizacija svih karcinoma dijagnostikovanih kod žena širom sveta. U Republici Srbiji u 2020. godini, karcinom dojke je na prvom mestu sa učešćem od 22,6%. Rana dijagnoza bolesti može dovesti do dobre prognoze i visoke stope preživljavanja. Cilj nacionalnog i oportunog skrininga bio je obavljanje preventivnih mamografskih pregleda kod žena starosti 50−69 godina. Vakuum-asistirana biopsija vođena tomosintezom urađena je kod pacijentkinja kojima je ovakva dijagnostička procedura bila neophodna. **Materijal i metode.** Procedura biopsije dojke vođena tomosintezom traje približno upola kraće od one koja je potrebna za stereotaksičnu biopsiju. Postupak počinje planiranjem pristupa promeni i zavisi od njene lokalizacije u dojci. **Rezultati**. Prva vakuum-asistirana biopsija vođena tomosintezom u Srbiji obavljena je u Kliničkom centru Vojvodine, Centru za radiologiju decembra 2020. godine na mamografu *Selenia Hologic*. Od decembra 2020. do juna 2023. urađena je 161 vakuum-asistirana biopsija vođena tomosintezom kod 160 pacijentkinja, a kod jedne pacijentkinje operacija je obavljena na obe dojke. Postupak počinje planiranjem pristupa promeni i zavisi od njene lokalizacije u dojci. **Zaključak**. Većina autora navodi da su prilikom ove procedure dojke vođene tomosintezom, koristili tehniku vakuumskog uzorkovanja. S obzirom na verovatnoću potpunog uklanjanja promene ovom metodom, rutinska je praksa postavljanje markera na mesto biopsije. Porast incidencije raka dojke beleži se u svim razvijenim zemljama i zemljama u razvoju i pripisuje se porastu standarda i promeni načina života.

Ključne reči: karcinom dojke; mamografija; biopsija iglom; biopsija vođena slikom; trodimenzionalni imidžing; rana dijagnoza

Introduction

Breast cancer stands as the predominant form of cancer diagnosed in women worldwide, emerging as one of the leading public health concerns in recent decades. According to the World Health Organization (WHO) projections, the number of women affected with this disease is expected to double by 2030 [1]. In 2020, the International Fund for Cancer Research reported 2,261,419 newly diagnosed cases of breast cancer worldwide, with Belgium and the Netherlands ranking among the leading with standardized incidence rates of 113.2/100,000 and 100.9/100,000 respectively [2]. In the Republic of Serbia, breast cancer held the top position among cancer diagnoses in women in 2020, with preva-

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Abbreviations

WHO – World Health Organization
SVAB – stereotaxic vacuum assisted biopsy
VAB – vacuum assisted biopsy
2D – two dimensional
IDC – invasive ductal carcinoma

lence rate of 22.6%, surpassing lung cancer and bronchus (11.3%) and colon and rectal cancer (10.5%) [3].

In 2020, there were 4,368 new cases registered in Serbia and 1,246 in Vojvodina, accounting for approximately one quarter of all malignant diseases in women. Based on the data from the Cancer Registry in the Republic of Serbia, the standardized incidence rate of breast cancer in 2020 was 112.4/100,000 inhabitants for the Republic of Serbia and even higher at 121.6/100,000 inhabitants for Vojvodina [3]. The incidence of breast cancer is constantly increasing, which is partly attributed to demographic aging trends. Incidence and mortality rates are often linked to a country's level of development. Higher incidence rates are observed in highly developed countries, attributed to better and more advanced preventive healthcare measures. Conversely, higher mortality rates are prevalent in underdeveloped countries, indicating insufficiently developed preventive healthcare and limited access to healthcare services.

Breast cancer is one of the leading causes of premature death among women, ranking four in terms of years of lost life after ischemic cerebrovascular disease, ischemic heart disease and type 2 diabetes mellitus [4]. Globally, the average standardized mortality rate for breast cancer in 2020 was 13.6/100,000, with the highest number of deaths reported in Barbados and Fiji, at 42.2/100,000 and 41/100,000, respectively [2]. In the Republic of Serbia, based on data from the Cancer Registry, the standardized mortality rate for breast cancer in 2020 was 20.3/100,000, and 22.5/100,000 in Vojvodina. In the same year, 1,782 deaths were attributed to breast cancer in the Republic of Serbia, with 526 deaths reported in Vojvodina. Regarding mortality from various cancer types in women, breast cancer ranked highest in the Republic of Serbia in 2020, accounting for 19.5% of deaths, ahead of lung and bronchus cancer (17.5%) and colon and rectum cancer (10.4%) [3].

Early detection of breast cancer is paramount for improving outcomes and survival rates. In the Republic of Serbia, organized breast cancer screening has been underway since 2012 as a decentralized program. Defined by regulations on the content and scope of the right to health care from mandatory healthcare coverage and participation, the screening targets women aged 50-69, with a population coverage goal of at least 75% of women within the specified age group. However, it is recommended that all women within this age range participate in screening [5]. In Vojvodina, Novi Sad was included in this program in December 2012, followed by Subotica, Senta, Zrenjanin, Sremska Mitrovica, and Ruma, where opportunistic screening has been implemented in these healthcare centers.

Over the past two decades, research concerning breast cancer has shown remarkable advancements in early diagnosis and treatment, leading to prolonged survival and better quality of life post-therapy.

Breast cancer has the ability to metastasize, spreading to distant organs such as bones, liver, lungs, and brain, which largely accounts for its incurability. Early diagnosis of the disease can result in favorable prognoses and high survival rates [6,7].

Breast tumors typically originate from ductal hyperproliferation, progressing to benign tumors or metastatic cancers under the continuous stimulation of various carcinogenic factors. The tumor microenvironment, including stromal influences or macrophages, plays a vital role in the initiation and progression of breast cancer [8]. Several risk factors contribute to the likelihood of developing breast cancer, including gender, aging, estrogen exposure, family history, gene mutations, smoking, and an unhealthy lifestyle [9]. The majority of breast cancer cases occur in women, with incidence rates approximately 100 times higher in women compared to men [10].

Presentation of the situation

Breast cancer poses a global public health challenge, not only due to its epidemic proportions but also because its consequences affect virtually all sectors of society.

In Serbia, breast cancer ranks as the most common malignant tumor in terms of both morbidity and mortality among women. Over the past five years, an average of about 4,500 newly diagnosed cases have been registered annually, with an average of 1,723 deaths attributed to breast cancer during the same period.

According to estimates from the Global Breast Cancer Initiative of the WHO, women in Serbia face a medium risk of developing breast cancer and a high risk of mortality from this malignancy [11].

Imaging techniques such as mammography, mammography with tomosynthesis, ultrasound, magnetic resonance imaging, and contrast mammography play pivotal roles in breast cancer diagnosis.

Any suspicious findings should be subject to cytological or histological evaluation. Minimally invasive methods, including targeted cytological puncture, core needle biopsy, stereotaxic vacuum-assisted biopsy (SVAB), or vacuum-assisted biopsy (VAB) guided by tomosynthesis, are utilized for preoperative diagnosis. The first such biopsy was performed in June 2013 at the University of Pittsburgh Medical Center Magee-Womens Hospital in the United States of America.

The objective of the national and opportunistic screening was to conduct preventive mammography examinations for women aged 50-69. Any suspicious findings should be subject to cytological or histological evaluation. To ensure timely and definitive diagnosis, VAB guided by tomosynthesis was performed in cases where such diagnostic procedure was deemed necessary.

Material and Methods

The introduction of tomosynthesis into clinical practice enabled the detection of changes that may not be visible with two-dimensional (2D) mammography, thereby necessitating biopsies guided by tomosynthesis.

In biopsies guided by tomosynthesis, tomosynthesis images are utilized to identify the lesion without the need for additional imaging of the breast from different angles and triangulation, resulting in significantly shorter procedure durations. According to literature, the tomosynthesis-guided breast biopsy procedures last approximately half as long as stereotaxic biopsies [12].

The radiation dose during tomosynthesis is slightly higher compared to 2D mammography: CC: 2D =1,366 mGy, 3DT=1,858 mGy; p<0.0001; MLO: 2D=1,374 mGy, 3DT=1,877 mGy; p<0.0001 [13]. Due to fewer exposures (up to 1/4), the average radiation dose in tomosynthesis-guided biopsy is lower than that in stereotaxic biopsy [14].

According to the available literature, the success rate of sample retrieval under the guidance of tomosynthesis ranges from 99 to 100%, while the success rate of stereotaxic biopsy ranges from 87 to 98%. Inadequate visualization of the lesion on stereotaxic images is the primary cause of technical failure in the procedure [15].

Vacuum-assisted biopsy guided by tomosynthesis is a method that enables biopsying soft tissue changes not visualized on 2D mammograms but detectable on tomosynthesis, especially those devoid of microcalcifications. It is also allows biopsy of changes/suspicious microcalcifications located in hard-to-reach areas.

Results

The first VAB guided by tomosynthesis in Serbia was conducted at the University Clinical Centre of Vojvodina Radiology Center in December 2020, utilizing Selenia Hologic mammography unit. From December 2020 to June 2023, a total of 161 tomosynthesis-guided VABs were performed in 160 patients, with one patient undergoing the procedure on both breasts. Prior to each procedure, patients received explanations regarding the necessity to perform VAB with tomosynthesis. Anamnesis was obtained in regard to any antiplatelet or anticoagulant therapy, coagulopathies, and allergies, especially concerning administered anesthesia. Before the beginning of the biopsy, the patients signed their informed consent to the procedure.

Attempts were made to perform this type of biopsy in two additional patients. In the first patient, despite several efforts to approach the lesion from different projections and multiple adjustments in the patient's position due to the small thickness of the breast, the apparatus did not permit continuation of the procedure. In the second patient, the presence of microcalcifications detected on the mammography initially suggested their location within the breast parenchyma. However, upon attempting to biopsy them, the system did not allow the procedure to continue as anticipated. Only after repositioning the patient did it become apparent that the microcalcifications were actually situated in the skin itself rather than within the breast parenchyma.

The procedure begins with planning of the approach to the lesion and depends on its localization within the breast. For this purpose, a specially constructed attachment for biopsies is employed, which connects to the tomosynthesis device, effectively converting the diagnostic 3D mammography suite into a biopsy device. Depending on the localization of the suspicious lesion, the patient is positioned on the mammography chair, either in a sitting or in a side-lying position. The approach to the lesion was selected so that the needle passes the shortest way from the skin to the lesion.

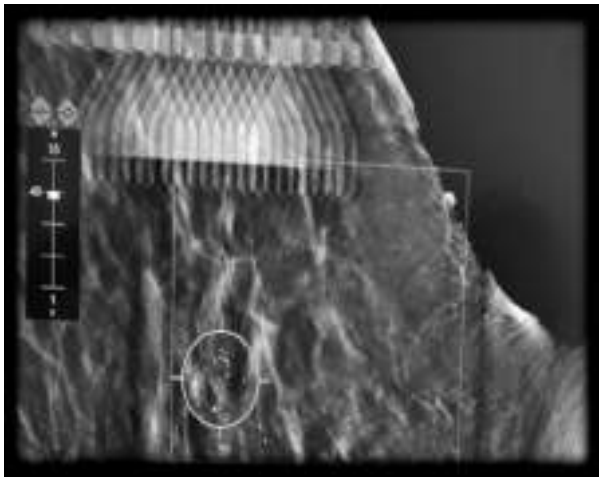

Figure 1. Target determination by tomosynthesis
Slika 1. *Određivanje cilja tomosintezom*

After skin disinfection, local anesthesia is administered by injecting 10 ml of 2% Lidocaine subcutaneously and in depth along the expected trajectory of the biopsy needle. For VAB, with negative pressure, Eviva needles of 9 G are used, with lengths of 10 cm and 13 cm, and openings of 12 mm and 20 mm, enabling retrieval of 9 to 12 samples. The breast is immobilized to ensure that the area of interest aligns with the opening (5 x 5 cm) of the compression pad. An initial tomosynthesis is performed, allowing for the marking of the suspicious lesion on the layer of the image where it is most visible **(Figure 1).** The biopsy software then automatically determines all three coordinates as the depth of the layer is also the depth of the lesion **(Figure 2).** Following local anesthesia, the needle is automatically introduced until the previously calculated coordinates are reached. Using tomosynthesis, the position of the needle tip can be checked before and after sampling **(Figure 3).** During the sampling procedure, another 10 ml of anesthetic is dispensed automatically. The position of

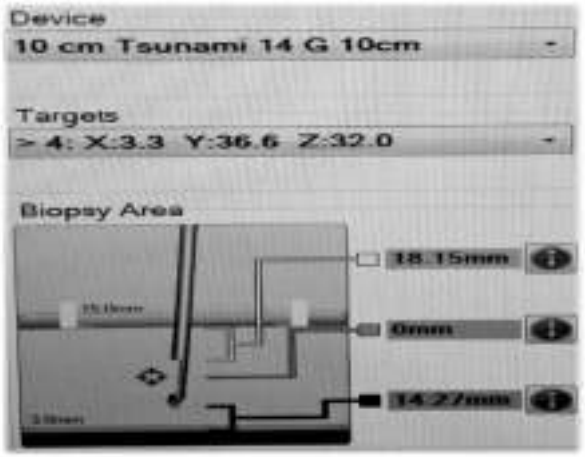

Figure 2. Automatic determination of coordinates
Slika 2. *Automatsko određivanje koordinata*

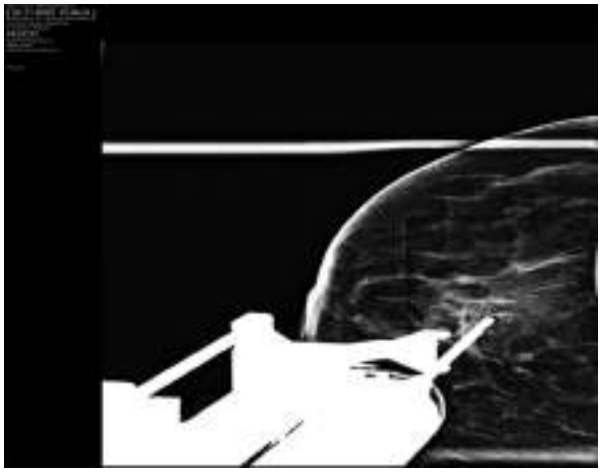

Figure 3. The position of the needle tip can be checked before and after sampling
Slika 3. *Položaj vrha igle se može proveriti pre i posle uzorkovanja*

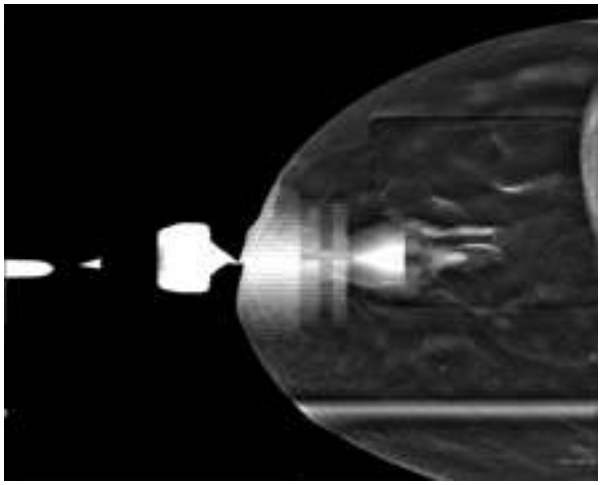

Figure 4. Checking after sampling
Slika 4. *Provera nakon uzorkovanja*

the needle tip can be checked before and after sampling **(Figure 4).** A marker is then placed in the cavity created after the biopsy, for the purpose of applying a sparing surgical procedure or monitoring **(Figure 5).** Finally, the obtained tissue samples are re-

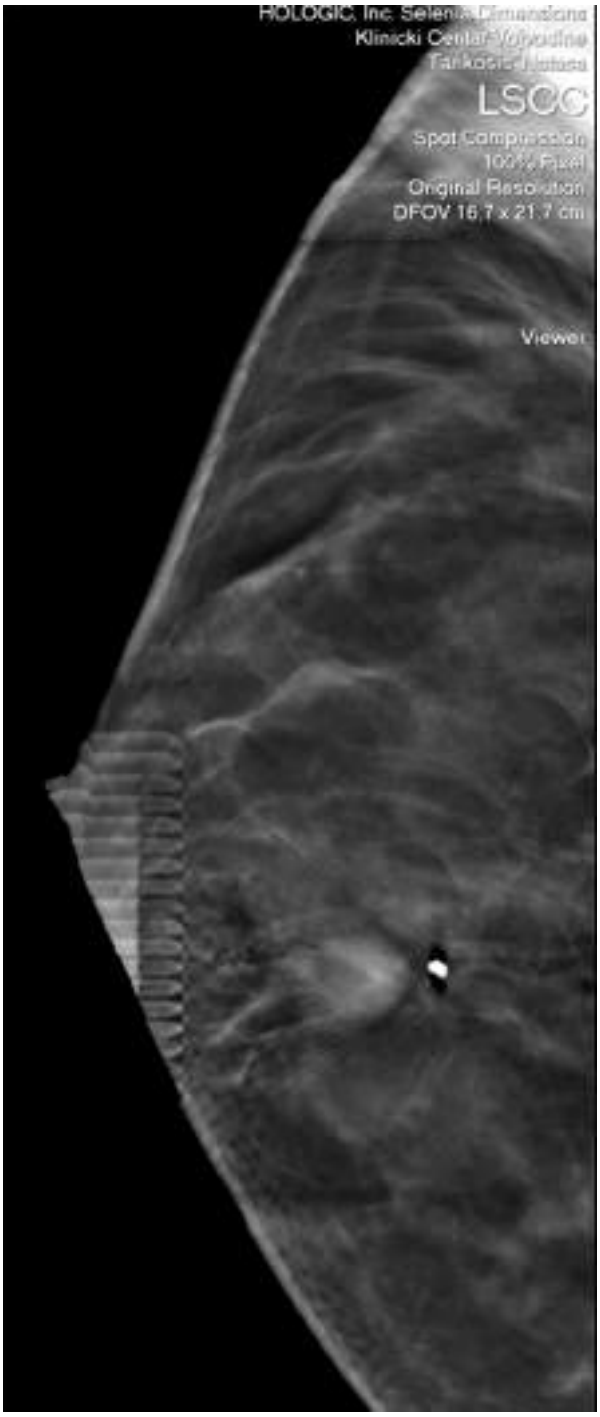

Figure 5. Marker is placed in the cavity created after the biopsy
Slika 5. *Marker se postavlja u šupljinu nastalu nakon biopsije*

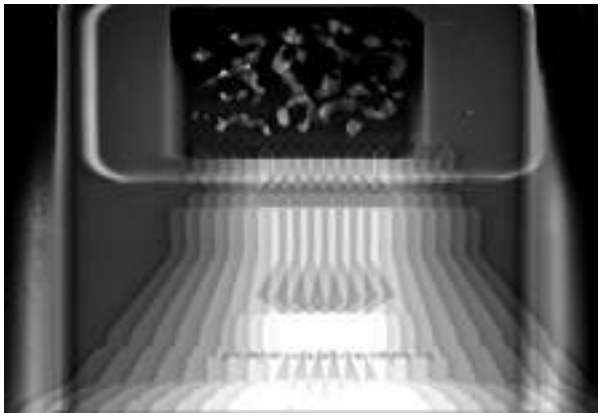

Figure 6. Obtained tissue samples are recorded, with those containing microcalcifications separated from those without
Slika 6. *Dobijeni uzorci tkiva se snimaju, odvajaju se oni sa mikrokalcifikacijama i oni bez mikrokalcifikacija*

corded, with those containing microcalcifications separated from those without **(Figure 6).**

The most common approach to the lesion was craniocaudal, which was used in 146 cases or 90.6%, followed by lateromedial in 12 cases or 7.4%, and mediolateral in two cases (1.2%). No biopsies were performed caudocranially. The decision regarding the approach was based on selecting the shortest path from the skin to the lesion.

The youngest patient was 43, and the oldest 80 years old, the average age was 59.4 years. The vast majority of biopsied lesions consisted of grouped microcalcifications, comprising 97.5% (157/161), while tumor shadows accounted for only 4 cases or 2.4%. All 161 lesions were biopsied with patients in a sitting position.

Our research analyzed the data of 160 women who underwent 161 VABs, with one patient undergoing biopsy of both breasts as Ductal Carcinoma in situ (DCIS) was proven in one breast and Invasive Ductal Carcinoma (IDC) in the other.

The increase in the incidence of breast cancer is recorded in all developed and developing countries, and is attributed to various risk factors. In our research, the respondents completed a survey aimed at gathering information of particular importance to us, including family history of breast malignancy, use of oral contraceptives and smoking habits.

Discussion

Tomosynthesis-guided breast biopsy is a relatively recent addition to clinical practice, and comparative studies with stereotaxic biopsy, particularly on large samples, remain scarce. However, the published works indicate distinct advantages of this method over conventional stereotaxic biopsy. By utilizing tomosynthesis images for lesion identification, the need for additional imaging from different angles is eliminated, leading to shorter procedure durations and faster lesion identification [16].

The majority of authors advocate for the use of vacuum sampling technique during the VAB guided by tomosynthesis breast biopsy procedures.. Considering the likelihood of complete lesion removal with this method, it has become routine practice to place a marker at the biopsy site [17].

In our research, the majority of biopsied changes, comprising 114 cases or 71%, were benign [18]. Histopathological analysis of biopsies confirmed 47 cases or 29% malignant breast changes, of which 33 were diagnosed as DCIS, ten as IDC, three as invasive lobular carcinomas, and one as mucinous invasive carcinoma. This distribution roughly aligns with the ratio reported by the Stony Brook Cancer Center in New York.

A 2017 research by Sun et al. from China identified risk factors for breast cancer, including gender, age, genetic factors, reproductive factors, exposure to estrogens and lifestyle choices. In addition to gender, age stands as one of the most significant risk factors, as the incidence of breast cancer increases with age [7].

According to a study conducted by Brewer et al. [19] in the United Kingdom in 2017, 15% of subjects diagnosed with breast cancer reported having a positive family history of the disease. In our study, among patients diagnosed with breast cancer, 11.8% reported having a positive family history of breast malignancy, a percentage that aligns with the findings of Brewer et al.

Previous use of oral contraceptives is not associated with an increased risk of breast cancer. However, current use of oral contraceptives is associated with a higher risk of breast cancer [20]. In our study, 41 respondents (25.6%) reported using oral contraceptives for a significant period during their lifetime. None of the subjects were using oral contraceptives at the time of breast cancer diagnosis or immediately prior to it. Therefore, there was no statistically significant difference between the number of subjects with a history of oral contraceptive use who did not have confirmed breast cancer by biopsy and those who did.

Smoking has been associated with a moderate but noticeable increase in the risk of breast cancer, especially among women who started smoking during adolescence or the perimenarchal period. The relative risk of breast cancer among women who smoke is notably higher if they also have a positive family history of the disease [21].

Conclusion

The rise in the incidence of breast cancer worldwide is attributed to improvements in standards of living and lifestyle changes. While primary prevention strategies for breast cancer are currently very limited, preventive activities are focused on early detection and reduction of mortality rates.

Organized programs for breast cancer prevention and early detection, coupled with timely treatment, have contributed to a significant drop in mortality rates in many developed countries over the past decade.

Given the importance of the problem, it is necessary to continue raising awareness among women

of all ages, particularly those over 40, about the importance of regular preventive examinations through both national and opportunistic stereotaxic vacuum assisted biopsy screening.

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MEDICAL STUDENTS' PERCEPTION OF THE ROLE OF ARTIFICIAL INTELLIGENCE IN HEALTHCARE

PERCEPCIJA STUDENATA MEDICINE O ULOZI VEŠTAČKE INTELIGENCIJE U ZDRAVSTVU

Darko MIKIĆ[1, 2], Hajdana GLOMAZIĆ[3] and Andrijana MIKIĆ[4, 5]

Summary

Introduction. Artificial intelligence is defined as a part of computer science capable of manipulating extensive data through machine learning. The aim of this study is to investigate medical students' perceptions regarding the use of artificial intelligence in the field of healthcare. **Material and Methods.** This research was conducted as a cross-sectional study using the Computer Assisted Web Interviewing technique for data collection by surveying students through social networks. The sample consists of 160 students who were surveyed in November 2023. The aim was to provide answers to the question of how students perceive the use of new technology – artificial intelligence in the field that represents their future profession. **Results.** The results have shown a well-developed awareness among students regarding the potential application of artificial intelligence in the medical field, emphasizing a positive perception of the benefits that artificial intelligence can bring. They have also recognized the importance of incorporating artificial intelligence training into medical education. Students have expressed concerns, primarily about potential misuse of artificial intelligence and ethical issues related to its use in medicine. **Conclusion.** Medical students are aware not only of the benefits but also the risks associated with the implementation of artificial intelligence in medicine.

Key words: Artificial Intelligence; Professional Role; Students, Medical; Attitude; Medicine

Sažetak

Uvod. Veštačka inteligencija definisana je kao deo računarske nauke, sposobna da putem mašinskog učenja manipuliše obimnim podacima. Cilj rada je ispitivanje percepcije studenata medicine o upotrebi veštačke inteligencije u oblasti zdravstva. **Materijal i metode.** Istraživanje je spovedeno kao studija preseka, uz korišćenje tehnike prikupljanja podataka anketirajući studente preko društvenih mreža (*Computer-assisted web interviewing*). Uzorak je činilo 160 studenata koji su anketirani novembra 2023. godine. Cilj je bio pružanje odgovora na pitanje kako studenti percipiraju upotrebu nove tehnologije – veštačke inteligencije u oblasti koja je njihov budući profesionalni izbor. **Rezultati.** Rezultati su pokazali razvijenu svest studenata o potencijalu primene veštačke inteligencije u medicinskom sektoru, ističući pozitivnu percepciju benefita koje veštačka inteligencija može doneti. Takođe su prepoznali važnost uključivanja obuke o veštačkoj inteligenciji u medicinsko obrazovanje. Studenti su iskazali i zabrinutost, pre svega oko mogućih zloupotreba veštačke inteligencije i etičkih pitanja u vezi sa upotrebom veštačke inteligencije u medicini. **Zaključak.** Studenti medicine svesni su benefita ali i rizika koji donosi primena veštačke inteligencije u medicini.

Ključne reči: veštačka inteligencija; profesionalna uloga; studenti medicine; stavovi; medicina

Introduction

With technology continually advancing, the use of Artificial Intelligence (AI) is becoming a standard means to enhance society in various fields. As the authors note, it 'employs heuristics and represents knowledge,' contributing to easier problem-solving and improved learning [1]. The literature also says that the deployment of these large models has deeply transformed the society, representing one of the most significant transformations in the history of society [2].

In this context, is certainly interesting to research the way young people perceive the significance of artificial intelligence. As suggested by research data, every second millennial believes they will work with robots and use artificial intelligence [3]. Considering that today's medical students will become key figures in the future healthcare system, it is important to understand how they perceive the role of AI in their field. By exploring their attitudes, beliefs, and opinions, we expect to gain insights into how young medical professionals perceive these technological changes and envision the integration of artificial intelligence into their future professional experience.

There is a growing interest in the scientific community regarding the role of AI in medicine [4]. The rapid evolution of AI technology has opened new possibilities in diagnosis, therapy, research, and the organization of medical data. Medicine is therefore considered a field with great potential in terms of utilizing artificial intelligence. Based on their previous experience, the authors note that artificial intel-

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Abbreviations
AI – Artificial Intelligence
FDA – Food and Drug Administration
SD – Standard deviation

ligence has demonstrated its value in the domain of administrative and clinical tasks, reducing medical errors in diagnostics, increasing efficiency and impartiality in task performance, mitigating healthcare workforce shortages, enhancing the capacity for medical data search, analyzing images in radiology and histopathology, interpreting electrocardiograms and heart diseases, minimizing human errors, aiding in drug treatments and surgeries, making prescription decisions, integrating health data, educating users, as well as contributing to pandemic and epidemic prevention [3]. Furthermore, the authors state that the confirmed ability of AI to synthesize large volumes of patient data and generate reports has been established. Additionally, its proven equivalence with medical professionals in terms of performance has been demonstrated for simple radiological, dermatological, and pathological diagnostic tasks [2]. In addition, it is important to note that the literature emphasizes that such integration of AI into processes related to medical practice eases the workload for healthcare professionals, contributes to reducing potential burnout, and enhances the patient experience [3]. It is also mentioned that artificial intelligence has been incorporated into numerous education programs in the field of medical education [3]. The authors also highlight a significant piece of information, pertaining to the registration of 71 medical devices related to artificial intelligence in the field of oncology, all of which have received official Food and Drug Administration (FDA) approval [5]. These devices are not intended for performing traditional diagnostic procedures independently, but they are rather considered as integrative tools to be used based on the assessment of medical professionals. The application of AI in medical rehabilitation is expanding [6]. For the full effectiveness of using artificial intelligence in medicine, it is necessary to work on building trust among healthcare professionals in terms of actual capabilities and potential outcomes in this field [7].

Numerous studies have been conducted among medical students to explore their attitudes and opinions regarding the potential use of AI in medicine. Some research results indicate that there is an awareness among students about the potential of artificial intelligence in healthcare. To this end, they also showed willingness to use AI independently, both in their professional roles and in their personal lives [3]. Pang Yi Xuan (2023) et al. report the results from several studies conducted among medical students regarding the use of AI in healthcare. One study in the U.S. revealed that the majority of students have positive attitudes towards the use of AI in medicine. They believe that its use can be beneficial for patient care. Another study conducted among pathologists showed a positive perception regarding the use of AI in pathology as it would increase efficiency and quality in the field of pathology. Furthermore, these authors report that students in another study also had predominantly positive attitudes towards the use of AI in pathology and radiology. This includes research conducted in Timisoara among students of technical sciences and humanities, as well as research conducted in multiple U.S. states (ibid.). A large-scale study involving over three thousand participants from 63 countries on all continents [8] showed that predominantly medical students do not perceive the use of artificial intelligence in their field as a 'competitor' but rather as a 'partner.' A study conducted in Canada [9] revealed that medical students consider radiology as the top choice for specialization in medicine, but over 67.7% of them fear that AI will reduce the demand for radiologists in the future. Results of another study [10], which evaluated 19 published studies on the views of medical students and radiology residents on nearly all continents toward the use of AI in medicine – radiology, showed that opinions among students are divided. However, the authors report that there is still evidence that students demonstrate interest and optimism regarding the use of AI. A study conducted with healthcare professionals in Saudi Arabia on a sample of 250 participants [11] showed that the majority of them are afraid of the effects of using AI in healthcare.

They believe that AI will replace employees. An interesting piece of information from the above study is that only 8% of the participants received some training or systematic information on this topic [10]. Nevertheless, 87% of the ones trained on the use of AI in medicine and radiology consider the training useful. Another study also shows that students recognize the importance of incorporating AI training into medical education [3]. Information obtained from the study indicating that students who have accepted to attend trainings on the use of AI for professional purposes have a more positive attitude and feel more confident in its practical application seems particularly important. Therefore, the authors believe that AI education for medical students can help improve their views about the role of AI in healthcare.

Although the benefits of using artificial intelligence in medicine are evident, there is a valid concern about its negative effects. These concerns primarily stem from the sensitive nature of the medical profession itself [4], particularly in the process involving the management of patients' medical records, which contains personal information that must be protected. In this regard, strict ethical requirements, privacy demands, and data protection standards need to be applied rigorously [2]. At the same time, there is also a patient concern about the possibility of unauthorized use of their data for commercial purposes.

Material and Methods

Our research is a cross-sectional study aimed at determining the perceptions of medical students regarding the role of artificial intelligence in healthcare, and the frequency of using new digital technologies by this population. A questionnaire was

designed for the purposes of the study to investigate students' perceptions of AI use in medicine. The scale consists of 13 items, where participants assess their level of agreement on a five-point Likert scale (1 = strongly disagree, 5 = strongly agree). Over 10 items assessed students' perception of possible benefits of artificial intelligence in medicine (e.g., 'Artificial intelligence could reduce healthcare costs'), while four items relate to the concerns of future doctors in terms of using new digital technologies (e.g., 'I am concerned that healthcare workers might lose their jobs in the future'). All questionnaire items demonstrate good reliability ($\alpha = 0.711$ to $\alpha = 0.888$).

General questions pertain to socio-demographic variables: Gender (male/female), Year of study (Y1 / Y2 /Y3 /Y4 /Y5 /Y6 /graduate), University they attend (University of Belgrade / University of Novi Sad / University of Niš / University of Kragujevac / University of Pristina, temporary settled in Kosovska Mitrovica). The use of artificial intelligence by medical students was examined through the frequency of current use of artificial intelligence (very often (daily) / often (several times a week) / rarely (several times a month) / very rarely (several times a year) / do not use artificial intelligence), the dominant purpose (education / improvement of business activities / entertainment / other), and information sources about artificial intelligence (social media / internet search / family and friends / faculty / other).

Categorical data were presented using frequencies and percentages, while mean and standard deviation were used for the description of numerical data. Reliability was tested using the Cronbach's alpha coefficient. Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

The study included 160 medical students in Serbia, 81.9% of which were female. Moreover, 28.7% of the participants were in their Year 1 of study, 13.1% in Year 2 year, 11.2% in Year 3, 12.5% in Year 4, 16.3% in Year 5, 11.3% in Year 6, and 6.9% were graduate students of medical faculties. The sample encompassed students from five universities: University of Belgrade (50.6%), University of Novi Sad (16.3%), University of Niš (13.1%), University of Kragujevac (9.4%), and University of Priština (10.6%). General participant information is presented in **Table 1**.

A total of 81.9% of medical students use artificial intelligence, with 7.5% using it daily. This technology is used several times a week by 34.4% of participants; 26.3% use it several times a month, while 13.7% of students use artificial intelligence several times a year. Almost half of the students (42.5%) gather information about this technology through social media. Predominantly, students use artificial intelligence for entertainment purposes (57.2%). One third of the participants (28.2%) primarily use artificial intelligence for educational purposes, as shown in **Table 2**.

Students' perception of the importance of using artificial intelligence in medicine was assessed through 14 items describing beliefs and concerns regarding the use of this technology in medicine. Students believe that artificial intelligence can signifi-

Table 1. Respondents' general information
Tabela 1. *Opšti podaci o ispitanicima*

	N/*Br.* (%)
Gender/*Pol*	
Male/*Muški*	29 (18.1%)
Female/*Ženski*	131 (81.9%)
Year of study/*Godina na studijama (G)*	
Y/*G*1/I	46 (28.7%)
Y/*G*2/II	21 (13.1%)
Y/*G*3/III	18 (11.2%)
Y/*G*4/IV	20 (12.5%)
Y/*G*5/V	26 (16.3%)
Y/*G*6/VI	18 (11.3%)
Graduate/*Apsolvent*	11 (6.9%)
University/*Univerzitet*	
University of Belgrade/*Univerzitet u Beogradu*	81 (50.6%)
University of Novi Sad/*Univerzitet u Novom Sadu*	26 (16.3%)
University of Nis/*Univerzitet u Nišu*	21 (13.1%)
University of Kragujevac/*Univerzitet u Kragujevcu*	15 (9.4%)
University of Pristina temporary settled in Kosovska Mitrovica *Univerzitet u Prištini sa privremenim sedištem u Kosovskoj Mitrovici*	17 (10.6%)

Table 2. Use of artificial intelligence
Tabela 2. *Upotreba veštačke inteligencije*

	N/*Br.* (%)
Frequency of using artificial intelligence/*Učestalost korišćenja veštačke inteligencije*	
Very often (daily)/*Veoma često (svakodnevno)*	12 (7.5%)
Often (several times a week)/*Često (nekoliko puta nedeljno)*	55 (34.4%)
Rarely (several times a month)/*Retko (nekoliko puta mesečno)*	42 (26.3%)
Very rarely (several times a year)/*Veoma retko (nekoliko puta godišnje)*	22 (13.7%)
I do not use artificial intelligence/*Ne koristim veštačku inteligenciju*	29 (18.1%)
Sources of information about artificial intelligence/*Izvori informacija o veštačkoj inteligenciji*	
Social media/*Društvene mreže*	68 (42.5%)
Internet search/*Pretraživanje interneta*	50 (31.2%)
Family and friends/*Porodica i prijatelji*	25 (15.6%)
Faculty/*Fakultet*	3 (1.9%)
Other/*Drugo*	14 (8.8%)
Artificial intelligence predominantly used for/*Dominanta upotreba veštačke inteligencije u svrhu*	
Education/*Edukacije*	37 (28.2%)
Improvement of business activities/*Unapređenja poslovnih aktivnosti*	8 (6.2%)
Entertainment/*Zabave*	75 (57.2%)
Other/*Drugo*	11 (8.4%)

Table 3. Students' perception of the importance of using artificial intelligence in medicine
Tabela 3. *Percepcija studenata o značaju upotrebe veštačke inteligencije u medicini*

Questionnaire items/*Stavke upitnika*	Min–Max *Min–Maks*	M/*M*	SD/*SD*	α/*α*
Artificial intelligence can significantly improve diagnostics in medicine. *Veštačka inteligencija može značajno poboljšati dijagnostiku u medicini.*	1 - 5	4.1	1.5	0.871
Artificial intelligence can effectively reduce medical errors. *Veštačka inteligencija može efikasno smanjiti medicinske greške.*	1 - 5	3.8	2.3	0.886
I am willing to rely on diagnoses made with the help of artificial intelligence./*Spreman/ na sam da se oslonim na dijagnoze koje su postavljene uz pomoć veštačke inteligencije.*	1 - 5	2.3	1.2	0.855
Artificial intelligence has the potential to improve the efficiency of treatment. *Veštačka inteligencija ima potencijal da poboljša efikasnost lečenja.*	1 - 5	3.5	1.8	0.814
Artificial intelligence could reduce healthcare cost. *Veštačka inteligencija mogla bi smanjiti troškove zdravstvene nege.*	1 - 5	4.2	2.1	0.817
Artificial intelligence can efficiently support research in medicine. *Veštačka inteligencija može efikasno podržati istraživanja u medicini.*	1 - 5	4.4	2.2	0.878
Artificial intelligence could replace certain medical jobs. *Veštačka inteligencija mogla bi zameniti određene medicinske poslove.*	1 - 5	2.9	1.3	0.845
Artificial intelligence could improve the patient's experience during treatment. *Veštačka inteligencija mogla bi poboljšati pacijentovo iskustvo tokom lečenja.*	1 - 5	3.7	1.4	0.871
The use of artificial intelligence should be legally regulated. *Upotrebu veštačke inteligencije trebalo bi zakonski regulisati.*	1 - 5	4.6	2.4	0.846
It is ethically acceptable to use artificial intelligence in medical procedures. *Etički je prihvatljivo koristiti veštačku inteligenciju u medicinskim postupcima.*	1 - 5	2.8	1.1	0.711
Concerns about the potential misuse of artificial intelligence in medicine. *Zabrinut/a sam zbog moguće zloupotrebe veštačke inteligencije u medicini.*	1 - 5	4.3	2.7	0.888
Concerns that healthcare workers might lose their jobs in the future. *Zabrinut/a sam da bi u budućnosti zdravstveni radnici mogli ostati bez posla.*	1 - 5	4.1	2.2	0.856
Concerns about the protection of patients' personal data. *Zabrinut/a sam za zaštitu podataka o ličnosti pacijenata.*	1 - 5	3.8	2.4	0.755
The data used in artificial intelligence are secure enough. *Podaci korišćeni u veštačkoj inteligenciji dovoljno su sigurni.*	1 - 5	1.6	0.6	0.866

Legend: Min - Max = Minimum - Maximum, M = Mean, SD = Standard deviation, α = Cronbach's alpha coefficient.
Legenda: Min-Max = Minimalna vrednost – Maksimalna vrednost, M = Aritmetička sredina, SD = Standardna devijacija, α = Krombah alfa koeficijent

cantly improve diagnostics in medicine (4.1 (standard deviation (SD) = 1.5)) and reduce healthcare costs (4.2 (SD = 2.1)). The majority of medical students (4.4 (SD = 2.2)) highly agree with the statement 'Artificial intelligence can efficiently support research in medicine'. However, students believe that the data used in artificial intelligence are not secure enough (1.6 (SD = 0.6)), and they are not willing to rely on diagnoses made with the use of artificial intelligence (2.3 (SD = 1.2)). When it comes to concerns about the use of artificial intelligence for medical purposes, students express the greatest concern about the potential misuse of artificial intelligence (4.3 (SD = 2.7)), the possibility of healthcare workers losing their jobs (4.1 (SD = 2.2)), and the protection of patients' personal information (3.8 (SD = 2.4)). The data are presented in **Table 3**.

Discussion

The results of our study on the perception of medical students regarding the role of artificial intelligence (AI) in healthcare complement findings from extensive scientific literature. A review of relevant papers indicates that students are aware of the potential application of AI in healthcare [4]. Our research confirms this belief and points to a significant level of student involvement in the use of AI, illustrating the fact that over 80% of students actively use AI, with 7.5% on daily bases. Students in our study also believe that AI can significantly improve diagnostics, reduce healthcare costs, and support medical research. This positive perception indicates students' openness to the integration of AI into the medical field.

Although, students predominantly use AI for entertainment according to the data from our research, we can still say that there is a trend of its use for education purposes, which is in line with the results of other studies [8].

As we can see from the previous analysis, students recognize the importance of incorporating AI training into medical education, where students who have participated in AI training show a more positive attitude toward its use [3]. This indicates the need for the integration of AI educational programs into medical education to support students' positive attitudes and avoid prejudice while reducing misinformation. Interesting findings from other studies [3] highlight the positive attitudes of students toward the use of AI, particularly in medical fields such as radiology and pathology.

However, in addition to the positive perception of certain aspects of AI use in healthcare, our study also reveals some concerns among students. Participants express doubts about the reliability of data used in AI, emphasizing the fact that they are not secure enough. The students also express concern regarding the potential misuse of artificial intelligence. Some of these dilemmas have also been noted in other studies [7].

In addition, data from other studies, such as the one conducted in Canada [9], emphasize the concern of medical students about the possibility of job loss due to the introduction of AI into medical practice. Other studies indicate concern related to this topic not only among students [11] but also among healthcare professionals. This emphasizes the need for additional efforts to inform and empower students regarding the future of healthcare professions [9].

In terms of ethical dilemmas, there is a concern about the potential misuse of patient personal information [2].

The above studies can serve as a foundation for further consideration of introducing artificial intelligence into medical education, with a focus on areas that students recognize as crucial for improving healthcare practices.

Conclusion

The conclusion of our study on the perceptions of medical students about the role of artificial intelligence in healthcare complements the relevant literature and provides insights into the attitudes, optimism, but also concerns of students regarding this innovative technology.

The finding that young individuals in the area of medicine are highly aware of the potential application of artificial intelligence in the field of medicine is especially noteworthy. However, it has been revealed that they lack sufficient information about all the pros and cons of using artificial intelligence in medicine. We believe it is crucial to identify the importance of integrating AI training into medical education to fully leverage the potential of artificial intelligence to improve and advance medical practice. In addition, this approach could emphasize the importance of responsible and ethical use of artificial intelligence in medicine.

These studies provide a foundation for further consideration of integrating artificial intelligence into medical education, with a focus on areas that students recognize as crucial for improving healthcare practices. This highlights the need for ongoing research and development to strengthen positive perceptions and adequately address challenges arising from the use of artificial intelligence in medicine.

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CHILD AND ADOLESCENT PSYCHIATRY – CHANGE IN THE DYNAMICS OF TREATMENT CAUSED BY THE CORONAVIRUS PANDEMIC

DEČJA I ADOLESCENTNA PSIHIJATRIJA – PROMENA DINAMIKE LEČENJA USLOVLJENA PANDEMIJOM KORONAVIRUSA

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Summary

Introduction. The coronavirus pandemic caused a restructuring of mental health services, marked by a decrease of hospital work capacity and increased reliance on telemedicine. Children and adolescents are a particularly vulnerable group that has been affected by the newly arisen corona virus-19 pandemic. The objective was to evaluate the correlation between the coronavirus pandemic and alternations in hospitalization rates, seasonal distribution, and sociodemographic characteristics of patients admitted to the Department of Child and Adolescent Psychiatry. **Material and Methods.** The study was conducted at the Psychiatry Clinic of the Department of Child and Adolescent Psychiatry at the University Clinical Center of Vojvodina in the period from March 6, 2017 to March 5, 2021. The sample comprised 1114 inpatients and individuals undergoing partial hospitalizations, diagnosed with mental disorders classified according to the International Classification of Diseases. Participants were categorized into two groups: one treated before the onset of the pandemic (March 2017-March 2020) and another treated during the pandemic (March 2020-March 2021). Statistical analysis was performed on the collected data, with the results presented in tables and graphs. **Results.** During the pandemic, an overall reduction in admissions (-32.34%) was observed, accompanied by a noticeable decrease in admissions during the spring compared to the pre-coronavirus period ($p=0.011$). The most prevalent diagnoses were F9 and F4, respectively ($p<0.01$). A higher number of hospitalizations were noted in middle adolescence ($p<0.001$), among females ($p=0.006$) and those residing in urban areas ($p=0.009$). **Conclusion.** The coronavirus pandemic led to alternations in the functioning and dynamics on Department of Child and Adolescent Psychiatry. The sociodemographic characteristics of the youth changed during the pandemic.

Key words: COVID-19; Pandemics; Mental Disorders; Hospitalization; Sociodemographic Factors; Risk Factors; Child; Adolescent

Sažetak

Uvod. Pandemija koronavirusom je uslovila reorganizaciju psihijatrijske zdravstvene zaštite u vidu smanjenog kapaciteta rada klinika i sve veće upotrebe telemedicine. Deca i adolescenti predstavljaju naročito vulnerabilnu grupu, koju je pogodila novonastala pandemija koronavirusom. Cilj je bio ispitivanje povezanosti pandemije koronavirusa sa promenom učestalosti hospitalizacija, sezonskom distribucijom i sociodemografskim karakteristikama pacijenata na Odeljenju za dečju i adolescentnu psihijatriju. **Materijal i metode.** Studija je sprovedena na Klinici za psihijatriju, na Odeljenju za dečju i adolescentnu psihijatriju Univerzitetskog kliničkog centra Vojvodine, tokom perioda od 6. marta 2017. godine do 5. marta 2021. godine. Uključila je 1.114 kompletnih i parcijalnih hospitalizacija pod ispisnim dijagnozama mentalnih poremećaja po Međunarodnoj klasifikaciji bolesti. Ispitanici su podeljeni u dve grupe: grupa bolesnika lečenih pre pandemije (mart 2017−mart 2020. godine) i grupa bolesnika lečenih tokom pandemije (mart 2020−mart 2021. godine). Podaci su statistički obrađeni, a rezultati predstavljeni tabelarno i grafički. **Rezultati.** Tokom pandemije je zabeležen ukupan pad broja hospitalizacija (-32,34%) i vidljiv pad tokom proleća u odnosu na period pre pandemije ($p = 0,011$). Najzastupljenije dijagnoze su bile iz grupe F9 i F4, redom ($p < 0,01$). Više hospitalizacija je zabeleženo u drugoj fazi adolescencije ($p < 0,001$), kod ženskog pola ($p = 0,006$) i ispitanika iz urbane sredine ($p = 0,009$). **Zaključak.** Pandemija koronavirusom je dovela do promene u radu i dinamici na Odeljenju za dečju i adolescentnu psihijatriju. Tokom pandemije je zabeležena promena sociodemografskih karakteristika mladih.

Ključne reči: COVID-19; pandemija; mentalni poremećaji; hospitalizacija; sociodemografski faktori; faktori rizika; dete; adolescent

Introduction

Since the onset of the COVID-19 pandemic, all segments of human life experienced significant changes.

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Abbreviations
UCCV – University Clinical Center of Vojvodina
PTSD – Post-traumatic stress disorder

The organization of work within healthcare institutions adapted to the epidemic situation. Consequently, the work dynamics at the Psychiatry Clinic of the University Clinical Center of Vojvodina (UCCV) underwent changes in line with recommendations from the relevant authorities. These adjustments impacted, among other things, the reduced contact of children and adolescents with their designated psychiatrist through outpatient treatment and partial hospitalization.

Being in the phase of psychological development, children and adolescents are more sensitive to external influences than adults. Thus, it was assumed that the pandemic would negatively affect them [1–4]. The declaration of a state of emergency and the closure of schools/colleges brought about significant changes for this age group. Factors such as physical distance and isolation from peers and teachers, discontinuation of classes and extracurricular activities, separation from family members, concerns about the infection of loved ones, and the fear of death are identified as major adverse influences on the mental health of children and adolescents during the pandemic. Post-traumatic stress disorder (PTSD) may have neuroanatomical and neurofunctional consequences, and its occurrence in a certain number of young people triggered by the pandemic necessitates further investigation [1]. Given that the defense mechanisms of children and adolescents are often embedded in daily activities, the interruption of such routines during the state of emergency and curfew potentially led to relapses of psychiatric disorders that were previously under control [1, 3, 4]. The role of the family emerged as a crucial factor in the mental health of children and adolescents during this period. While increased time spent with the family could foster closer relationships, such effects have not yet been conclusively confirmed. On the other hand, the increased amount of time spent at home with the family heightened instances of violence in certain cases, as supported by some studies [1, 5].

Telemedicine

Experts in the field of mental health promptly drew attention to the need for greater psychological and psychiatric support during this period, leading to additional emphasis on telemedicine. On March 16, 2020, the Republic of Serbia introduced helplines to provide psychosocial support, aiming to safeguard mental health during the pandemic. A dedicated helpline named "How are you?" was established for young people and parents of children under 18, intending to offer essential information regarding the pandemic and dispense advice on managing fear and anxiety [6]. Telemedicine, including tele-child-psychiatry, also experienced a surge in other countries in order to preserve mental health [5, 7, 8]. Throughout the state of emergency, the UCCV Psychiatry Clinic facilitated telephone consultation with psychiatrists, psychologists and social workers providing their services to the broader population.

The objective of this paper was to explore the correlation between the coronavirus pandemic and alternations in the frequency, seasonal distribution and representation of various psychiatric hospitalizations among children and adolescents. The sociodemographic characteristics of the hospitalized patients were also examined.

Material and Methods

All patients who were treated at the Psychiatry Clinic of the Department of Child and Adolescent Psychiatry at the UCCV, during the four-year period from March 6, 2017 to March 5, 2021, were included in the study. Clinical data of the patients including gender, age, place of residence, number of hospitalizations, seasonal distribution, and clinical diagnoses, were taken from the electronic medical records through the clinical information system of the UCCV Psychiatry Clinic. Approval for the research was obtained from the Director of the Psychiatry Clinic and the Ethics Committee of the University Clinical Center of Vojvodina (approval number and date: 00-231, December 29, 2021). Inclusion criteria for patients in the study were as follows:

1. Complete or partial hospitalization at the UCCV Psychiatry Clinic, Department of Child and Adolescent Psychiatry, from March 6, 2017 to March 5, 2021.
2. Hospitalization with documented diagnoses of mental disorders according to the International Classification of Diseases (ICD-10) [9].
3. Patients must not be older than 24 years.

For further statistical data analysis, the respondents were categorized into two groups: patients treated before the pandemic (March 6, 2017 - March 5, 2020) and patients treated during the pandemic (March 6, 2020 - March 5, 2021).

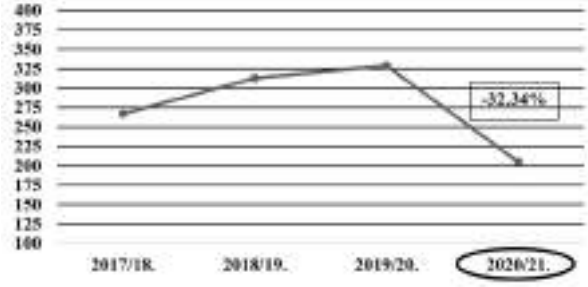
In terms of seasonal distribution, hospitalizations were categorized into four groups based on seasons: spring (March 20 – June 20), summer (June 21 – September 21), fall (September 22 – December 20), winter (December 21 – March 19).

In terms of age, the respondents were divided into 4 groups: children (0-9 years), early adolescence (10-14 years), middle adolescence (15-17 years), and late adolescence (18-24 years).

The respondents were also classified based on their place of residence into those from urban (≥25,000 inhabitants) and the ones from rural areas (<25,000 inhabitants).

Diagnoses of mental disorders were grouped based on the International Classification of Diseases – ICD-10: F0-F9.

Numerical characteristics are presented through mean values (arithmetic mean), minimum and maximum values, and measures of variability (standard deviation). Attributive characteristics are presented using frequencies and percentages. The χ^2-test was employed to assess the difference in frequencies of attributive characteristics, while the Kruskal-Wallis test was utilized to examine differences in attributive char-



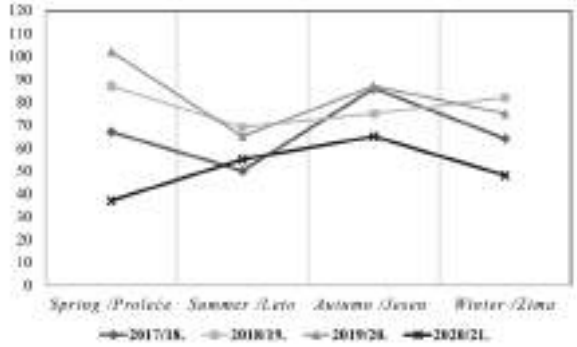
Graph 1. Number of hospitalizations throughout the years
Grafikon 1. *Broj hospitalizacija po godinama*

acteristics between three or more groups. Values with a significance level of $p<0.05$ were considered statistically significant. Microsoft Excel 2019 and JASP 0.16 were used for statistical data processing, and the results are illustrated through tables and graphs.

Results

The study included 1114 admissions at the Department of Child and Adolescent Psychiatry of both complete and partial hospitalization over a four-year period. The total number of patients during that period amounted to 613. **Graph 1** illustrates the dynamic pattern of hospitalizations over the four years. The lowest number of hospitalizations was recorded during the year of the pandemic, indicating a substantial decrease (-32.34%). This difference in the number of hospitalizations between the period during and before the pandemic was statistically significant ($p<0.05$).

Regarding the number of hospitalizations per patient, there was no significant difference during the four-year period. The median number of hospitalizations for all observed years was 1. However, during the pandemic, the highest number of hospitalizations per patient reached 10.



Graph 2. Seasonal distribution of hospitalizations
Grafikon 2. *Sezonska distribucija hospitalizacija*

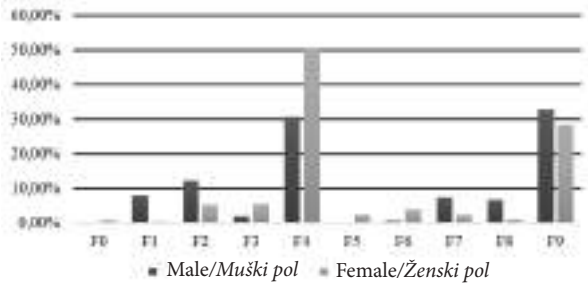
The season-related dynamic of hospitalizations is shown graphically for each year **(Graph 2).** During 2020/21, the fewest hospitalizations were recorded in the spring, while the highest number was recorded in the fall. This difference is statistically significant ($\chi^2=11.110$, $p=0.011$, Cramer's $V=0.100$).

The highest prevalence of mental disorders in the three years before the pandemic was within the F4 group, constituting 42.024%, while during the 2020/21 period, the F9 group took the lead with 47.805%. Disorders within the F9 group were in the second place in the three years before the pandemic, with 30.253%, while during the 2020/21 period, the second position was occupied by the F4 group with 24.878% ($\chi^2=48.685$, $p<0.01$, Cramer's $V=0.209$).

Sociodemographic data of patients, including age, gender, and place of residence, are presented in **Table 1.** Over the four-year period, the highest percentage of patients were in middle adolescence (Before vs. During the pandemic; 48.295% vs. 53.171%), while the lowest percentage was recorded in children. This variation in the representation of age categories is highly statistically significant

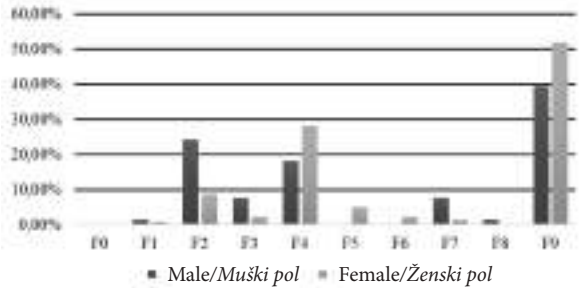
Table 1. Patients' sociodemographic data
Tabela 1. *Sociodemografski podaci bolesnika*

Patient characteristics *Karakteristike bolesnika*		Before the pandemic *Pre pandemije*						During the pandemic *Tokom pandemije*	
		2017/18		2018/19		2019/20		2020/21	
		N/*Br.*	%	N/*Br.*	%	N/*Br.*	%	N/*Br.*	%
Gender/*Pol*	Male/*Muški*	109	40.82	139	44.41	132	41.12	66	32.20
	Female/*Ženski*	158	59.18	174	55.59	189	58.88	139	67.80
Age group *Starosna kategorija*	Children (age 3 – 9)/*Deca (3–9 godina)*	23	8.61	26	8.31	6	1.82	1	0.49
	Early adolescence (age 10–14) *I faza adolescencije (10–14 godina)*	71	26.59	76	24.28	110	33.43	59	28.78
	Middle adolescence (age 15–17) *II faza adolescencije (15–17 godina)*	119	44.57	157	50.16	163	49.54	109	53.17
	Late adolescence (age 18–24) *III faza adolescencije (18–24 godina)*	54	20.22	54	17.25	50	15.20	36	17.56
Residence area *Mesto prebivališta*	Urban/*Urbano*	157	58.80	195	62.30	167	50.76	136	66.34
	Rural/*Ruralno*	110	41.20	118	37.70	143	43.47	63	30.73
	No data/*Bez podataka*	0	0.00	0	0.00	19	5.78	6	2.93



Graph 3. Percentage rate of gender-related psychiatric diagnosis - Before the pandemic
Grafikon 3. *Procentualna zastupljenost psihijatrijskih dijagnoza u odnosu na pol – pre pandemije*

(χ^2=120.054, p<0.001). The number of children under the age of 9 is significantly lower in the year of the coronavirus pandemic than the expected number observed before the pandemic (χ^2=11.124, p=0.011, Cramer's V=0.100). The female gender is statistically significantly more represented than the male gender in the observed period both before and during the pandemic. During the pandemic, the number of admissions of male children and adolescents was significantly lower than expected (χ^2=7.468, p=0.006, Cramer's V=0.082). In terms of place of residence, the number of people from urban areas was greater every year, but during the pandemic, the ratio of admissions from urban and rural areas changed significantly, with a larger share of admissions from cities than from villages (χ^2=6.822, p=0.009, Cramer's V=0.079).



Graph 4. Percentage rate of gender-related psychiatric diagnosis – During the pandemic
Grafikon 4. *Procentualna zastupljenost psihijatrijskih dijagnoza u odnosu na pol – tokom pandemije*

Graphs 3 and 4 illustrate the percentages of psychiatric diagnoses concerning gender, both before and during the pandemic. During the pandemic, there was an increase in diagnostic groups F9 and F5 among female patients. There was also a decrease in the percentage representation of diagnostic groups F4 and F3. For male patients during the pandemic, there was an increase in diagnostic groups F2 and F3, while a decline in the percentage representation of diagnostic groups F1, F4 and F8 was observed (χ^2=48.685, p=0.006, Cramer's V=0.209).

Discussion

The pandemic caused by the new SARS-CoV-2 virus brought about major changes in the organization of health systems worldwide. At our Clinic, partial hospitalization was canceled in line with the recommendations from authorities responsible for preventing the spread of the coronavirus. The discontinuation of services provided to low-urgency cases through partial hospitalizations was also visible in other countries [8]. These adjustments required identifying adequate alternatives to provide mental support to those in need. The solution was found in the development of and increasing reliance on telemedicine, a form of healthcare delivery reliant on remote telecommunication technologies, which proved highly effective for psychiatric patients during the pandemic [6, 8, 10].

Findings from a study in Italy suggest that analyzing hospital admissions is a useful approach in assessing the impact of the pandemic on people's mental health. This assessment of the pandemic's psychosocial impact is challenging due to the way data is collected and analyzed [7]. In the „COVID" year, an overall decrease in the number of hospitalizations at the Clinic in Novi Sad was observed when compared individually to the three years preceding the pandemic. Foreign authors also recorded reductions in admissions at their clinics for the general population [7, 8, 11, 12]. An American study that included adolescents [13] reported an overall decrease in hospitalizations from March 2020 to January 2021 compared to the same period before the pandemic. Notably, they conducted a keyword analysis of the subjects' medical records related to the pandemic („coronavirus", „quarantine", „pandemic", etc.), revealing a connection to the coronavirus pandemic in 53.24% of hospitalizations. Another American study looked at the number of hospitalizations among young people during and before the pandemic, and noted a 40% reduction in hospitalizations [14]. The decline in mental health clinic admissions was potentially caused by the fear of possible contagion, increased symptom tolerance in patients and their families, heightened caution among doctors regarding hospitalizations to reduce the virus spread in their departments, and a surge in outpatient activities for less urgent cases through telemedicine and online platforms [7, 8].

In the above studies from Italy and Malta, a sudden drop in hospitalization rates was observed in the first week following the implementation of lockdown measures in March, which is statistically significant when compared to the same period in the year prior to the pandemic [7, 8]. Similarly, our study identified a reduced number of hospitalizations during the spring, showing statistically significant difference compared to the „pre-COVID" period (spring - % of hospitalizations during and before the pandemic: 18.05% vs. 28.16%) (p=0.011). Reflecting on the anti-coronavirus measures in the Republic of Serbia, the state of emergency was lifted in May, accompanied by a more favorable epidemic situation. Subsequently, there was an increase in hospitalizations during the

summer, which, at the Clinic, had lower rate of hospitalization compared to spring before the pandemic. In the same period of time, the number of infected people decreased, and anti-coronavirus measures were relaxed in Malta. This paper also noted the increase in the number of hospitalizations already in May. This raises the question of whether the improved epidemic situation led to an increase in hospitalizations or if a certain cohort of patients had lingering symptoms, leading to decompensation at that specific moment [8]. Another plausible explanation, relevant to the group of respondents of our study, is that children and adolescents do not attend school during the summer, which may cause different crises due to reduced contact with peers and fewer extracurricular activities, compounded by the entire pandemic situation [13]. The growing trend in the number of hospitalizations at the Clinic continued in the fall. Notably, the percentage of hospitalizations during the fall of 2020 did not differ significantly compared to the period before the pandemic (fall - % of hospitalizations during and before the pandemic: 31.71% vs. 27.28%).

The sociodemographic characteristics revealed certain statistically significant differences. During the pandemic, the mean age of the patients was 15.82 years (SD=2.28), with a median of 16. Comparative literature data from studies reported values of 14.6 years (SD=2.21, $p < 0.05$) [14] and 15 years [13]. Middle adolescence (15-17 years) showed a slight increase during the pandemic, with a highly statistically significant difference in the representation of age categories ($p=<0.001$). Although ranking last in the representation of age categories during and before the pandemic, the group that includes children displayed a lower value than expected during the pandemic ($p=0.011$). There is no corresponding literature information in the research of other authors regarding this data. The female gender was more represented throughout the observed period, with an additional increase compared to the male gender during the pandemic. In other words, male respondents were less represented during the pandemic than expected ($p=0.006$). Studies [14] and [13] also noted a higher percentage of women (58% and 62.43%, respectively) among their respondents.

Concerning the representation of diagnostic groups, the two most prevalent groups were behavioral and emotional disorders with an onset usually in childhood and adolescence (F9) and neurotic, stress-related and somatoform disorders (adjustment disorders/adolescent crises) (F4). These two groups together accounted for 72.68% of all hospitalizations at the Department of Child and Adolescent Psychiatry at the UCCV during the pandemic. If disorders from the F2 group are added, this percentage amounts to 86.34%. In our study, F4 group disorders showed a decrease during the pandemic in both genders, declining from 42.02% to 24.88%, with a more pronounced decrease observed in women. Regarding the place of residence, a higher percentage of children and adolescents were from urban environments compared to rural areas, a trend consistent even before the pandemic. Across age categories, there was a decline in all age groups, most notably in middle adolescence (18-24 years). Studies from China indicated that the percentage of anxiety symptoms in children and adolescents were present in 18.9% and 37.6% of respondents, respectively [15, 16]. While the first study did not find a connection between gender and anxiety, other studies indicated that female gender was the risk factor [3, 16, 17]. In addition, one of the papers noted that anxiety symptoms were lower in urban than in rural areas, which contrasts slightly with our results [16]. It is important to note that our study presented subjects undergoing hospital treatment, and outpatient examinations or telemedicine consultations were not taken into account.

F9 group disorders showed an increase during the pandemic compared to the period before it, rising from 30.253% before to 47.805% during the pandemic. Regarding F9 group disorders, no specific studies investigating this group of disorders were found.

Concerning eating disorders (F5), which were recorded exclusively in women in our study, there was an increase in the percentage during the pandemic. Notably, this diagnosis was only represented in urban areas during the pandemic, while before the pandemic, the ratio was equal. It was most common in middle adolescence (15-17 years). Similar results were observed in a Canadian study conducted in a comparable period to ours (January 1, 2017 – December 26, 2020) [18]. It was determined that there was a statistically significant difference in the increase in the rate of hospitalizations for eating disorders during the pandemic compared to the „pre-COVID" period. The elevated prevalence of this diagnosis may be attributed to the stress induced by the pandemic and lockdown measures on young people, more time spent on social networks, increased feelings of anxiety, and loss of control [19] - all potential triggers for eating disorders [18]. Physical activity is an important thing for the mental health of young people. Adolescents were aware of the importance of everyday physical activity when it came to both anxiety and eating disorders (nutrition) during the pandemic. According to a study conducted in Serbia, female participants claimed that physical activity helped them cope with stress and anxiety. Also, both sexes confirmed that physical activity improved their sleep and rest patterns. It is necessary that the health care system pays more attention to physical activities as one of the significant prevention methods [20].

In our study, there was an increase in the percentage of schizophrenic and other psychotic disorders, with the male gender experiencing a more significant increase, aligning with literature data for the general population without a statistically significant difference [7, 8]. A study focusing on adolescents noted a decrease in the percentage representation, although without a statistically significant difference [14].

Conclusion

The findings of this research lead to the conclusion that crisis situations, including the coronavirus

pandemic, have a significant impact on the work organization at the Department of Child and Adolescent Psychiatry and alter the treatment dynamics for these age categories. The representation of sociodemographic characteristics among young people is changing, with girls more frequently requiring hospital treatment for behavioral and eating disorders, while boys are more commonly admitted due to worsening of schizophrenic and other psychotic disorders. This underscores the necessity for preventive measures targeting mental disorders, specifically directed towards the category of young people during crisis periods, recognizing them as an extremely vulnerable population group. Special attention should be given to the challenges that have escalated during this pandemic. It is important to carefully organize the psychiatric services to ensure that professional assistance is available at all times.

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REVIEW ARTICLES
PREGLEDNI ČLANCI

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POSTOPERATIVE ANALGESIA IN CHILDREN – A COMPREHENSIVE ASSESSMENT AND MANAGEMENT

POSTOPERATIVNA ANALGEZIJA KOD DECE – SVEOBUHVATNA PROCENA I TRETMAN

Anna URAM BENKA[1, 2], Izabella FABRI GALAMBOS[1, 2], Marina PANDUROV BRLIĆ[1, 2], Goran RAKIĆ[1, 2], Nemanja GALETIĆ[2] and Nikola BOŠKOVIĆ[1, 2]

Summary

Introduction. Pain is the most common cause of complaints in hospitalized pediatric patients. Pain continues to be underestimated and undertreated in childhood. The European Society of Pediatric Anesthetists has published guidelines for pain management in children. **Pain assessment.** Pain assessment is very important in the treatment of pain in children. **Basic pain management.** Administration of basic analgesics is crucial for pain management. **Paracetamol and non-steroidal anti-inflammatory drugs.** Generally, basic or simple analgesia includes the use of paracetamol and non-steroidal anti-inflammatory drugs. **Systemic opioids.** Opioids are reserved for early postoperative and intraoperative use when adequate monitoring and specially trained personnel are available around the clock. **Regional anesthesia and local anesthetics.** Regional anesthesia in children has been increasingly used in recent decades, particularly against the background of multimodal analgesia. **Conclusion.** Basic analgesics are crucial, and opioids are added only when needed. Regional anesthesia and local anesthetics play a superior role in pain management compared to systemic analgesics in such cases in pediatric patients.

Key words: Pain; Postoperative Care; Analgesia; Pain Measurement; Child; Anesthesia, Conduction; Anesthesia, Local; Anti-Inflammatory Agents, Non-Steroidal; Analgesics, Opioid

Sažetak

Uvod. Bol je najčešći uzrok žaljenja hospitalizovanih pedijatrijskih pacijenata. Bol se i dalje potcenjuje i ne leči adekvatno u dečjem uzrastu. Evropsko udruženje pedijatrijskih anesteziologa objavilo je smernice za tretman bola kod dece. **Procena bola.** Procena bola je veoma važna u lečenju bola kod dece. **Bazični tretman bola.** Primena osnovnih analgetika je ključna za lečenje bolova. **Paracetamol i nesteroidni antiinflamatorni lekovi.** Osnovna ili jednostavna analgezija uključuje upotrebu paracetamola i nesteroidnih antiinflamatornih lekova. **Sistemski opioidi.** Opioidi su rezervisani za ranu postoperativnu i intraoperativnu upotrebu kada su adekvatan nadzor i posebno obučeno osoblje na raspolaganju 24 sata dnevno. **Regionalna anestezija i lokalni anestetici.** Regionalna anestezija kod dece se poslednjih decenija sve više primenjuje, posebno na temelju multimodalne analgezije. **Zaključak.** Osnovni analgetici su ključni, opioidni analgetici se dodaju samo u slučaju potrebe. Regionalna anestezija i lokalni anestetici imaju superiornu ulogu u zbrinjavanju bola u odnosu na sistemske analgetike kod pedijatrijskih pacijenata.

Ključne reči: bol; postoperativna nega; analgezija; procena bola; dete; regionalna anestezija; lokalna anestezija; NSAIL; opioidni analgetici

Introduction

Pain is an unpleasant sensory and emotional experience associated with potential or actual tissue damage, caused by nociceptive stimuli [1] that can lead to a variety of potentially negative consequences [2]. Pain is triggered in the nociceptors and transmitted to the brain through a cascade of changes in the somatosensory system via appropriate nociceptive pathways. These changes can lead to an increased response to further stimuli and intensify the pain [1]. The most common cause of regret in hospitalized patients is pain [3], a reason they seek medical help. It is a subjective experience, so the severity should always be assessed on an individual basis [4]. The pain experienced by children in the hospital can be based on the following pathophysiology: acute, neuropathic, visceral, total, and chronic or persistent pain [5]. Pain in childhood continues to be underestimated and undertreated. The most vulnerable group of patients is infants and neonates in whom analgesic strategies are not used [6, 7]. One of the main difficulties in the treatment of childhood pain is the lack of dissemination of available pain assessment tools [8, 9].

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Abbreviations

FLACC – Face, Legs, Activity, Cry and Consolability
FPS-R – Face Pain Scale-Revised
VAS – Visual Analogue Scale
WHO – World Health Organization
NSAIDs – non-steroidal anti-inflammatory drugs
FDA – Food and Drug Administration

Pain assessment

Accurate and regular pain assessment is crucial in pain management. Various methods and scales are used to assess pain in childhood [10]. The ABCs of pain management, recommended many years ago by the Agency for Health Care Policy and Research (AHCPR), include the following: A. Ask about pain regularly. Assess pain systematically. B. Believe what the patient and family report about pain and what relieves it. C. Choose pain management options that are appropriate for the patient, family, and environment. D. Implement interventions in a timely, logical and coordinated manner. E. Empower patients and their families. Enable patients to take control [11].

One of the most commonly used scales for pain assessment in children is the Face, Legs, Activity, Cry and Consolability (FLACC) scale [4]. This scale is applicable to children and infants aged two months to seven years without contact with sleeping children **(Table 1).**

Another frequently used scale for assessing pain in children is the Faces Pain Scale-Revised (FPS-R). This scale utilizes faces arranged in a horizontal row **(Figure 1)**. A face on the left side of a row indicates no pain, while a face on the right side indicates the most severe pain possible [12].

In addition to the FPS-R, the Visual Analogue Scale (VAS) is also employed for school-age children.

Figure 1. Faces Pain Scale-Revised (FPS-R).
Slika 1. *Revidirana skala bola prema izrazu lica*

This scale consists of a line approximately 10 cm long, with the markings "0" and "10" on opposite sides. The "0" mark signifies no pain and the "10" mark indicates very severe pain (**Figure 2**) [13, 14].

In clinical practice, a numerical rating scale is frequently used to assess pain, especially in school-age and older children. This scale allows the patient to choose a number representing pain intensity or severity. The number zero denotes no pain and the number ten indicates severe pain [4].

Basic pain management

The World Health Organization (WHO) analgesic ladder offers a pain management framework that reflects modern considerations and techniques [15]. The updated WHO analgesic ladder **(Figure 3)** outlines some changes, including five recommendations for the regular use of analgesics: 1. Oral dosage forms should be used whenever possible; 2. Medications should be administered at regular intervals; 3. Medications should be administered based on pain as assessed by a pain intensity scale; 4. Doses of analgesics should be titrated individually; 5. Caution should be exercises when prescribing analgesics [16].

Table 1. FLACC scale
Tabela 1. *FLACC skala*

Category *Kategorija*	Scoring/S*kor*		
	0	1	2
Face *Lice*	No particular expression or smile./*Bez posebnog izraza ili osmeha.*	Occasional grimace or frown, withdrawn, disinterested./*Povremena grimasa ili mrštenje, povučeno, nezainteresovano.*	Frequent to constant frown, clenched jaw, quivering chin. *Često do stalno mrštenje, stisnuta vilica, drhtava brada.*
Legs *Noge*	Normal position or relaxes. *Normalan položaj ili se opušta.*	Uneasy, restless, tense. *Nelagodno, nemirno, napeto.*	Kicking, or legs drawn up. *Šutira, ili povlači noge.*
Activity *Aktivnost*	Lying quietly, normal position, moves easily./*Mirno leži, normalan položaj, lako se kreće.*	Squirming, shifting back and forth, tense./*Migolji se, pomera se napred-nazad, napeto.*	Arched, rigid of jerking./*Presavijeno, ukočeno od trzanja.*
Cry *Plač*	No cry (awake or asleep). *Ne plače (budno ili spava).*	Moans or whimpers, occasional complaint. *Stenje ili cvili, povremeno se žali.*	Crying steadily, screams or sobs, frequent complaints. *Stalno plače, vrišti ili jeca, često se žali.*
Consolability *Utešnost*	Content, relaxes. *Zadovoljno, opušta se.*	Reassured by occasional touching, hugging or being talked to, distractible./*Umiruje se povremenim dodirivanjem, zagrljajem ili razgovorom, ne zadržava pažnju.*	Difficult to console. *Teško ga je utešiti.*

Figure 2. Visual Analogue Scale (VAS)
***Slika 2**. Vizuelno analogna skala (VAS)*

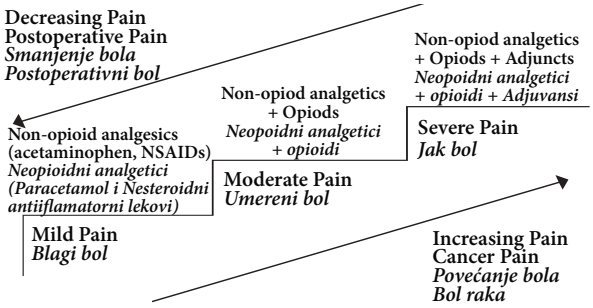

Figure 3. The World Health Organization pain ladder modified for Acute Pain Management
***Slika 3.** Izmenjena lestvica bola Svetske zdravstvene organizacije za lečenje akutnog bola*

Treating pain in children poses a challenge. Despite ongoing efforts to enhance perioperative pain management in children, many still suffer from perioperative pain in the hospital [17–19].

It is very important for children, irrespective of their age, to receive effective postoperative analgesia. The dosage and type of analgesic should be chosen based on scientific evidence. The administration of basic analgesics (non-steroidal anti-inflammatory drugs or paracetamol) is vital for pain management. These drugs can be administered intravenously, orally, or rectally. The effective use of these basic analgesics significantly influences the reduced use of opioids [20, 21]. Opioids are reserved for early postoperative and intraoperative use when adequate monitoring and specially trained personnel are available around the clock. To enhance pain management efficiency, the Pain Committee of the European Society of Pediatric Anesthesiology (ESPA) published guidelines for pain management in children in 2018, which are globally used [22]. Caution should be exercised when prescribing opioids in patients with obstructive sleep apnea due to the risk of ventilatory dysfunction after the procedure [23]. According to the standards of the American Society of Anesthesiologists (ASA), the use of multimodal analgesia is recommended whenever possible [24]. These standards call for the optimization of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) as analgesics, which should be administered at regular intervals rather than as needed [25, 26].

Paracetamol and non-steroidal anti-inflammatory drugs

This group of medicines contains basic analgesics for postoperative and general pain treatment in both children and adults, intended for managing mild to moderate pain. Basic or simple analgesia typically involves the use of paracetamol and NSAIDs.

Paracetamol is often combined with opioids for the treatment of more severe postoperative pain. Intravenous formulations are available and prove highly valuable in clinical pediatric practice. Despite its renal toxicity, acetaminophen is considered a safer but weaker analgesic. Infants, neonates, and children, however, have a significant hepatic production of glutathione, and are thus protected against its hepatic toxicity [27, 28]. The most commonly used NSAIDs as basic analgesics are ibuprofen, metamizole, ketorolac and diclofenac [5]. Ibuprofen is a first-choice drug for mild to moderate postoperative pain, often administered orally when feasible, with an analgesic effect almost comparable to that of paracetamol [29]. Another option is metamizole, a potent analgesic, though not globally available worldwide. Ketorolac, which can reduce opioid use, is also widely used potent drug. Diclofenac is daily postoperative pain treatment, more effective than paracetamol and ibuprofen but associated with more side effects. While the usual toxicities in adults are less pronounced in children due to a lack of comorbidities, common side effects of NSAIDs include nephrotoxicity, thrombocytopenia, asthmatic events, gastrointestinal ulceration and, less commonly, hepatotoxicity [30].

Systemic opioids

Opioids provide excellent pain relief for severe postoperative pain. The World Health Organization recommends the use of opioid analgesics in children experiencing persistent moderate to severe pain in addition to basic analgesia [31]. Morphine remains the gold standard in this group of drugs, although other opioids such as fentanyl and tramadol are also used in clinical practice. Fentanyl is primarily used intraoperatively. In neonates and infants during the first six months of life, there is a risk of developing respiratory arrest and periodic breathing even with small opioid doses. Opioid administration is safer in children over one year of age [32]. Strong opioids such as morphine, fentanyl, remifentanil and sufentanil have a high incidence of cardiorespiratory depression. Hence, close monitoring of cardiac and respiratory function is essential when using strong opioids. These opioids reduce the stress response during surgery [33–36]. Tramadol seems to play a key role in the early postoperative management of severe pain due to its fewer adverse effects and minimal cardiorespiratory depression while providing effective analgesia [5]. Studies and the Unites States Food and Drug Administration (FDA), which may lack scientific bases, reported cases of three children dying after taking opioids in the past 49 years and spoke out against the pediatric use of tramadol. This observation may put children at risk of unrelieved pain and other symptoms by either encouraging physicians to use strong opioids with a higher risk of respiratory depression or avoid opioid use altogether [37].

Regional anesthesia and local anesthetics

Pediatric regional anesthesia has been increasingly used in recent decades [38], particularly in the context of multimodal analgesia [39, 40]. Neurological complications associated with regional anesthesia in children are very rare. The French-Language Society of Pediatric Anesthesiologists study showed only five transient complications in 31,132 cases of regional anesthesia, with all five patients recovering without serious harm [41]. In 2018, the Pediatric Regional Anesthesia Network (PRAN) reported a study that found no cases of permanent neurological deficits. Out of 10,000 cases of regional anesthesia, only 25 cases resulted in temporary neurological damage [38]. There is an increased potential for neurologic complications in children older than 10 years, in contrast to infants and nonverbal children for whom it was challenging to record sensory deficits [42]. There were no differences in neurologic complications between peripheral nerve blocks and neuraxial anesthesia [43]. In 2018, Suresh et al. analyzed 40,121 cases of pediatric blocks and found that the systemic toxicity of local anesthetics during multiple peripheral nerve blocks was only 0.005%, with no persistent neurological deficits [44]. The European Society of Regional Anesthesia and Pain Management (ESRA) and the American Society of Regional Anesthesia (ASRA) have published dosage recommendations and guidelines to protect patients from systemic toxicity of local anesthetics [45].

Conclusion

Inadequate treatment of postoperative pain in children prolongs hospitalization and recovery. Pain should be assessed daily, using instruments and scales appropriate to the patient's age, language, cognitive ability, ethnicity, and type of illness. The most commonly used pain assessment scales for children are the Face, Legs, Activity, Cry and Consolability scale, Face Pain Scale-Revised, Visual Analogue Scale, and the numerical rating scale, depending on the child's age. The administration of basic analgesics is crucial for pain treatment. As a rule, basic or simple analgesia includes the use of paracetamol and non-steroidal anti-inflammatory drugs. Opioids are reserved for early postoperative and intraoperative use when adequate monitoring and specially trained personnel are available around the clock. Regional anesthesia in children has been increasingly used in recent decades, particularly in the context of multimodal analgesia. Regional anesthesia and local anesthetics play a superior role in pain management compared to systemic analgesics in such cases in pediatric patients.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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TYPE III DENS IN DENTE (DENS INVAGINATUS) AS A REASON FOR ENDODONTIC TREATMENT FAILURE – CASE REPORT

ZUB U ZUBU (DENS INVAGINATUS) TIP III KAO RAZLOG NEUSPEHA ENDODONTSKOG LEČENJA − PRIKAZ SLUČAJA

Aleksandar ANĐELKOVIĆ[1], Isidora NEŠKOVIĆ[1, 2] and Milan DROBAC[1, 2]

Summary

Introduction. Dens invaginatus is an infrequent developmental anomaly of teeth with an unknown etiology. The prevalence rate ranges from 0.25% to 10%. The most affected teeth are lateral maxillary incisors. Various classifications have been proposed to categorize the different types of dens in dente. However, the Oehlers classification, named after the dentist who first described it, is the most commonly used for this malformation. This classification has three primary types and was introduced in 1957. **Case Report**. A 17-year-old female patient appeared at the Dentistry Clinic of Vojvodina, Novi Sad with a lateral maxillary incisor exhibiting dens invaginatus (Oehlers type IIIA). The pulp was necrotic, accompanied by a large periradicular lesion. The patient had previously been prescribed penicillin antibiotics, and we initiated endodontic therapy. The patient returned for the scheduled check-up appointment with swelling in the area of the canine fossa above the upper left lateral incisor. In consultation with an oral surgeon, the tooth was extracted with purulent content. Four days after the extraction, the patient received a resin bonded bridge. **Conclusion**. The clinical significance and importance of dens in dente lie primarily in its potential to manifest with various symptomatic indications and its association with the occurrence and development of dental caries. It is crucial for clinicians and dental professionals to remain highly attentive, vigilant, and alert to the potential presence of dens in dente. This involves considering and acknowledging the wide array of diverse presentations and manifestations that this anomaly can exhibit.

Key words: Dens in Dente; Tooth Abnormalities; Endodontics; Dental Pulp Necrosis; Periapical Diseases; Denture, Partial, Fixed, Resin-Bonded

Sažetak

Uvod. Zub u zubu je retka anomalija razvoja zuba nepoznate etiologije. Stopa učestalosti je od 0,25% do 10%. Najčešće zahvaćeni zubi su maksilarni bočni sekutići. Postoje različite klasifikacije koje su predložene za kategorizaciju različitih tipova zuba u zubu. Međutim, Olerova klasifikacija, nazvana po stomatologu koji ju je prvi opisao, najrasprostranjenija je klasifikacija za ovu malformaciju. Ova klasifikacija ima tri osnovna tipa i uvedena je 1957. godine. **Prikaz slučaja**. Pacijentkinja stara 17 godina javila se na Kliniku za stomatologiju Vojvodine u Novom Sadu sa maksilarnim lateralnim sekutićem koji ima razvojnu anomaliju zvanu „zub u zubu“ (Oler tip IIIa). Pulpa je bila nekrotična sa udruženom velikom periradikularnom lezijom. Pacijentkinji je prethodno prepisan penicilinski antibiotik i započeto je endodontsko lečenje. Pacijentkinja se javila na zakazanu kontrolu sa otokom u predelu fose kanina iznad gornjeg levog bočnog sekutića. U konsultaciji sa oralnim hirurgom, zub je izvađen, uz obilan gnojni sadržaj. Četiri dana nakon ekstrakcije, pacijentu je izrađen adhezivni most. **Zaključak**. Klinički značaj i značaj zuba u zubu leži prvenstveno u njegovom potencijalu da se manifestuje različitim simptomatskim indikacijama kao i njegovoj korelaciji sa nastankom i razvojem zubnog karijesa. Za kliničare i stomatologe je od najveće važnosti da budu veoma pažljivi i predusretljivi na potencijalno prisustvo i postojanje zuba u zubu, uzimajući u obzir širok spektar raznovrsnih manifestacija koje ova anomalija može da ispolji.

Ključne reči: zub u zubu; anomalije zuba; endodoncija; nekroza zubne pulpe; periapikalna oboljenja; adhezivni most

Introduction

The concept of dens in dente, a developmental malformation of teeth, has long piqued the interest of dental professionals and researchers. The clinical implications of this condition, characterized by an invagination or deepening of the enamel and dentin layers, necessitate thorough investigation [1].

Dens in dente is an infrequent developmental anomaly of teeth with an unknown etiology, having a prevalence rate ranging from 0.25% to 10%. The upper lateral maxillary incisors are most often af-

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Abbreviations
CBCT – cone-beam computed tomography

fected by this abnormality, followed by maxillary central incisors, while mandibular teeth are rarely involved [1, 2].

This anomaly has been described as an infolding of the enamel organ into the dental papilla during the soft-tissue stage of tooth formation. It may be restricted to the pulp chamber, extend to the root, or, in extreme cases, reach the apex [2].

Various classifications have been proposed to categorize the different types of dens in dente; however, the Oehlers classification, named after the dentist who first described it, is the most commonly used for this malformation [3].

Oehlers classification is a method employed to classify dens invaginatus, also known as dens in dente, based on the gravity and profundity of the invagination. This classification was introduced by Oehlers in 1957. Within Oehlers classification, there are three primary types:

Type I: Invagination with Enamel Lining – this classification encompasses an invagination that possesses an enamel lining that does not extend beyond the enamel-dentin junction. It is regarded as the least severe variant.

Type II: Invagination Extending into the Dentin – the invagination extends beyond the enamel-dentin junction but does not communicate with the dental pulp. Although the invagination may extend into the dentin, it does not enter the pulp chamber.

Type III: Invagination Penetrating into the Pulp Chamber – this variant is considered the most severe, where the invagination penetrates into the pulp chamber, establishing a direct communication between the invagination and the pulp. Type III is associated with a heightened risk of infection or necrosis in the pulp tissue [4].

Clinical treatment includes different techniques, ranging from the simplest conservative to surgical techniques.

If surgical extraction of the tooth becomes necessary, it becomes imperative to identify a suitable approach for replacing the extracted tooth, as exemplified in our specific scenario.

Case Report

A 17-year-old female patient appeared at the Dentistry Clinic of Vojvodina, Novi Sad, seeking medical treatment. Her medical records indicate that she has been undergoing treatment with the antibiotic penicillin for the past three days, as prescribed by the dentist to alleviate severe pain in the upper left jaw area, specifically in the projection of the upper left lateral incisor and canine. The general dentist performed an intervention to drain the upper left lateral incisor, resulting in subjective improvement for the patient. Subsequent dental examination and analysis of a retroalveolar X-ray revealed the presence of a periapical lesion in the region of teeth 21 and 22 **(Figure 1)**. Tooth 22

Figure 1. Initial retroalveolar X-ray showing periapical lesion of tooth 22
Slika 1. *Početni retroalveolarni rendgenski snimak na kom se uočava periapikalna lezija zuba 22*

exhibited an access cavity. The examination further detected a distal perforation of the crown in the cavity. A comprehensive clinical examination led to the diagnosis of false pathway in the cervical region of tooth 22. The initial step in treatment involved repairing the perforation using MTA (MTA Universal OptiCaps, Harvard, Germany). The X-ray revealed the existence of an additional canal, which is caused by the presence of type III dens invaginatus (Oehlers). The primary canal of the tooth is located, and both canals are treated with copious irrigation of 2.5% NaOCl solution (Sodium Hypochlorite Solution, i-dental, Lithuania). The working length of the distal canal is 22.5 mm, while the mesial canal is 12 mm. The root canal procedure was performed using stainless steel hand K-files (K-Files, NIC, China). The distal canal was enlarged with ISO 35, while the mesial canal was enlarged with ISO 25. After disinfection of the canal with 2.5% NaOCl (Sodium Hypochlorite Solution, i-dental, Lithuania) and 17% EDTA (i-EDTA, i-dental, Lithuania), medication in the form of calcium hydroxide paste (TempCanal, Pulpdent Corp, USA) was placed. Gutta Percha Points (NIC, China) were used as a carrier of medication, placed at an appropriate working length, following which a control retroalveolar X-ray was taken (**Figure 2**). The check-up was scheduled 9 days later, and the access cavity was sealed with temporary restoration (Orafil-G, PrevestDenPro, India).

Figure 2. Control retroalveolar X-ray showing the length of canals on tooth 22
Slika 2. *Kontrolni retroalveolarni rendgenski snimak na kom se vidi dužina kanala zuba 22*

The patient returned for the scheduled check-up appointment with swelling in the area of the canine fossa above the upper left lateral incisor. The swelling appeared that morning along with pain in the same region. In consultation with an oral surgeon and a pediatric dentist, the proposed treatment plan was extraction of the upper left lateral incisor followed by the creation of a resin-bonded bridge, pending the age conditions for implantology therapy to be met. The patient agreed to the proposed therapy plan. The extraction was performed by an oral surgeon, and purulent content was obtained after the extraction. The oral surgeon prescribed antibiotic therapy (Clindamycin film tbl 600 mg S: 2x1) (**Figures 3 and 4**).

Figure 5. The stage of establishing resin bonded bridge
Slika 5. *Faza postavke adhezivnog mosta*

Figure 3. Postoperative intraoral photography four days after the extraction of tooth 22
Slika 3. *Postoperativna intraoralna fotografija četiri dana nakon vađenja zuba 22*

Figure 4. Access cavity of tooth 22 photographed after the extraction
Slika 4. *Pristupni kavitet zuba 22 fotografisan nakon ekstrakcije*

Four days after the intervention, the patient reported to the Clinic, where the resin-bonded bridge was made using the direct method (**Figures 5 and 6**).

Discussion

Dens in dente, also known as dens invaginatus, is a developmental anomaly characterized by the invagination of the enamel organ in the dental papilla, the

Figure 6. Final outcome after the therapeutic intervention
Slika 6. *Krajnja situacija nakon terapijskog zahvata*

embryonic structure responsible for tooth formation. This condition can affect both primary and permanent dentitions, with the maxillary lateral incisor, located on the upper jaw, being the tooth most commonly affected by this anomaly [5]. The etiology, or cause, of dens in dente is not fully understood; however, it is believed to result from an abnormality that occurs during the tooth development process [6].

Regarding treatment options for dens in dente, several approaches can be considered. These include root canal treatment, involving the removal of infected or damaged pulp tissue from the tooth and the sealing of root canals to prevent further infection. Another option is extraction, which involves the complete removal of the affected tooth [7]. To accurately diagnose and plan treatment for dens in dente, cone-beam computed tomography (CBCT) and magnification are commonly utilized as valuable tools that provide detailed information about the affected tooth and its surrounding structures. In our case, CBCT imaging was not performed due to complications in the form of swelling and the need for emergency tooth extraction.

Clinical identification of the radicular variant of dens in dente poses a complex challenge due to its predominantly asymptomatic nature, exhibiting a clinically normal-looking crown, and its incidental discovery through radiographic imaging. Pain and inflammation, as observed in our case and reported by researchers, are common features in symptomatic cases. Some instances have also been associated with dental caries, where caries progression is accelerated due to dilated root canals, creating "pathways" for infection spread and resulting in an unfavorable prognosis [8, 9]. To confirm the involvement of a tooth with the radicular variant of dens in dente, a clinician should conduct a comprehensive dental and radiographic examination, assess tooth vitality, and look for signs of discharge. In recent times, clinicians have utilized spiral computed tomography to obtain more detailed information about root anatomy, thereby improving clinical outcomes [8]. The execution of appropriate restorative/endodontic procedures should be approached with caution to prevent the need for extraction of the affected tooth [9–12]. Nevertheless, in the current instance, the presence of inflammation and infection made it unattainable to retain the tooth, regardless of all attempts to perform endodontic treatment, resulting in its extraction.

The extraction of dens in dente is often considered a last resort, with various treatment options available depending on the severity of the anomaly. Successful endodontic treatment has been reported, emphasizing the importance of early and correct diagnosis [8, 13]. Complications such as halitosis and purulent exudate can occur, requiring root canal treatment and restoration [6].

In our case report, we observed the radicular variant of dens in dente, accompanied by significant pain and inflammation. These symptoms are consistent with documented cases in the literature that exhibited same symptoms. The predominantly asymptomatic nature of this anomaly poses a challenge for clinical identification. Therefore, conducting thorough dental and radiographic examinations is crucial. Our findings support previous research reporting an association between dens in dente and dental caries. The dilated root canals in this anomaly may facilitate the spread of infection. In recent times, spiral computed tomography has emerged as a valuable tool for detailed assessment of root anatomy, with the potential to enhance diagnostic precision and treatment planning.

Recognizing the specific type of dens in dente is very important as it influences the severity and potential complications associated with the anomaly. Despite having various treatment options, ranging from successful endodontic treatments to tooth extraction as a last resort, our case required tooth removal due to inflammation and infection. When managing dens in dente, it is crucial to consider individual variations and clinical circumstances in the decision-making process.

The significance of early and accurate diagnosis is underscored by the varied presentations and complications of dens in dente, as demonstrated in our case. Ongoing research in this field is crucial for refining diagnostic approaches and treatment methods. This will ensure that clinicians can effectively address the diverse manifestations of dens in dente.

Conclusion

The clinical significance and importance of dens in dente primarily lie in its potential to manifest with various symptomatic indications, its association and correlation with the occurrence and development of dental caries, and the numerous challenges encountered in terms of accurate diagnosis and effective treatment methods. It is of utmost importance for clinicians and dental professionals to remain highly attentive, vigilant, and alert to the potential presence and existence of dens in dente. This involves considering and acknowledging the wide array of diverse and varied presentations and manifestations that this anomaly can exhibit. It is also important to recognize and address the unique challenges and obstacles associated with its diagnosis and treatment, as demonstrated and exemplified in our particular case study.

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RENAL LEIOMYOMA – CASE REPORT AND LITERATURE REVIEW

LEJOMIOM BUBREGA − PRIKAZ SLUČAJA I PREGLED LITERATURE

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Summary

Introduction. Leiomyoma is a mesenchymal benign tumor that seldom manifests in the kidney. Typically, these tumors are small, asymptomatic, and often detected accidentally. Differentiating leiomyomas radiologically from other renal neoplasms, particularly renal cell carcinomas, poses a considerable challenge before surgical intervention. Moreover, the conclusive diagnosis of leiomyomas can only be established through histopathological and immunohistochemical evaluation following surgical intervention. **Case Report.** We present a case of a 44-year-old woman who was diagnosed with right kidney leiomyoma accidentally during a computed tomography examination following exploratory curettage by a gynecologist. An enhanced computed tomography scan revealed a 10 mm tumor located on the upper pole of the right kidney, extending beyond its boundaries. The imaging differential diagnosis was renal cell carcinoma of the right kidney. A laparoscopic partial nephrectomy was performed. Macroscopically, the tumor appeared subcapsular, well-defined, with a firm consistency and a tan-white whorled cut surface. The histological characteristics and the supporting immunohistochemical profile confirmed the diagnosis of renal leiomyoma. The postoperative course was uneventful, and the patient was discharged on the 3rd postoperative day. **Conclusion.** Leiomyomas are rare kidney tumors. A conclusive diagnosis is established through histopathological findings. The pre-operative differentiation of leiomyomas radiologically from other renal neoplasms, particularly renal cell carcinomas, poses a considerable challenge in radiological assessment.

Key words: Leiomyoma; Kidney Neoplasms; Diagnosis, Differential; Tomography, X-Ray Computed; Nephrectomy; Morphological and Microscopic Findings

Sažetak

Uvod. Lejomiom je benigni tumor mezenhimalnog porekla koji se retko javlja u bubregu. Ovi tumori su generalno mali, asimptomatski i najčešće se otkrivaju akcidentalno. Veliki je izazov radiološki razlikovati lejomiome od drugih bubrežnih neoplazmi pre operacije, posebno karcinoma bubrežnih ćelija. Konačna dijagnoza lejomioma može se postići samo histopatološkom i imunohistohemijskom evaluacijom nakon hirurške intervencije. **Prikaz slučaja.** Prikazan je slučaj pacijentkinje stare 44 godine, kod koje je kompjuterizovanom tomografijom rađenom nakon ginekološke intervencije, akcidentalno otkriven lejomiom desnog bubrega. Na kompjuterizovanoj tomografiji opisana je tumorska masa veličine 10 mm na gornjem polu izvan kontura desnog bubrega. Diferencijalna dijagnoza je bila karcinom bubrežnih ćelija. Urađena je laparoskopska parcijalna nefrektomija. Makroskopski, tumor je bio supkapsularan, dobro ograničen i čvrste konzistencije. Dijagnoza lejomioma desnog bubrega postavljena je na osnovu histoloških karakteristika i pratećeg imunohistohemijskog profila. Postoperativni tok je protekao bez komplikacija, a bolesnica je otpuštena trećeg postoperativnog dana. **Zaključak.** Lejomiomi predstavljaju retke tumore bubrega. Definitivna dijagnoza postavlja se isključivo patohistološkim nalazom. Veoma je teško radiološki razlikovati lejomiom od drugih tipova tumora preoperativno, naročito od karcinoma bubrežnih ćelija.

Ključne reči: lejomiom; neoplazme bubrega; diferencijalna dijagnoza; CT; nefrektomija; morfološki i mikroskopski nalazi

Introduction

Leiomyomas are benign mesenchymal tumors that seldom manifest in the kidney. Typically, these tumors are asymptomatic, tiny, and often detected by accident. Large renal leiomyomas are uncommon but may manifest as abdominal mass or pain. Differentiating leiomyomas radiologically from other renal neoplasms, particularly renal cell carcinomas, prior to surgery is challenging. Unenhanced computed tomography (CT) scans may show common imaging characteristics such as hyperattenuation, peripheral placement, and well-defined margins. The definitive confirmation of leiomyoma diagnosis is only possible through histopathological and immunohistochemical evaluation following surgical intervention [1, 2].

Case Report

In our case, the patient was an asymptomatic 44-year-old woman who was accidentally diagnosed with a solid renal mass during the follow-up CT scan

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Abbreviations
CT – computed tomography
SMA – smooth muscle actin

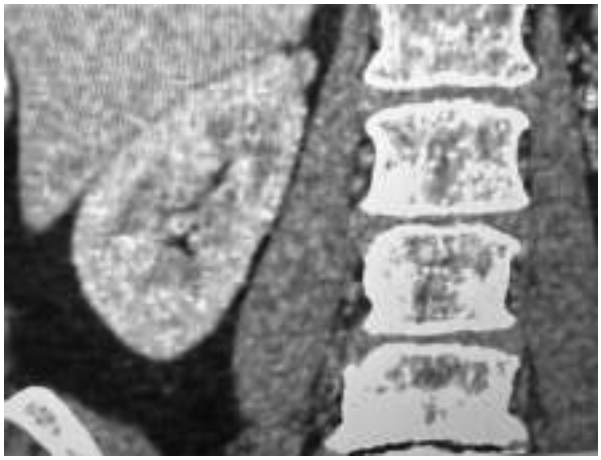

Figure 1. Renal mass on the upper pole, contrast-enhanced CT scan
Slika 1. *Bubrežna masa na gornjem polu, kompjuterizovana tomografija sa kontrastom*

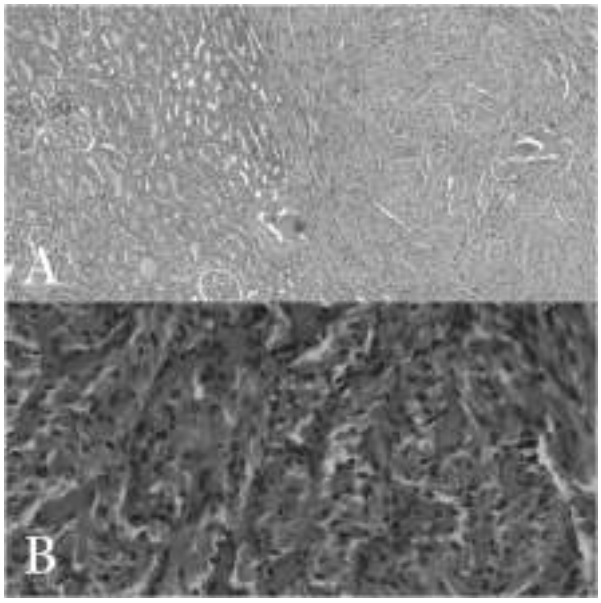

Figure 2. Hemotoxylin eosin, 5x (A), Hemotoxylin eosin, 20x (B)
Slika 2. *Hematoksilin-eozin, 5 x (A), Hematoksilin-eozin, 20 x (B)*

after exploratory curettage by a gynecologist. The enhanced CT scan revealed a 10 mm tumor on the upper pole of the right kidney that extended beyond its boundaries **(Figure 1).** The imaging differential diagnosis indicated that the patient had renal cell carcinoma of the right kidney. Subsequently, a laparoscopic partial nephrectomy was performed.

Macroscopically, the tumor appeared subcapsular and well-defined, with a firm consistency and a tan-white whorled cut surface. No cystic defects, hemorrhaging, or necrosis were identified. Microscopically, the tumor nodule was surrounded by the renal capsule and compressed renal parenchyma **(Figure 2A).** It was composed of spindle cells arranged in intersecting fascicles and whorls, displaying minimal pleomorphism, elongated blunt-ended nuclei, inconspicuous nucleoli, and tapering eosinophilic cytoplasm, with the presence of moderately abundant collagenized and partly hyalinized stroma **(Figure 2B).** Mitoses and necrosis were not observed. The entire tumor was removed. The cells stained positive for Caldesmon and smooth muscle actin (SMA) **(Figure 3)** and negative for Pancytokeratin, Desmin, MelanA, HMB-45, CD34, and PAX8. The Ki-67 staining demonstrated a very low proliferation rate (<1%). The diagnosis of renal leiomyoma was established based on the histological characteristics and the accompanying immunohistochemical profile.

The patient recovered after surgery without any complications, and she was discharged on the 3rd postoperative day.

Discussion

Leiomyomas are benign mesenchymal tumors that typically originate in smooth muscle–lined hollow organs, usually in the uterus and the gastrointestinal tract. Although uncommon, renal leiomyoma accounts for 4.2% to 5.2% autoptic cases. A 10-year study by the J. B. Brady Urological Institute (Baltimore, MD) involving 1030 nephrectomies revealed that renal leiomyomas constituted 1.5% of benign renal tumors and 0.3% of all treated tumors [2–4]. In a 2015 study analyzing around 4000 renal neoplasms over a 22 years, only four renal leiomyomas were identified, resulting in an incidence of 0.001% [5]. With a 2:1 female predilection, these tumors are usually incidentally discovered in adults, with the mean onset age of 47 years. Limited cases involving pediatric age have been documented [6, 7].

Renal leiomyomas originate from smooth muscle cells in the renal capsule, renal pelvis, or the tunica media layer of renal cortical vascular structures. These tumors manifest as subcapsular, capsular, or subpelvic types. The lower pole of the kidney is the most common site for tumor detection (74%), with an equal incidence in both kidneys [1, 7]. In contrast to previous reports, our patient's mass lesion was located on the upper pole of the kidney.

Renal leiomyomas usually remain asymptomatic until they produce a mass effect. Symptomatic cases are presented with a palpable mass (57%), abdominal/flank pain (53%), and microscopic or gross hematuria in 20% of cases. The average lesion size reported in the literature is 12.3 cm [7, 8]. The current largest renal leiomyoma measures 57.5 cm in diameter and weighs 37.2 kg [9].

The differential diagnosis of renal leiomyoma includes smooth muscle predominant angiomyolipoma, fibroma, oncocytoma, renal cell carcinoma, and leiomyosarcoma [6, 7, 10].

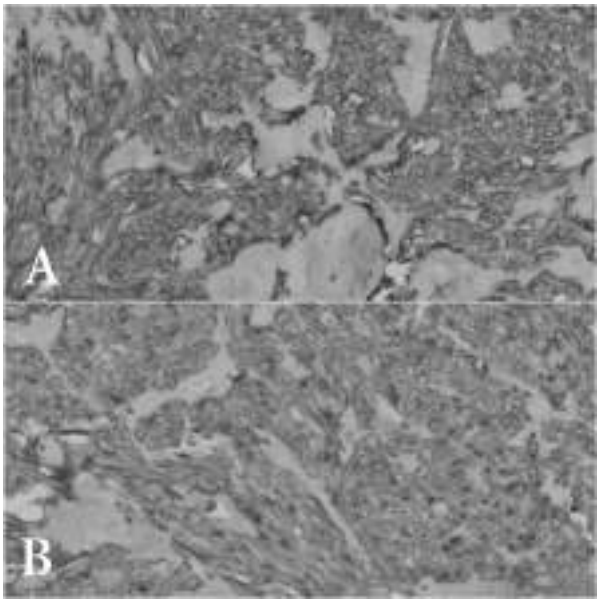

Figure 3. Caldesmon, 20x (A), SMA 20x (B).
Slika 3*. Caldesmon, 20x (A), aktin glatkih mišića (SMA) 20x (B)*

Renal leiomyomas often appear as solid masses with well-defined boundaries situated in the periphery on CT and magnetic resosnance imaging. Large tumors may contain hemorrhagic or cystic degenerative regions, posing an increased risk of malignancy [11]. While radiographic examination does not reveal specific features for renal leiomyomas, some typical imaging features include clear edges, position on the edge, absence of invasion into nearby tissues, and increased signal intensity unenhanced CT images. A key feature of CT scans aiding in differential diagnosis is density. Before contrast, all studied leiomyomas appeared hyperdense compared to the kidney, with a density similar to that of muscles. After contrast medium injection, the lesions showed less enhancement than the surrounding renal parenchyma [12–14].

The final diagnosis of kidney leiomyomas depends on histopathology, which is usually performed after surgical removal of the tumor. Histologically, renal leiomyomas appear to be made of fusocellular elements, with absence of mitotic figures, pleomorphism, hyperchromatism, and perilesional invasivity. The presence of these conditions is characteristic of leiomyosarcoma [12, 13].

In the majority of documented cases, patients diagnosed with kidney leiomyoma were initially presumed to have renal cell carcinoma and were treated with partial nephrectomy, which is currently considered the gold standard [14].

Conclusion

We presented the case of a 44-year-old woman with renal leiomyoma, which tumor was diagnosed accidentally. As a result of the radiological differential diagnosis of renal cell carcinoma, the tumor was surgically excised. Histopathology of the surgically resected mass confirmed this rare renal tumor – leiomyoma.

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CORONARY DISEASE AND AORTOPATHY IN ACHONDROPLASIA

KORONARNA BOLEST I AORTOPATIJA KOD AHONDROPLAZIJE

Borislav DOLAMIĆ[1], Ana ALADIN DOLAMIĆ[2], Maja STEFANOVIĆ[3], Golub SAMARDŽIJA[3, 4], Dragoslava ŽIVKOV ŠAPONJA[4, 5] and Anastazija STOJŠIĆ MILOSAVLJEVIĆ[3, 4]

Summary

Introduction. Achondroplasia is an inherited autosomal dominant disorder and the most prevalent cause of dwarfism in humans. **Case Report.** A 38-year-old male with achondroplasia required cardiothoracic surgical treatment. Standing at 150 cm, weighing 68 kg, with a body surface area index of 1.68 m², he had a history of diagnosed hypertension and Chiari malformation. A transthoracic echocardiogram five years ago revealed mild aortic regurgitation. In the recent cardiac examination, moderate-to-severe aortic regurgitation, dilation of the Valsalva sinus, and coronary artery disease were observed. The elective cardiothoracic surgery included mechanical aortic valve replacement and myocardial revascularization with a single bypass. Histopathological analysis of the aortic wall indicated mucoid degeneration, atherosclerosis, and focal adventitial hemorrhages. The postoperative course was uneventful, and normal blood pressure values were confirmed with a Holter monitor. **Conclusion.** A comprehensive cardiac evaluation is crucial for patients with achondroplasia, emphasizing the significance of considering echocardiographic parameters in the context of anthropometric characteristics. The proficiency and readiness of adult physicians to consistently provide accurate diagnosis and treatment, especially in urgent interventions or surgical procedures, are essential.

Key words: Coronary Disease; Achondroplasia; Aortic Valve Insufficiency; Transcatheter Aortic Valve Replacement; Coronary Artery Bypass

Sažetak

Uvod. Ahondroplazija je nasledna bolest koja se autosomno dominantno nasleđuje i najčešći je uzrok patuljastog rasta kod ljudi. **Prikaz slučaja.** Muškarac, starosti 38 godina, sa ahondroplazijom, čije lečenje je zahtevalo kardiohirurški tretman. Visina 150 cm, težina 68 kg, indeks telesna mase 1,68 m², od ranije dijagnostikovana hipertenzija i Kjarijeva malformacija. Transtorakalni ehokardiografski pregled pre pet godina ukazivao je na lako-blagu aortnu regurgitaciju. Pri poslednjem kardiološkom pregledu utvrđena je umereno-teška aortna regurgitacija, dilatacija sinusa Valsalve i koronarna bolest. Elektivna kardiohirurška operacija obuhvatala je zamenu aortne valvule mehaničkom dvolisnom valvulom i revaskularizaciju miokarda jednostrukim bajpasom. Patološko-histološkom analizom zida aorte uočena je mukoidna degeneracija, ateroskleroza i fokalno podlivena krvarenja adventicije. Postoperativni tok je bio uredan. Holterom krvnog pritiska potvrđene su normalne vrednosti. **Zaključak.** Potrebna je uvek kompletna kardiološka obrada kod pacijenata sa ahondroplazijom, uz važnost sagledavanja ehokardiografskih parametara u kontekstu antropometrijskih osobenosti. Neophodna je uvežbanost i spremnost lekara da uvek mogu da pruže adekvatnu dijagnostiku i lečenje posebno u urgentim interventim ili hirurškim procedurama.

Ključne reči: koronarna bolest; ahondroplazija; aortna regurgitacija; zamena aortnog zaliska; koronarni bajpas

* The study was presented at the congress: Spring Cardiology Workshop, Kopaonik, April 14-17, 2022

***** *Rad je prikazan na kongresu: Prolećna kardiološka radionica, Kopaonik, 14.-17. april 2022.*

Introduction

Achondroplasia is an inherited disorder transmitted in an autosomal dominant manner, with a 50% chance for newborns to inherit the syndrome if either parent carries it. However, 75% to 80% of patients with achondroplasia may be born to parents of average height due to a de novo dominant mutation in the fibroblast growth factor receptor 3 (FGFR3) gene, which is responsible for this condition [1]. Achondroplasia is the most common cause of dwarfism in humans. Affected individuals typically exhibit short limbs, an enlarged head circumference, and a normal trunk, often accompanied by musculoskeletal and cardiovascular complications. Diagnosing anomalies of the locomotor system prenatally can be particularly challenging, emphasizing the importance of actively searching for them during each prenatal examination. Arterial hypertension emerges as a prevalent risk factor for cardiovascular diseases in this population [2–4]. Reports highlight a tenfold increase in the prevalence of cardiovascular diseases in these patients between the ages of 25 and 35 [5]. In this study, we present the case of a

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Abbreviations

BSA	– body surface area
TTE	– transthoracic echocardiogram
LVIDd	– left ventricular internal diameter in diastole
LVMI	– left ventricular mass index
CT	– computed tomography
LAD	– left anterior descending artery

38-year-old patient at the time of diagnosis, whose treatment required elective cardiothoracic intervention, involving aortic valve replacement with the interposition of a tubular graft and aortocoronary bypass.

Case Report

A 38-year-old male sought consultation with an internist at a private clinic in early 2021 for an examination due to uncontrolled hypertension, a condition he had been managing since the age of 18. The patient had achondroplasia, standing at a height of 150 cm, weighing 68 kg, and having a body surface area (BSA) index of 1.68 m^2. Secondary hypertension had been ruled out in prior assessments. The patient was aware of his Chiari malformation, and his last transthoracic echocardiographic examination (TTE), conducted five years ago, revealed mild aortic regurgitation (AR) without aortic dilation. He reported no subjective complaints, holding a New York Heart Association (NYHA) functional class of 1. His complete blood count (CBC) was within normal range, and the lipid profile showed cholesterol at 7.3 mmol/L, triglycerides at 3.68 mmol/L, and LDL at 4.6 mmol/L. Renal function parameters were within normal limits. Blood pressure measured 160/80 mmHg on both arms, and an electrocardiogram (ECG) indicated sinus rhythm with a heart rate of approximately 70/min, displaying a normal waveform and no signs of ischemia or rhythm disturbances. The TTE revealed slightly increased endocavitary dimensions of the left ventricle (left ventricular internal diameter in diastole (LVIDd) = 5.6 cm, LVIDd/BSA = 3.33 cm/m^2), preserved overall systolic function of the left ventricle, and significantly increased mass (interventricular septum thickness in diastole (IVSd) = 1.2 cm/left ventricular posterior wall thickness in diastole (LVPWd) = 1.2 cm, left ventricular mass indexed - LVMI = 174.9 g/m^2). The morphology and function of the right ventricle were preserved. Aortic regurgitation (AR) was observed to be moderately severe, qualitatively 3/4+, semiquantitatively with a pressure half-time (PHT) over 260 ms, and holodiastolic flow reversal in the descending aorta (end-diastolic velocity = 36 cm/s). This was associated with sinus of Valsalva dilation measuring 4.7 cm, sinus of Valsalva/BSA = 2.79 cm/m^2, and intraintimal dimensions **(Figure 1)**. The patient's therapy was adjusted, and an expert TTE was recommended at the Institute of Cardiovascular Diseases of Vojvodina, where the diagnosis was confirmed. A computed tomography (CT) aortography verified sinus

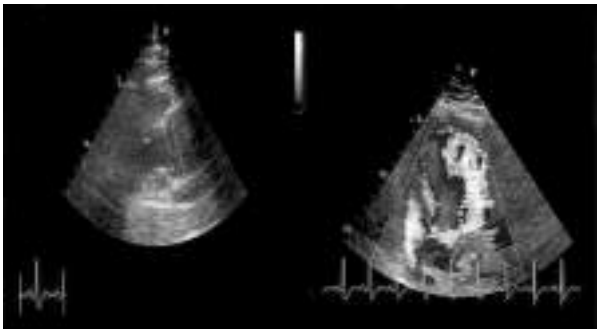

Figure 1. TTE – Sinus Valsalva dimensions of 47 mm with color signal of aortic regurgitation
Slika 1. *Transtorakalni ehokardiogram – dimenzije sinusa Valsalve od 47 mm sa kolor signalom aortne regurgitacije*

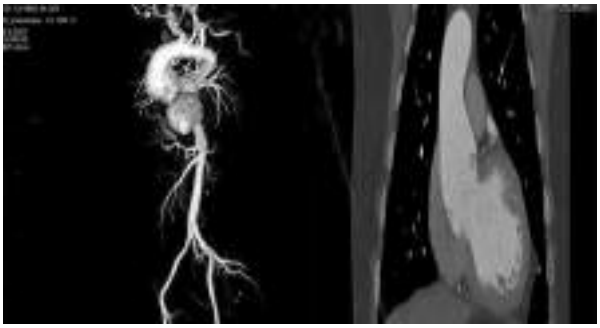

Figure 2. CT aortography: Aneurysmal dilatation of the aortic sinus of Valsalva measuring 53 mm
Slika 2. *Kompjuterizovana tomografija aortografija: Aneurizmatsko proširenje sinusa Valsalve aorte 53 mm*

of Valsalva dilation, specifically in the left coronary sinus, measuring 5.3 cm. Other segments of the thoracic aorta displayed normal dimensions **(Figure 2)**. Subsequent CT coronary angiography revealed a borderline significant stenosis in the medial part of the left anterior descending artery (LAD). A preoperative left selective coronary angiography confirmed an 80% stenosis in the medial segment of the LAD. Following the diagnostic procedures, an elective cardiothoracic operation was performed, involving the mechanical bileaflet aortic valve replacement (St. Jude Medical- mechanical heart valves Size 23) with the interposition of an aortic tubular graft (Size 28). Additionally, myocardial revascularization was achieved with a single bypass: left internal mammary artery myocardial revascularization with single bypass. Histopathological analysis of the aortic wall revealed focal adventitial hemorrhage, disrupted media architecture with areas of mucoid degeneration, and pronounced atherosclerosis **(Figure 3)**. The early postoperative course was uneventful, followed by cardiac rehabilitation. Holter blood pressure monitoring confirmed normal values with preserved circadian rhythm. Subsequent echocardiographic examinations post-surgery confirmed the proper functioning of the mechanical aortic valve.

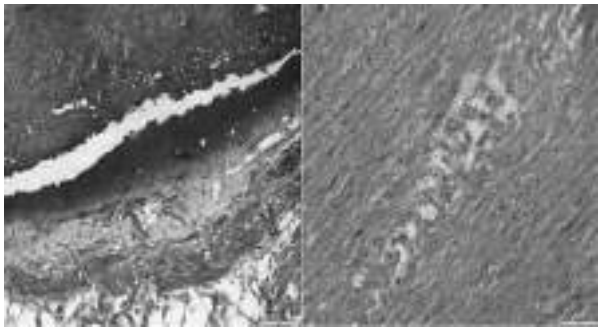

Figure 3. Ph analysis of the aortic section. **Left image** - 20x H&E, showing adventitia stained with blood. **Right image** - 40x H&E. Aortic wall with areas of disrupted elastic fibers and regions of mucoid degeneration. ***Slika 3.*** *Patohistološka analiza isečka aorte.* ***Leva slika*** *– 20 x HE gde se vidi krvlju podlivena adventicija.* ***Desna slika*** *– 40 x HE. Zid aorte sa delom raskidanih elasičnih vlakana i područijima mukoidne degeneracije.*

Discussion

We presented a case of a young patient with achondroplasia who, amidst the challenges of the coronavirus-19 pandemic, also exhibited cardiac weakness. Despite the difficulties of the time, a relatively swift and comprehensive non-invasive cardiac diagnostic assessment was conducted, enabling timely and adequate treatment and resulting in significant improvement in cardiac morphology and function [6]. Verstraeten A. et al. in a 2020 publication, explained the association between achondroplasia and thoracic aortic aneurysms. The underlying cause of the disease lies in a pathological variant resulting in the heightened function of the fibroblast growth factor receptor 3 gene. They noted that dysregulations of the extracellular matrix, abnormal transforming growth factor-beta (TGF-β), and endoplasmic reticulum stress are common substrates for these diseases [7]. From the perspective of aortic pathology, although the abdominal region is more frequently affected, thoracic aortic diseases are more commonly associated with hereditary conditions. Over 20 gene bases for this have been identified so far, yet they account for less than 30% of the total cases [8]. Georgios and Tagarakis, et al., in a 2010 publication, illustrated the peculiarities of elective cardiothoracic revascularization, specifically aortocoronary bypass (CABG), in patients with achondroplasia. The patient, aged 41, was diagnosed with a three-vessel disease (90% stenosis of the proximal left anterior descending artery, 70% stenosis of the first obtuse marginal branch of the ramus circumflex artery, and 90% stenosis of the right coronary artery) before the decision for the planned operation. Despite his young age, he had no significant family comorbidities, and aside from high-normal blood pressure values, he had no other major risk factors that would be particularly relevant at his age. Echocardiography and ventriculography were normal. The operation proceeded without complications, involving a triple bypass, mammary artery to the proximal LAD, and two venous grafts to the other two diseased coronary vessels [9]. Sukhvasi et al.conducted a retrospective study analyzing outcomes of cardiothoracic surgical and interventional non-surgical cardiological procedures in patients with achondroplasia. Out of a total of 5274 identified articles, 14 met the criteria for inclusion in the analysis. Among the included cases, 53.8% (7/13) exhibited coronary artery disease, and 30.8% (4/13) of patients had a history of myocardial infarction. Among eight patients who underwent heart surgery, 37.5% (3/8) underwent multivessel coronary artery revascularization, 37.5% (3/8) had aortic valve replacement surgery, 25% (2/8) underwent surgery for type A aortic dissection, and the remaining 12.5% (1/8) had pulmonary thromboendarterectomy. Six patients underwent percutaneous coronary intervention. In 16.7% (1/6) of patients, an interventional procedure on the aortic and pulmonary valves was performed, and a pacemaker was implanted in another 16.7% (1/6). The mean size of arterial cannulas was 20.0 Fr. (French). Despite the small number of patients in this analysis, it precisely defined the cardiac substrate of this entity [10].

Conclusion

Given the increased prevalence of cardiovascular comorbidities in individuals with achondroplasia, a comprehensive cardiac assessment is imperative. Echocardiographic parameters should be consistently evaluated, taking into account anthropometric characteristics, with particular attention to the body surface area index. Adult physicians must demonstrate proficiency and readiness to consistently deliver accurate diagnosis and treatment, especially in urgent interventions or surgical procedures.

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SEMINAR FOR PHYSICIANS
SEMINAR ZA LEKARE U PRAKSI

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OUR VIRUSES AND SAPROPHYTIC BACTERIA

NAŠI VIRUSI I SAPROFITSKE BAKTERIJE

Milorad ŽIKIĆ

Summary

Introduction. The paper presents the facts about the inevitable presence of microbes in the human body and the key role of viruses in the evolution, shaping and development of the living world. **Contemporary research.** Experimental scientific research on mice, examining the influence of saprophytic bacteria on their physical activity and behavior through the produced N-lactoyl-phenylalanine substance, provides foundation for further research within the human population. **Discussion.** The above positive impact of viruses and the consequential risks of their presence on people's health are discussed along with the adverse cross-effects of planetary and human health arising from harmful behavior and wrong life habits of the contemporaries. **Conclusion.** Recommendations are given for preventive possibilities to avoid such risks and achieve good or satisfactory health both for each and every individual and the global community of people through a lifestyle in harmony with nature.

Key words: Microbiota; Viruses; Biological Evolution; Phenylalanine; Health; Risk Factors; Microbial Interactions

Sažetak

Uvod. U radu su iznete činjenice o nezaobilaznoj prisutnosti mikroba u ljudskom organizmu i ključnoj ulozi virusa u evoluciji, oblikovanju i razvoju živog sveta. **Savremena istraživanja**. Eksperimentalna naučna istraživanja na miševima o uticaju saprofitskih bakterija na njihovu fizičku aktivnost i ponašanje putem proizvedene N-laktoil-fenilalanin supstancije otvaraju prostor za dalja istraživanja i u humanoj populaciji. **Diskusija**. Raspravlja se o navedenom pozitivnom uticaju virusa kao i o posledičnim rizicima njihovog prisustva po zdravstveno stanje ljudi, o ukrštenim uticajima planetarnog i ljudskog zdravlja koji, u negativnoj konotaciji, proističu iz štetnog ponašanja i pogrešnih životnih navika savremenika. **Zaključak**. Date su preporuke za preventivne mogućnosti da se iste izbegnu, da se načinom života u skladu sa prirodom ostvari dobro ili zadovoljavajuće zdravlje, kako za svakog pojedinca tako i za celokupnu svetsku zajednicu ljudi.

Ključne reči: mikrobi; virusi; evolucija; fenilalanin; zdravlje; faktori rizika; interakcije mikroba

Introduction

Viruses shape the living world

Viral infections are the most prevalent human diseases and we live in a world of viruses that is incomparably diverse. Mammals alone can carry at least 320,000 different types of viruses, and when you add viruses that infect non-mammalian animals, plants, terrestrial bacteria, and every conceivable host, the total number is enormous. Despite their potential threat to the health of the living world, viruses also yield significant positive consequences for life on Earth as many of them bring adaptive benefits rather than harm. Viruses have also played a key role in initiating major evolutionary transitions [1, 2].

It is unusual that we learn about millennial events of vital importance for all people, which are evidently unfolding, only on the margins of our daily lives. Today, we know that microorganisms generate many chemical substances that affect the human body, physical and mental health, and consequently our behavior, which contribute to the onset and development of chronic heart diseases, type 2 diabetes, obesity, depression, anxiety, degenerative neurological diseases- the most common diseases of modern humanity.

About 8% of our current DNA originates from viruses that infected our ancient ancestors. These viruses integrated their genes into the ancestral genomes, and now, some of these genes play a key role in the early stages of embryo development and the placenta that surrounds the fetus. Today, we know that the two DNA strands derived from the proviruses, now found in the genomes of humans and other primates, are indispensable for pregnancy, and that the inception of life would not have been possible, and its continuity would be unattainable without their presence [1,3].

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Other genes co-opted from viruses also contribute to the growth of embryos, regulate the immune system, and occasionally resist malignancies. Moreover, there is viral DNA found among the genes of terrestrial animals, including humans, which aids in the recollection of the past by depositing memories and storing them in small protein bubbles within nerve cells. The impact of many chemical substances of microbes can rarely be fatal to the physical and mental health of people [1, 3, 4].

Contemporary research

Microbe genes affect the human body

The results of an experimental study comparing the behavior of a cohort of mice that exercised on a treadmill with mice that did not exercise revealed differences in the microbiome of intestinal microbes. The exercising mice had more bacteria that produced the chemical substance N-lactoyl-phenylalanine (Lac-Phe), a signaling molecule that, during the running, transmitted signals from the gut to the brain, stimulating the reward centers and motivating the exercising mice to reach their peak and continue running. In contrast, a different microbiome left the sedentary mice without such reward and in a static position. When the *exerciser's* gut microbiome was injected into the sedentary mice, they began running on a wheel and exercising.

It was concluded from the results of the above experiment that the same encouraging effect could likely be achieved in humans as a stimulus to activate physical activity, especially in a static population that lacks spontaneous motivation to engage in physical exercise - a habit of paramount importance for achieving and maintaining of good health [5].

Analysis of current knowledge about the consequential risks of harmful forms of behavior and wrong lifestyle habits for the planet and human health

Once thought of as mere saprophytes that use our bodies to get food and shelter, the trillions of microbes living on our skin and deep inside us are now recognized for their role in creating many chemicals that have a positive effect on our body. However, this understanding also reveals their role on the development and the onset of heart and blood vessel diseases, malignancies, type 2 diabetes, obesity, depression, anxiety and some degenerative neurological diseases. These conditions have been proven to develop into silent killers that collectively contribute to three out of five global deaths each year. We are aware of the fact that health is not everything, but also of the fact that everything is nothing without health as health is the foundation of life itself [6].

In addition, we must keep in mind that anything that happens on Earth is interconnected, therefore, we have a task to master the understanding of how individual health intertwines with the planetary health, and what to do in order to correct mistakes in human behavior towards the Planet and avoid or mitigate the related consequences for human health. Earth Day is marked as a day of people's awareness of environmental issues, and a reminder that establishing a correct awareness among people regarding our environment has never been more important than now.

The impacts of climate change on Earth, including phenomena like fires, stormy winds, floods, droughts, heat waves, rising sea levels, and the extinction of many living species, pose direct or indirect threats to the survival of everyone and everything, especially the most vulnerable representatives within each ecosystem. The pollution of the air with fossil fuels and the escalating emissions of carbon dioxide that consequently elevate air warming, are the cause of increasingly devastating fires and the massive emergence and development of more chronic diseases. Furthermore, the shifting of geographical and seasonal boundaries altering the habitats for ticks and mosquitoes, which are carriers of many infectious diseases that spread with the speed of the wind, endangers human health all over the Planet.

The events we are witnessing have complex and interconnected effects. The concept of planetary health confirms the inseparable link between the ecosystem and human health. Therefore, it becomes imperative to implement all necessary interventions urgently and effectively in order to prevent the negative consequences with increasingly frequent devastating outcomes.

How to prevent, suppress and/or eliminate the consequences of the mentioned risks for human health?

There are several ways to counteract and avoid the risk of unfavorable outcomes. Establishing and maintaining a healthy lifestyle for people is one possibility. It goes without saying that adherence to daily healthy lifestyle activities should be strictly exercised. The more preventive and/or curative measures are taken before application, the sooner the risk of unwanted consequences will be avoided or suppressed.

Organic vegetable and essential foods defeat inflammation. This also applies to physical activity, especially deep breathing exercises and weight management. Reducing abdominal fat removes the type of fat cells that produce pro-inflammatory chemicals, aiding thus to the reduction of the effect that sugar has on body weight. Then, enough invigorating sleep, giving up the habit of smoking, which results in a significant reduction in the level of inflammation within just a few weeks, and limiting the use of alcohol, with a note that small amounts of alcohol, such as up to two glasses of quality wine, particularly taken with fish, or a glass of natural spirit after a good meal, have health-protective benefits [3, 7].

The questions that yet need to be answered are whether contemporaries frequently adopt unhealthy lifestyle habits due to a lack of understanding and/or lack of focus on their harmful impact on health, or is it a failure to recognize the importance of preventive measures due to their simplicity and mandatory default?

Discussion

The paper emphasizes the essential role of viruses in shaping the evolution of ecosystems on Earth, a role that is crucial for the development and survival of the living world. Although viruses are feared as the cause of disease, discussions about them are just beginning to unfold in that context. Therefore, it is justified and reasonable to learn about them every day [2].

Changes are often necessary to correct previous wrong and often harmful behaviors and habits, whether individual or environmental. What works positively for one person may not necessarily work for another person. Will the orientation towards the choice of diet, exercise and the choice of commuting in the local environment be suitable to the specific requirements of a job, place of residence, educational and economic status, and individual character traits? In any case, the decision to start corrective procedures with goal setting is the way to a good life commitment [3, 8].

The latest experimental scientific study on mice examining the influence of saprophytic bacteria on their physical activity through the produced N-lactogi-phenylalanine substance, a signal molecule transmitted from the intestine to the brain's reward center, stimulating the response of increasing the activity that prompts its production, opens wide space for further research in the human population as well [5, 9].

Conclusion

If the gut microbiome can influence the motivation of animals to be very physically active, could the saprophytic microbiome also influence the motivation of people to use or avoid addictive substances, eat healthier foods, have more harmonious work and social communication, socialize better and easier, and do anything useful for themselves and others.

Correcting wrong and often harmful forms of behavior and other everyday life habits will trigger the decision about healthy lifestyle and a goal to a good life commitment.

Establishing coexistence with the natural environment and adopting a model of daily healthy living habits is recognized as a crucial measure to achieve good or, at least, satisfactory health condition. This approach is essential in counteracting the presence of chronic non-infectious systemic diseases, almost unavoidable and seemingly hidden silent killers that endanger human lives, and in ensuring health and protection against consequential damage to the organism.

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Erratum

In the double issue no. 7-8/2023, on page 235, in the Seminar for practicing physicians section, in the paper titled:

DO NOT ATTEMPT CARDIOPULMONARY RESUSCITATION – ETHICAL ASPECTS
ODLUKA O NEZAPOČINJANJU KARDIOPULMONALNE REANIMACIJE – ETIČKI ASPEKTI
Mihaela Preveden[1, 2], Nataša Marković[1, 4], Andrej Preveden[1, 2], Ranko Zdravković[2, 4], Vanja Drobnjak[2] and Milanka Tatić[1, 3]

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UDK 616.12-008.315-083.98:614.253
https://doi.org/10.2298/MPNS2308235P
The paper participants have noticed that they had made an unintentional mistake with the affiliation of the co-author Ranko Zdravković. We are hereby making a correction at their request, thus 2, 4 should read 1, 2.

Erratum

U dvobroju 7-8/2023 na strani 235, rubrika Seminar za lekare u praksi, u radu pod naslovom:
DO NOT ATTEMPT CARDIOPULMONARY RESUSCITATION – ETHICAL ASPECTS
ODLUKA O NEZAPOČINJANJU KARDIOPULMONALNE REANIMACIJE – ETIČKI ASPEKTI
Mihaela Preveden[1, 2], Nataša Marković[1, 4], Andrej Preveden[1, 2], Ranko Zdravković[2, 4], Vanja Drobnjak[2] and Milanka Tatić[1, 3]
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Učesnici u radu su primetili da su napravili nenamernu grešku kod afilijacije koautora Ranka Zdravkovića, te na njihovu molbu dajemo ispravku, tako da umesto 2, 4 treba da stoji 1, 2.

Erratum

In the Supplement no. 2/2022 on page 32, in the paper titled:

PHYSICAL ACTIVITY AND FALL PREVENTION - SOLVING CLINICAL PROBLEMS
FIZIČKA AKTIVNOST I PREVENCIJA PADA - REŠAVANJE KLINIČKIH PROBLEMA
Slobodan Pantelinac[1, 2], Dušica Simić Panić[1, 2], Nataša Janjić[3], Tijana Spasojević[1, 2] and Snežana Tomašević Todorović[1, 2]
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An unintentional mistake has been made – affiliation 3 is indicated with the co-author Nataša Janjić and it should read 1,3 instead.

Erratum

U Suplementu 2/2022 na strani 32, u radu pod naslovom:

PHYSICAL ACTIVITY AND FALL PREVENTION - SOLVING CLINICAL PROBLEMS
FIZIČKA AKTIVNOST I PREVENCIJA PADA - REŠAVANJE KLINIČKIH PROBLEMA
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došlo je do nenamerne greške – kod koautora Nataše Janjić navedena je afilijacija 3, a treba da stoji 1, 3.

IN MEMORIAM
IN MEMORIAM

Dr NADA GRUJIĆ
(1936–2024)

Dr Nada Grujić, specijalista anesteziologije, preminula je 4. januara 2024. u Novom Sadu, u osamdeset osmoj godini.

Rođena se 28. juna 1936. u Novom Sadu, gde je završila osnovnu školu i gimnaziju. Medicinu je diplomirala na Medicinskom fakultetu Univerziteta u Beogradu 27. juna 1961. godine. Vrativši se u rodni grad, radila je nekoliko godina kao lekar opšte prakse, prvo u Domu zdravlja u Rumenačkoj ulici, a kasnije u Zdravstvenom domu železničara. Godine 1966. započinje specijalizaciju iz anesteziologije na Klinici za ginekologiju i akušerstvo.

Kao lekar specijalista anesteziologije 1971. godine počinje da radi na Institutu za grudne bolesti i TBC u Sremskoj Kamenici, gde ostaje do penzije. Radeći na grudnoj hirurgiji, u timu hirurga dr Fajgelja, imala je prilike da učestvuje u nekim od pionirskih poduhvata kao što su operacije na otvorenom srcu uz pomoć aparata za vantelesnu cirkulaciju, otklanjanje urođenih srčanih mana kod odojčadi, rešavanje urođenih deformiteta grudnog koša kod dece i mladih i sl.

Usavršavala se na studijskim boravcima u Kliničkom centru u Mariboru i na Univerzitetskoj klinici u Majncu (Nemačka). Godinu dana je provela u Univerzitetskoj bolnici u Valeti (Malta), kao učesnica tehničke pomoći Republici Malti. Tamo je imala najviše stručno zvanje, zvanje konsultanta.

Zajedno sa svojim kolegama – anesteziolozima (dr Ljilana Kuprešanin, dr Zora Kolarović, dr Melanija Bekvalac, dr Iboljka Feldeždi i dr Ljuborad Petrović) objavljivala je stručne radove u najznačajnijim časopisima iz oblasti anesteziologije i učestvovala na brojnim kongresima i stručnim skupovima u zemlji i svetu.

Pred kraj karijere doživela je da mora na posao da odlazi čamcem i skelom preko Dunava, pa peške do Instituta u Sremskoj Kamenici, jer su mostovi našeg grada bli srušeni u NATO bombardovanju 1999. godine. Ipak, nikad nije odustala od svoje predanosti i entuzijazma jer je zvanje anesteziologa za nju bilo i čast i ljubav.

Penzionisala se 28. juna 2001. godine u zvanju načelnika Odeljenja anestezije na Klinici za grudnu hirurgiju Instituta za plućne bolesti u Sremskoj Kamenici, posle 40 godina rada u medicini. Sa suprugom Milanom Zdrnjom, od koga se kasnije razvela, imala je kćerku Vesnu, od koje je dobila najveći poklon u životu – unuka Marka. Sve do samog kraja ostala je lucidna, radoznala i puna životnog elana.

Prof. dr Milanka Tatić

UPUTSTVO ZA AUTORE

Časopis ***Medicinski pregled*** objavljuje radove koji prethodno nisu objavljeni niti poslati u drugi časopis. U Časopisu mogu biti objavljeni radovi iz različitih oblasti biomedicine, koji su namenjeni lekarima različitih specijalnosti.

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Primaju se samo radovi koji su napisani na engleskom jeziku, uz sažetak rada i naslov rada koji treba da budu napisani na engleskom i srpskom jeziku.

Radove koji su pristigli u časopis *Medicinski pregled* pregleda jedan ili više članova Uređivačkog odbora Časopisa. Oni radovi koji su napisani prema pravilima Časopisa šalju se na anonimnu recenziju kod najmanje dva recenzenta, stručnjaka iz odgovarajuće oblasti biomedicine. Načinjene recenzije radova pregleda glavni urednik ili članovi Uređivačkog odbora i one nisu garancija da će rad biti prihvaćen za štampu. Materijal koji je pristigao u časopis ostaje poverljiv dok se rad nalazi na recenziji, a identitet autora i recenzenata su zaštićeni, osim u slučaju ako oni odluče drugačije.

U časopisu *Medicinski pregled* objavljuju se: uvodnici, originalni članci, prethodna ili kratka saopštenja, pregledni članci, stručni članci, prikazi slučajeva, članci iz istorije medicine i drugi članci.

1. Uvodnici – do 5 strana. Sadrže mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.

2. Originalni članci – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

3. Pregledni članci – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

4. Prethodna ili kratka saopštenja – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

5. Stručni članci – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

Priprema rukopisa

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings, MeSH.*

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

3. Tekst članka

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

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.