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CONTENTS

M E D I C I N S K I P R E G L E D
ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
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EPIDEMIOLOGICAL STUDY OF ZYGOMATIC BONE FRACTURES: A FIVE-YEAR RETROSPECTIVE ANALYSIS OF A SINGLE-CENTER EXPERIENCE

EPIDEMIOLOŠKA STUDIJA PRELOMA ZIGOMATIČNE KOSTI: PETOGODIŠNJA RETROSPEKTIVNA ANALIZA U OKVIRU JEDNE INSTITUCIJE

Saša MIJATOV[1], Aleksandar KIRALJ[1, 2], Miroslav P. ILIĆ[1, 2], Denis BRAJKOVIĆ[1, 2], Ana TADIĆ[3, 4] and Ivana MIJATOV[1, 2]

Summary

Introduction. Zygomatic bone fractures are prevalent in the maxillofacial region. This study aims at analyzing the epidemiology and clinical presentation of isolated zygomatic bone fractures. **Material and Methods.** The retrospective study, conducted at the Clinic of Maxillofacial Surgery of the University Clinical Center of Vojvodina, included 128 patients diagnosed with isolated zygomatic bone fractures. The following parameters were taken into consideration: gender, age, trauma etiology, clinical presentation, computed tomography analysis of the fracture localization and pattern. The fractures were classified into five groups according to Zingg classification system. **Results**. The study included patients aged 10-82 divided into four groups, with the most affected group being 30-49 years old. Men were more often treated for zygomatic bone fractures (male: female ratio 3:1). Left-sided fractures of the zygomatic bone occurred more often (55.2%) than the right-sided ones. Type B was the most common type of fracture, while the zygomaticomaxillary buttress fracture was the most common injury. Early treatment was administered in 78 patients (60.94%), while 50 patients (39.06%) underwent delayed reconstruction. The analysis of complications concerning the time of surgical intervention revealed a higher incidence of ectropion in cases treated early, while infraorbital paresthesia and facial asymmetry were more prevalent in cases treated late. **Conclusion**. Zygomatic bone fractures have high morbidity risk, and may cause temporary incapacity to work, and potentially permanent and functional damage.

Key words: Zygomatic Fractures; Fractures, Bone; Facial Bones; Epidemiology; Risk Factors; Surgical Procedures, Operative; Postoperative Complications

Sažetak

Uvod. Prelomi zigomatične kosti spadaju u najčešće prelome u maksilofacijalnoj regiji. Studija koju predstavljamo ima za cilj da analizira epidemiološke karakteristike i kliničku sliku preloma zigomatične kosti. **Materijal i metode.** Retrospektivna studija koja je sprovedena na Klinici za maksilofacijalnu hirurgiju Univerzitetskog kliničkog centra Vojvodine u Novom Sadu uključila je 128 bolesnika sa dijagnostikovanim izolovanim prelomima zigomatične kosti. U obzir su uzeti sledeći parametri: pol, starost, etiologija traume, klinička slika, nalaz kompjuterizovane tomografije, analiza lokalizacije preloma i obrazac preloma. Prelomi su klasifikovani u pet grupa korišćenjem Zingove klasifikacije (*Zingg classification*). Dobijeni podaci su analizirani pomoću statističkog paketa SSPS20. **Rezultati**. Studijom su obuhvaćeni bolesnici starosti 18−82 godine podeljeni u četiri grupe, pri čemu je prelom najučestaliji bio u grupi 30−49 godina. Muškarci su češće pogođeni od žena (odnos muškarci žene 3 : 1). Levostrani prelom se javljao češće (55,2%) nego desnostrani. Najčešći tip preloma je prelom tipa B, dok je najčešće bila povređena zigomatičnomaksilarna sutura. Imedijentno lečenje primenjeno je kod 78 bolesnika (60,94%) dok je kod 50 bolesnika načinjena odložena rekonstrukcija. Analizom komplikacija u pogledu vremena hirurške intervencije utvrđena je veća incidencija ektropiona kod rano lečenih slučajeva dok su infraorbitalne parestezije i asimetrija lica bile češće kod bolesnika koji su lečeni odloženo. **Zaključak**. Prelomi zigomatične kosti imaju visok morbiditet, izazivaju privremu nesposobnost za rad, a potencijalno i trajna funkcionalna i estetska oštećenja.

Ključne reči: prelomi zigomatične kosti; prelomi kosti; kosti lica; epidemiologija; faktori rizika; operativne hirurške procedure; postoperativne komplikacije

Introduction

The zygomatic bone is integral to the maxillofacial skeleton, that is, the structure of the floor and the lateral wall of the orbital cavity, and the zygomatic arch. Malar eminence is the most prominent part of the zygomatic region, which defines the facial appearance [1]. The position of the zygomatic

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bone in the facial region is exposed to different forces, which makes it the second most frequently injured facial bone, following the mandible. Since the bone itself comprises a pair of quadrangular bones with three sides, four edges and three processes, the zygomatic bone attaches to the skull through these processes (temporal, frontal and maxillary and posteromedial edge of the bone). Typically, these structures are fractured individually as single-process fractures or collectively as classic tetrapod fractures [1].

The etiology of zygomatic bone fractures includes factors such as traffic accidents, assault, falls, sport-related injuries and work-related injuries. The predominant etiological causes of fractures vary in different geographical areas [2]. Socioeconomic, cultural and lifestyle factors have a significant influence on these variations.

The zygomatic bone fractures have a classical clinical appearance, potentially causing facial asymmetry, deformity of the midface, sensory disturbance, occlusion disruptions, and disturbance in ocular function. Diagnosis is based on anamnesis, clinical findings and imaging (plain radiography, computed tomography, ultrasound or nuclear magnetic resonance) [2, 3]. Early diagnosis, accurate evaluation and timely intervention are crucial for perfect treatment.

This study aims at analyzing retrospectively the epidemiology and clinical presentation of isolated zygomatic bone fractures treated at the Clinic of Maxillofacial Surgery, University Clinical Center of Vojvodina, Novi Sad.

Material and Methods

Study design and population: The retrospective study was conducted on patients treated at the Clinic of Maxillofacial Surgery, University Clinical Center of Vojvodina, Novi Sad from January 1, 2017, to December 31, 2022 (duration of five years).

Inclusion criteria: The study included all patients older than 18 with isolated zygomatic bone fractures.

Exclusion criteria: Patients with isolated zygomatic arch fractures, other facial bone fractures, and patients with incomplete data records were excluded.

The study was approved by the Ethical Committee of the University Clinical Center of Vojvodina.

All patients signed their informed consent for participation in the study.

Parameters: Data were collected from medical records focusing on the following parameters: gender, age, etiology of trauma, clinical presentation, computed tomography (CT) analysis of the fracture site, and fracture pattern.

Classification: Fracture sites were classified according to Zingg zygomatic fracture classification system into five groups (A1, A2, A3, B, C). A1 is isolated zygomatic arch fracture, A2 is the separation of frontozygomatic suture, A3 indicates infraorbital separation, B represents monofragment type with a fracture on all sites of articulation and C signifies multifragment fractures [4].

Ophthalmic examination: Preoperative ophthalmic examination included the assessment of visual activity and evaluation of extraocular muscle movements.

Surgical technique: All patients underwent surgery under general anesthesia, and the time of surgery was determined individually based on clinical findings (presence of edema, periorbital hematoma). The surgery was categorized as early treatment (12-24 hours after injury) or delayed (up to two weeks after injury).

Preoperative medication (antibiotics, analgesics) was administrated and continued postoperatively for ten days.

Statistical analysis: data were analyzed using the Statistical Package for Social Science (SPSS) version 20. The Chi-square test was used to compare qualitative variables (p-value < 0.05).

Results

A total of 128 patients were included in the study, ranging in age from 15 to 78 (mean age of 43.2 SD±18.2). The patients were divided into four groups: I (18-29), II (30-49), III (50-69), IV (80+). The study included 96 males and 32 females, with male to female ratio 3:1 **(Graph 1)**.

Assault was the primary cause of trauma, showing the age-related correlation. In age groups I and II, assault was the main cause of injury, while falls prevailed in the age group III. Gender analysis showed that females are more susceptible to injury when falling, while males are mostly injured in assaults **(Graph 2)**.

Clinical presentation of fractures included epistaxis, subconjunctival bleeding and palpable step-off in most cases **(Table 1)**.

In addition to clinical examination, CT and posterior-anterior radiography (occipitomental-Waters view) were used for the evaluation of the patients. The fractures occurred more frequently on the left side (54.68%) compared to the right side (45.31).

Our study excluded isolated zygomatic arch fractures because of their specificity. Types A3 and B fractures were predominant, with the zygomaticomaxillary buttress being the most commonly affected site (in 96 cases) **(Graph 3)**.

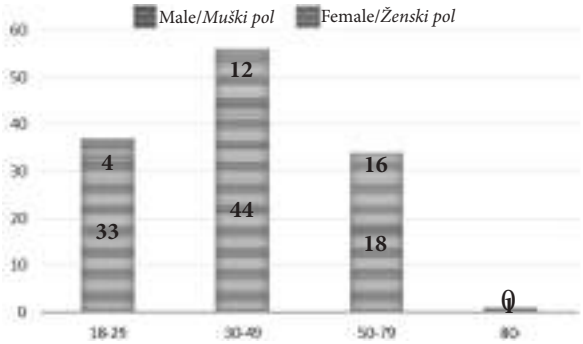
In the study, early treatment was administered to 78 patients (60.94%), while delayed reconstruction was performed in 50 patients (39.06%) because of the local status (facial edema, general condition, etc.).

Different surgical approaches were used for zygomatic bone fracture treatment: upper buccal approach (64.84%), lateral eyebrow approach (27.34%), subciliary approach (21.09%) and transcutaneous approach (33.59%) **(Table 2)**.

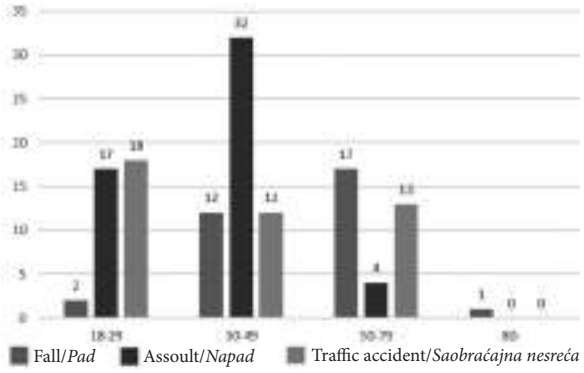
During the follow-up period of six months, all complications were documented: infraorbital paresthesia (29.68%), ectropion (7.81%), enophthalmos (0.78%), diplopia (1.56%) and facial asymmetry (3.90%) **(Graph 4)**. Analysis of complications concerning the time of surgical intervention showed a higher incidence of ectropion in cases treated earlier

Table 1. Clinical presentation of zygomatic bone fractures
Tabela 1. *Klinička prezentacija preloma zigomatične kosti*

Clinical presentation/*Klinička prezentacija*	Number of patients/*Broj bolesnika*	Percentage/*Procenat*
Facial asymmetry/*Facijalna asimetrija*	84	65.62%
Depression of malar eminence/*Depresija malarne eminencije*	65	50.78%
Subconjunctival hemorrhage/*Subkonjuktivalno krvarenje*	114	89.06%
Periorbital hematoma/*Periorbitalni hematom*	85	66.40%
Antimongoloid position of the eye/*Antimongoloidni položaj oka*	75	58.59%
Diplopia/*Diplopija*	9	7.03%
Limited mouth opening/*Ograničeno otvaranje usta*	14	10.93%
Malocclusion/*Poremećaj okluzije*	56	43.75%
Paresthesia/*Parestezija*	62	48.43%
Epistaxis/*Epistaksa*	124	96.87%
Palpable step-off/*Palpabilan koštani stepenik*	96	75%



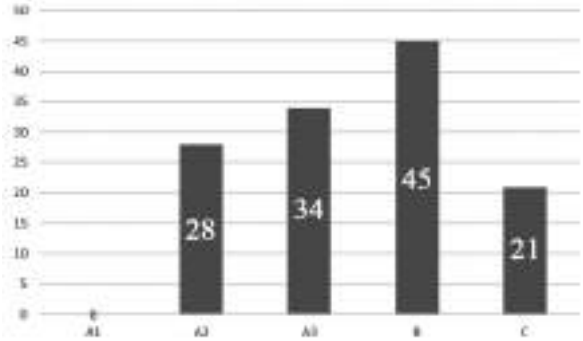
Graph 1. Gender and age distribution of zygomatic bone fracture
Grafikon 1. *Polna i starosna distribucija preloma zigomatične kosti*



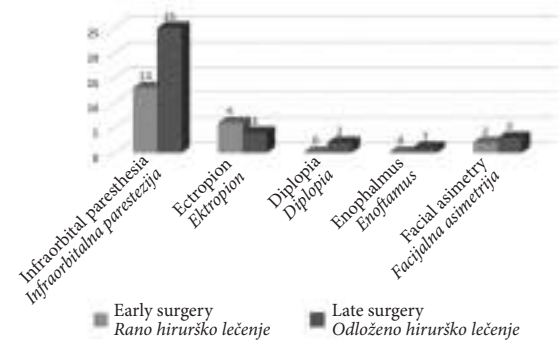
Graph 2. Etiological distribution of zygomatic bone fractures
Grafikon 2. *Etiološka distribucija preloma zigomatične kosti*

Table 2. Surgical approach used for zygomatic bone fracture treatment
Tabela 2. *Hirurški pristup korišten za lečenje preloma zigomatične kosti*

Surgical approach/*Hirurški pristup*	Number of patients/*Broj bolesnika*	Percentage/*Procenat*
Upper buccal approach/*Gornji bukalni pristup*	83	64.84%
Lateral eye brow approach/*Lateroorbitalni pristup*	35	27.34%
Subciliary approach/*Subcilijarni pristup*	27	21.09%
Transcutaneous approach/*Transkutani pristup*	43	33.59%



Graph 3. Zygomatic bone fractures classification according to Zyngg classification system
Grafikon 3. *Klasifikacija preloma zigomatične kosti prema Zingovoj klasifikaciji*



Graph 4. Postoperative complications in early and delayed surgical bone repairs
Grafikon 4. *Postoperativne komplikacije kod rano operisanih i odloženih hirurških repozicija*

and infraorbital paresthesia and facial asymmetry in cases treated late. Diplopia and enophthalmos had equivocal outcomes in both early and late treatments.

Discussion

The middle-aged (30-49) male population was most frequently affected by zygomatic bone trauma, potentially attributed to high activity levels and outdoor occupations in this period of their life. Male predominance can be explained by the lifestyle, in which case it can be concluded that the male population is more exposed to trauma than the female population. The male-to-female ratio in our study was similar to other studies in Europe, while the studies in Asia and Africa showed a higher ratio [5, 6].

The assault was the main cause of trauma in the age groups I and II, predominantly in the male population. In age group III, falls were the main cause of trauma, potentially due to the patients' age and changes in the quality of life.

Traffic accidents (motor vehicle accidents) were the most frequent etiology factor in the age group 18-29 in the study and it was more often in the age group II than in others. This trend can be explained by the inexperience of traffic participants, especially young drivers [7].

Our study revealed that fracture of the left zygomatic bone was more frequent than fracture of the right zygomatic bone, especially in the cases of assault-related fractures. This can be explained by the observation that a right-handed attacker hits directly the left half of the victim's face, which is consistent with our study, with the assault being the main cause of injury.

The zygomaticomaxillary buttress was the most common fractured site in our study, differing from other studies where zygomaticofacial suture was the most common site of injury [4, 8].

Fractures are differently classified in various studies. In our study, we used Zingg modified method of classification because it was the most applicable one [3, 4]. Type B was the most common type of fracture, which is a classic tetrapod fracture and the most common type in some studies [9].

The surgical approach used for bone repair depended on the fracture localization and type, and it was selected to provide maximal visualization of fracture sites and minimal complications (pain, nerve injuries, cosmetic deformities, etc.) [10, 11]. In our treatments, we used upper buccal and transcutaneous approaches, which were selected based on the surgeons' experience, clinical findings and radiological findings. The early repair was done in most cases to ensure adequate bone repairs.

Complications following zygomatic bone fracture treatment are not very often. Infraorbital paresthesia was reported as the most common complication in our study, aligning with the existing studies [12]. Buccal paresthesia was a direct consequence of infraorbital nerve affection. In our study, 48.42% of patients were diagnosed with infraorbital nerve paresthesia preoperatively and 29.68% after reduction. Proper reduction of the fracture and decompression of the infraorbital nerve were important in the recovery of sensory disturbance. Postoperative paresthesia of the infraorbital nerve could also result from improper fracture reduction or severe injury of the nerve. Six months after surgery, most of our patients recovered from infraorbital paresthesia. However, Folkestadt and Grandström showed in their study that recovery of neurosensory affection of infraorbital nerve could take up to one year, and some patients could still have infraorbital nerve paresthesia despite proper reduction [13].

Postoperative enophthalmos can be caused by periorbital fat atrophy, and one case was detected in our study, which possibly occurred after delayed surgery [14].

In our study, 7.03% of patients had preoperative diplopia, while postoperative diplopia was detected in 1.56%. A study conducted by Calderoni shows that 7.01% of patients had persisting diplopia after treatment, and a study conducted by Zigg et al. states that diplopia persisted in 17% of cases and enophthalmos in 11% of cases [4]. In our study, the percentage was significantly lower, but we did not consider the orbital 'blowout' fractures, in which cases diplopia is a common symptom, and we focused on isolated zygomatic bone fractures only.

Postoperative ectropion was reported in 7.81 cases, with a higher frequency in late surgical repairs. The ectropion was caused due to subciliary incision leading to the formation of a hypertrophic scar. Anti-scar treatment was used for the ectropion repair. The incidence of ectropion due to surgical incision varied [15].

Surgical delayed repairs may be useful if we consider that surgical incision can be better planned in pre-existing skin creases after the resolution of soft tissue edema. However, delayed reparation increases the difficulty in manipulating the bone fragments due to callus formation, which can cause inadequate fracture reduction [16].

Our study showed relatively different complications in early and late repairs. Diplopia and enophthalmos were similar in both types of repairs, while ectropion was more prevalent in early repairs and infraorbital paresthesia and facial asymmetry in late repairs [17, 18].

Some studies show that there was no significant association between early or delayed repairs, and no statistically significant correlation was found between postoperative complications and the time of operation [19, 20].

The limitation of our study was its retrospective character. This can be overcome by recording a large number of patients who can be evaluated retrospectively. Inadequate data records were another limitation, which was the reason why many cases were excluded from the study.

Conclusion

Zygomatic bone fractures are one of the most common maxillofacial injuries resulting mainly

from assault and traffic-related injuries, and they significantly impact the young population, leading to temporary work incapacity due to injuries and surgical treatment. This fact has important socioeconomic significance. Epidemiological studies need larger datasets to achieve more precise evaluation. Conducting a detailed multicentric study is crucial for legal and therapeutic strategies in our region.

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EARLY OUTCOMES OF SURGICAL TREATMENT WITH MICRODISCECTOMY IN PATIENTS WITH LUMBAR DISC HERNIATION

RANI REZULTATI HIRURŠKOG LEČENJA MIKRODISKEKTOMIJOM BOLESNIKA SA LUMBALNOM DISKUS HERNIJOM

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Summary

Introduction. The treatment of patients with lumbar disc herniation can be conservative or surgical, depending on the patient's characteristics, the disease, and treatment possibilities. This study aims to compare the intensity of pain, the presence of Lasègue's sign, and the degree of neurological deficits in patients with lumbar disc herniation before and after the operation. Additionally, the degree of intervertebral disc degeneration, evaluated by magnetic resonance imaging findings on the outcome will be determined. **Material and Methods.** A retrospective study involved 50 patients aged 18 to 45 who underwent microdiscectomy procedure. Parameters including pain intensity on the visual-analog scale, Lasègue's nerve stretching test, sensory deficits, motor deficits, and the degree of intervertebral disc degeneration according to the Pfirrmann grading system were assessed preoperatively and in the early postoperative period. **Results.** Intervertebral disc herniation most commonly occurred at the L4-5 and L5-S1 levels in our patients. Pain intensity significantly decreased from a preoperative score of 7.6 to 2.4 postoperatively. There was also a significant decrease in the number of patients with positive Lasègue's sign. According to the Pfirrmann grading system, 38% of patients had mild degenerative changes in the intervertebral disc, while 62% had severe degenerative changes. **Conclusion.** Microdiscectomy is the gold standard in surgical treatment of lumbar disc herniation. In the early postoperative period, patients experience a significant reduction in pain intensity with subsequent improvement of sensory and motor deficits. Surgical treatment of lumbar disc herniation, when indicated appropriately, carries a high success rate.

Key words: Intervertebral Disc Displacement; Treatment Outcome; Microdissection; Pain; Lumbar Vertebrae; Postoperative Period

Sažetak

Uvod. Tretman bolesnika sa lumbalnom diskus hernijom može biti konzervativni, primenom medikamenata i fizikalno-terapijskih procedura ili hirurški u zavisnosti od karakteristika bolesnika, bolesti i mogućnosti lečenja. Cilj rada je poređenje intenziteta bola, pozitivnosti Lazarevićevog znaka, te stepena ispada senzibiliteta i motorike kod bolesnika sa lumbalnom diskus hernijom pre i nakon hirurškog lečenja. Utvrđivanje značaja stepena degeneracije intervertebralnog diska, vrednovanog na nalazu magnetne rezonancije, za ishod. **Materijal i metode.** Sprovedena je retrospektivna studija u kojoj je učestvovalo 50 bolesnika starosti od 18 do 45 godina, operisanih zbog lumbalne diskus hernije metodom mikrodiskektomije. Preoperativno i u ranom postoperativnom periodu, prilikom otpusta bolesnika praćeni su parametri: intenzitet bola po vizuelno-analognoj skali, test istezanja nerva po Lazareviću, ispad senzibiliteta, ispad motorike i stepen degeneracije intervertebralnog diska po Firmanu. **Rezultati.** Hernijacija intervertebralnog diska se kod naših bolesnika najčešće javljala na L4-5 i L5-S1 nivoima. Postoperativno je intenzitet bola statistički značajno smanjen na vrednost 2,4 u odnosu na preoperativno 7,6. Postoperativno je zabeležen takođe i značajno manji broj bolesnika koji su imali pozitivan test istezanja nerva 14 u odnosu na preoperativno 41. Blage degenerativne promene intervertebralnog diska (po Firmanu) imalo je 38% bolesnika, a izražene degenerativne promene imalo je 62% bolesnika. **Zaključak.** Mikrodiskektomija je zlatni standard u hirurškom lečenju lumbalne diskus hernije. Kod ovih pacijenata u ranom postoperativnom periodu registruje se značajno smanjenje intenziteta bola, uz naknadno poboljšanje i senzibiliteta i motornog deficta. Operativno lečenje lumbalne diskus hernije kod adekvatno postavljenih indikacija ima visok stepen uspešnosti.

Ključne reči: diskus hernija; ishod lečenja; mikrodisektomija; bol; lumbalni pršljenovi; postoperativni period

Introduction

Intervertebral discs are subject to metabolic, structural, and functional changes due to factors such as genetics, age, diet, and spinal load [1]. The basic pathophysiological mechanism is a disc nutrition disorder caused by atherosclerotic changes in the blood vessels or calcification of the cartilaginous plate, leading to the lack of glucose and oxygen and reduction of the pH value, resulting thus in the degradation of the disc structural molecules and its dehydration, fragmentation and herniation [2].

Lumbar disc herniation is a local displacement of the disc contents outside the intervertebral space. It

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Abbreviations

VAS – visual analog scale
MMT – manual muscle test
MRI – magnetic resonance imaging
T1W – T1 Weighted
T2W – T2 Weighted
IVD – intervertebral disc

most often occurs at the lumbosacral junction and the segment above (L5-S1 and L4-L5) [3, 4]. There are anterior and posterior disc herniations. Factors such as diabetes, heavy physical exertion, axial loading, and twisting of the spine contribute to the occurrence of herniation [5]. The clinical presentation depends on the segment where it occurs and may include pain, motor deficits, and sensory disturbances.

The treatment method for lumbar disc herniation depends on the patient characteristics, the disease, and the institution where the patient is treated. The choice of treatment is influenced by the patient's general condition, age, and comorbidities. The degree of the intervertebral disc herniation, presence of neurological deficit, as well as the intensity and trend of the development of complaints also influence the choice of treatment method. The last factor is the institution where the patient is treated, whether it is a primary, secondary, or tertiary institution, staff, and equipment with the necessary medical instruments to perform various procedures. When all the mentioned factors are taken into account, the treatment method is tailored individually for each patient.

Surgical treatment of lumbar disc herniation includes different surgical methods: macroscopic discectomy, microdiscectomy, and endoscopic discectomy. Different techniques in all three methods of bone-connective structure are performed depending on the extent of the lesion. Microdiscectomy is performed with the use of an operating microscope and involves removing a prolapsed or protruding disc through a small skin incision, and after dissecting the paravertebral muscles with the removal of the ligamentum flavum. Today, this method represents the gold standard in the surgical treatment of lumbar disc herniation in most neurosurgical institutions worldwide, in addition to endoscopic procedures that have somewhat more narrow indications [6]. Recovery after surgery usually lasts 3-4 days, after which the patient is discharged for further treatment at home.

Material and Methods

The study was conducted retrospectively at the Neurosurgery Clinic of the University Clinical Centre of Vojvodina for the period between October 2019 and October 2020. This study includes patients who were operated for lumbar disc herniation at one or two levels with the microdiscectomy method, which provided the total of 50 patients that were operated on. The patient age ranged from 18 to 45.

Data including gender, age, type of surgery, patient history, and physical examination at admission and after discharge from the hospital were taken from the medical history.

Evaluation of pain (lumbar or radicular) was carried out on a visual-analog scale (VAS) preoperatively and on the third day after surgery (the day of discharge). The VAS is used in clinical practice as a standardized method for assessing pain intensity. The scale ranges from 0 to 10, where 0 means no pain, and 10 is unbearable pain [7].

All patients underwent a preoperative and postoperative straight leg raise test (Lasègue), and a positive stretch test was in the range from 30 to 70 degrees [8].

Neurological status was noted:

1. Sensory deficit (hypesthesia, hyperesthesia, anesthesia) according to distribution of dermatomes. Presence or absence of sensitivity to touch was registered preoperatively and it was compared to the postoperative status. Based on the results, the patients were divided into three groups:
   – status identical to the preoperative one,
   – status improved after surgery,
   – status worsened after surgery.
2. Muscle strength of the foot plantar and dorsiflexor muscles were tested in all patients using the manual muscle test (MMT). Muscle strength scored from 0 to 5, where grades 0, 1, and 2 were considered as plegia, and 3 and 4 weakness [9].

Magnetic resonance imaging (MRI) findings of the lumbosacral spine were analyzed. The MRI examination was performed according to the standard protocol for examining the lumbosacral spine. The examination included the spinal column segment from the 10th thoracic (T10) to the 2nd sacral (S2) vertebra. T1-weighted and T2-weighted sagittal images and axial T2-weighted images were made. Based on this examination, the degree of degeneration of the operated intervertebral disc was assessed according to Pfirrmann [10]. In the display of the results, the degree of the intervertebral disc degeneration was grouped into:

– Milder degree (grade I, II, III according to Pfirrmann) of degenerative changes
– Pronounced degree (grade IV, V according to Pfirrmann) of degenerative changes

Criteria for the Pfirrmann grading system:

– Grade I: Intervertebral disc structure is homogeneous, with hyperintense signal of the nucleus pulposus, and preserved height of the intervertebral space.
– Grade II: Intervertebral disc structure is inhomogeneous, with horizontal gray bands, and hyperintense signal, clear difference between the nucleus pulposus and the annulus fibrosus, with preserved height of the intervertebral space preserved.
– Grade III: Intervertebral disc structure is inhomogeneous, with intermediate gray signal intensity. The difference between the nucleus and annulus is unclear, with the height of the intervertebral space normal or slightly reduced.
– Grade IV: Intervertebral disc structure is inhomogeneous, with hypointense dark gray signal intensity. The difference between the nucleus and annulus is lost, with the height of the intervertebral space slightly to moderately reduced.

– Grade V: Intervertebral disc structure is inhomogeneous, with black signal intensity. The distinction between the nucleus and the annulus is lost, with collapsed intervertebral space.

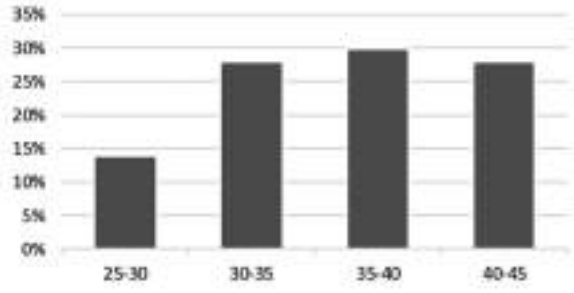
Results

The research included 50 patients, of which 33 men (66%) and 17 women (34%) **(Graph 1)**. According to age structure, there were 7 patients aged 25 to 30, 14 patients aged 31 to 35, 15 patients aged 36 to 40, and 14 patients aged 41 to 45. The youngest patient was 25 years old, and the oldest 45 years old. The average age of the patients was 36.7 **(Graph 2)**.

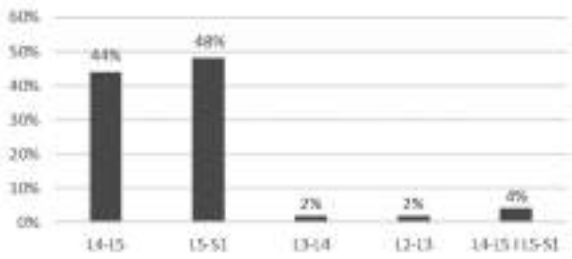
Graph 1. Distribution of patients by gender
Grafikon 1. *Distribucija bolesnika po polu*

Disc herniation was operated on one level and on two levels in 98% and 2% of patients respectively. Microdiscectomy at the L5-S1 and L4-5 level was performed on 24 patients (48%) and 22 patients (44%) respectively. In the remaining 4 patients (8%), microdiscectomy was performed at L3-4 (2%), L2-3 (2%) and combined at L4-5 and L5-S1 levels (4%) **(Graph 3)**.

Of the applied operative techniques, interhemilaminectomy was performed on 29 (58%) patients, and flavectomy was performed on 21 patients (42%). Interlaminectomy and laminectomy were not present as operative techniques in this group of patients.



Graph 2. Age structure of patients
Grafikon 2. *Starosna struktura pacijenata*



Graph 3. Operated levels
Grafikon 3. *Operisani nivoi*

Indications for operative treatment were as follows:

3. Pain (lumbar and/or radicular) that lasted longer than 3 months and significantly disturbed the patient's ability to live and work - 31 patients (62%)

4. Muscle weakness (mostly in plantar or dorsiflexors of the foot) in 19 patients (38%).

Given that only elective surgical interventions were performed in the examined group, polyradicular syndrome (cauda equina syndrome – paraparesis with sphincter dysfunction) was not represented.

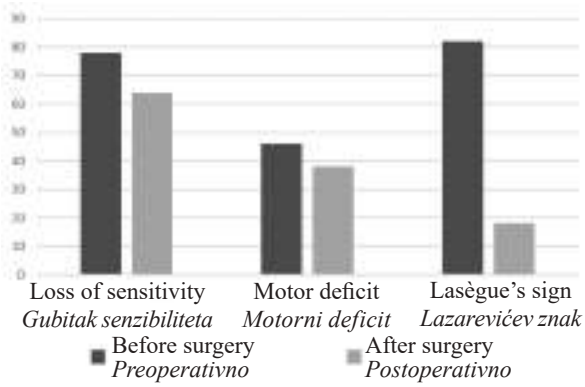
The average pain intensity was 7.6 preoperatively, and 2.4 postoperatively **(Graph 4)**. A statistically significant difference was determined in pain intensity, calculated according to VAS, when compared before and after the surgery.

Graph 4. Mean VAS values before and after surgery
Grafikon 4. *VAS srednje vrednosti pre i posle operacije*

Positive straight leg raise test preoperatively was registered in 41 patients (82%), while negative test was recorded in 9 patients (18%). After lumbar microdiscectomy, the positive straight leg raise test was found in 14 patients (28%). Using the χ^2 test, it was determined that the number of patients with positive straight leg raise test ($p < 0.05$) statistically significantly decreased after the operative treatment.

Sensory loss of varying degree was registered in 39 patients (78%), while sensitivity was preserved in 11 patients (22%). 32 patients (64%) reported certain degree of sensibility disorder on discharge. No patient reported worsening of tactile sensitivity. Using the χ^2 test, it was determined that the number of patients whose sensitivity improved after the surgery was not statistically significant ($p > 0.05$) **(Graph 5)**.

Muscle weakness, in the form of weakness or plegia of the plantar and dorsiflexors of the foot, was recorded in 23 patients (46%), of which 1 patient (4%) had grade 1 plagia according to MMT, and the other 22



Graph 5. The percentage of loss of sensitivity, motor deficit and Lasègue's sign before and after surgery
Grafikon 5. *Procenat gubitka senzibiliteta, motornog deficita i Lazarevićevog znaka pre i posle operacije*

patients had grade 3 and 4 weakness as per MMT. After the operative treatment, muscle weakness was observed in 19 patients (38%), of which 1 patient (5%) had plegia, and 18 patients had weakness.

Muscle weakness in the early postoperative period decreased in 4 patients. Using the paired t-test, no statistically significant difference in MMT scores was determined before and after operative treatment.

Classifying the degenerative changes of the intervertebral disc on MRI according to Pfirrmann, the patients were divided into two groups: Group A had 18 patients (36%) and it included grade I, II and III, and group B had 32 patients (64%), with grade IV and V.

After lumbar microdiscectomy, pain intensity in group A was reduced in 16 patients (89%), while 2 patients (11%) did not report any reduction in pain, and no patient reported any worsening of pain intensity.

In group B, 28 patients (87%) reported a decrease in pain intensity, while 4 patients (13%) reported that there had been no change in pain intensity compared to pain intensity prior to surgery.

Student t-test revealed a statistically significant reduction in pain intensity after surgical treatment ($p < 0.05$) both in patients with mild degenerative changes of the intervertebral disc (group A) and in patients with pronounced degenerative changes (group B).

In our group of subjects, all wounds primarily surgically healed and we had no infectious complications.

Discussion

Surgical treatment of lumbar disc herniation is, in addition to being one of the most common neurosurgical interventions, also the area with the greatest number of controversies in neurosurgery. Indications for operative treatment depend primarily on the clinical image and clinical course of the disease, MRI findings, as well as the technical possibilities for performing the procedure itself [11]. In modern literature, the field of indications for this type of treatment is increasingly expanding for various medical and economic reasons.

In the series of operated patients of younger age, the gender structure is in accordance with the literature. Men are dominantly represented, and possible reasons are greater physical strain at work, more stressful occupations, and certain congenital factors [12, 13]. On the contrary, longer duration of symptoms and female gender are associated with a worse outcome of operative treatment [6].

The average age of our group of respondents was 35, which is not in accordance with the literature, but it is in line with relevant studies that included a young population [14].

Most patients were operated at the L5-S1 and L4-5 levels, which is most likely due to the fact that 95% of lumbar flexion and extension takes place at these two levels [6]. Similar data can be found in the literature, and they range from 90 - 96% of those operated on the aforementioned two lumbar levels [7, 8]. We can also find data on a significant difference in the success of operative treatment when comparing the two levels, regardless of the surgical technique [10]. There was no such observation in the conducted research.

The conducted research once again showed that persistent radicular pain or sciatica resistant to conservative treatment can be very successfully treated surgically. This is indicated by a significant difference in the VAS value, regardless of age, type of indication, and the degree of degenerative changes of the intervertebral disc. It is important to emphasize that good results are achieved postoperatively in terms of regression of radicular pain regardless of the preoperative degree of distinction of degenerative changes of the intervertebral disc according to Pfirrmann [15].

According to the guidelines, elective operative neurosurgical treatment is indicated in patients having lumbar disc herniation with radicular pain that present for more than 4-6 weeks, regardless of the type of conservative treatment performed, and when there is a significant progression of pain intensity regardless of time [10, 11].

Studies show that complete recovery of sensitivity after the compression syndrome requires several months, while improvements are rarely observed in the early postoperative period [12].

The disappearance of the motor deficit caused by compression of the spinal nerves is rarely observed in the early postoperative period, while there is significant improvement after operative treatment and implemented rehabilitation therapy, and after several months [11].

In a more recent observational study conducted in Sweden – Swespine study, it was observed that adolescents and people of a younger age show better results after the lumbar disc herniation treatment, and they are more satisfied when returning to daily activities compared to the older population. The primary objective of this study was the self-assessment of patients before and after the surgical treatment [11].

A large number of neurosurgical studies indicate that there is reduction in symptoms after surgery in elderly patients, but the return to work and daily activities is less frequent [14].

In studies conducted in the United States of America, the results indicate that young and active

patients after surgical treatment of lumbar disc herniation can successfully return to physically demanding occupations and professional sports [13].

All studies indicate that lumbar microdiscectomy is a safe and reliable surgical method with a low rate of complications. It was also observed that the degree of complications in the younger population is lower, which is probably related to the rare comorbidity and very important previously performed spinal procedures [14, 15].

Conclusion

1. The conducted research confirms that lumbar microdiscectomy achieves good treatment results in terms of significant reduction in pain intensity postoperatively.

2. Regression of preoperative loss of tactile sensitivity after surgery is observed in a smaller number of patients, which correlates with the fact that the return of sensitivity in most patients is observed in a later period compared to the observed period.

3. The improvement of motor deficit postoperatively is not statistically significant, considering that a longer period of time is needed for the complete recovery of motor functi ons.

4. There is equal reduction of pain intensity after lumbar microdiscectomy both in patients with mild and the ones with pronounced degenerative changes on the disc.

5. When performed in the right indications by a competent surgical team, lumbar microdiscectomy is a safe procedure with few complications, short stay in the hospital, and good postoperative results.

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ACUTE APPENDICITIS – EXPERIENCES OF THE UNIVERSITY HOSPITAL IN FOČA, BOSNIA AND HERZEGOVINA

AKUTNI APENDICITIS – ISKUSTVA UNIVERZITETSKE BOLNICE U FOČI, BOSNA I HERCEGOVINA

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Summary

Introduction. Acute appendicitis is the most common cause of the acute abdomen. Based on the idea that appendicitis is a progressive disease eventually leading to perforation, removal of the appendix is the gold standard of treatment. **Material and Methods.** The objective of the study is to determine if there is any difference in the occurrence of postoperative complications, and if hospitalization differs depending on the appendicitis surgery method used with the patients. A retrospective analysis was made using the data from the hospital sample of patients admitted to the University Hospital in Foca in the period from January 2019 to December 2021. **Results.** In the period that was retrospectively analyzed, 107 patients diagnosed with acute appendicitis were operated on. There was no statistically significant difference between the treated groups in relation to the degree of appendicitis, type and duration of symptoms, diagnostic procedures and the time that had elapsed from admission to surgery. The Alverado Score in the probable appendicitis group was 41.1%. The most common symptoms were palpation sensitivity in the inguinal region (84.1%), and pain in the right lower quadrant (69.1%), intraoperative findings of uncomplicated appendicitis 58%, and 25.2% intraoperative findings inconsistent with the pathohistological ones. **Conclusion.** Acute appendicitis is one of the most common emergency surgical conditions, which requires surgical intervention if not treated in time, and causes life-threatening consequences. Surgical treatment with selected techniques for faster establishment of the gastrointestinal tract function, shorter stay in the hospital, faster recovery and return to daily activities.

Key words: Appendicitis; Acute Disease; Appendectomy; Laparoscopy; Postoperative Complications; Treatment Outcome; Diagnostic Imaging

Sažetak

Uvod. Akutni apendicitis je najčešći uzrok akutnog abdomena. Na osnovu ideje da je apendicitis ireverzibilna progresivna bolest, koja na kraju uzrokuje perforaciju, apendektomija je zlatni standard lečenja. **Materijal i metode.** Cilj studije je da se utvrdi da li postoji razlika u pojavi postoperativnih komplikacija, kao i da li je hospitalizacija ista, u zavisnosti od metode operacije slepog creva kojoj su pacijenti bili podvrgnuti. Retrospektivna analiza je sprovedena na osnovu podataka bolničkog uzorka pacijenata koji su primljeni u Univerzitetsku bolnicu u Foči, u periodu od januara 2019. do decembra 2021. godine. **Rezultati.** U retrospektivno analiziranom periodu operisano je 107 pacijenata sa dijagnozom akutnog apendicitisa. Nije bilo statistički značajne razlike između lečenih grupa u odnosu na stepen upale slepog creva, vrstu i trajanje simptoma, kao ni u dijagnostičkim procedurama i ukupnom vremenu od prijema do operacije. Alverado Score u grupi verovatnog apendicitisa bio je 41,1%. Najčešći simptomi su palpatorna osetljivost u ingvinalnoj regiji i bolna osetljivost u desnom donjem kvadrantu 69,1%, intraoperativni nalaz reverzibilnog apendicitisa je 58%, a u 25,2% intraoperativnih nalaza se ne poklapa sa patohistološkim. **Zaključak.** Akutni apendicitis je jedno od najčešćih hitnih hirurških stanja, koje zahteva hiruršku intervenciju ako se ne leči na vreme, izaziva posledice opasne po život. Hirurška intervencija odabranim tehnikama omogućava efikasnije uspostavljanje funkcionisanja gastrointestinalnog trakta, kraću hospitalizaciju, brži oporavak i povratak svakodnevnim aktivnostima.

Ključne reči: apendicitis; akutno oboljenje; apendektomija; laparoskopija; postoperativne komplikacije; ishod lečenja; dijagnostički imidžing

Introduction

Acute appendicitis (AA) is among the most common causes of acute abdominal pain [1]. Acute appendicitis is one of the most common dilemmas surgeons encounter in the emergency room [2]. Luminal obstruction resulting from different causes is believed to be the underlying factor in the development of appendicitis. This obstruction causes an increase in mucus production and bacterial overgrowth, which in turn increases the tension within the appendiceal wall, leading to necrosis and, potentially, perforation [3]. Appendicoliths or fecaliths, known as "appendix stones", along with benign or malignant tumors, are among the various factors that can lead to the obstruction of the appendix lumen [4]. While acute appendicitis is a frequent cause of acute abdomen, there are many other clinical conditions that can resemble the symptoms of this acute surgical emergency. Consequently, misdiagnosis

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Abbreviations

AA – acute appendicitis
RLQ – right lower quadrant
CRP – C-reactive protein
US – ultrasound examination
CT – computerized tomography
MRI – magnetic resonance imaging
WBC – white blood cells
ICD10 – International Classification of Diseases 10
CBC – complete blood count
MCV – mean corpuscular volume

may lead to unnecessary surgical explorations, which carry inherent risks of complications during and after the intervention [5]. Even with notable advancements in abdominal imaging [6], the risk of delayed diagnosis persists, magnifying the potential for complications and even fatal outcomes [7].

Clinical symptoms and signs suggestive of appendicitis include a history of central abdominal pain migrating to the right lower quadrant (RLQ), anorexia, fever, and nausea/vomiting. RLQ tenderness, along with classical signs of peritoneal irritation (e.g., rebound tenderness, guarding, rigidity, reflective pain), may be present on examination. Laboratory evaluations potentially useful for the diagnosis of appendicitis are white blood cell and granulocyte counts, the proportion of polymorphonuclear blood cells, procalcitonin, serum fibrinogen neutrophil-to-lymphocyte ratio and serum C-reactive protein (CRP). Given that many patients exhibit atypical symptoms, the utilization of laboratory or imaging tests becomes imperative in order to establish the diagnosis [8].

The ultrasound criteria for acute appendicitis include visualization of a non-peristaltic, non-compressible, tubular, blind-ending structure with a diameter of 6 mm or more in the right iliac fossa. An ultrasound (US) with graded compression has a sensitivity of 89% and specificity of 100%, and is a widely used technique for the diagnosis of acute appendicitis [9]. Computerized tomography (CT) has shown high sensitivity ranging from 90-100% and specificity ranging from 91-99% in diagnosing appendicitis. However, due to the potential risks associated with ionizing radiation, the use of CT scans in this context is restricted. Many healthcare professionals now reserve it for cases with atypical presentations or when there is a suspicion of cancer [10]. Magnetic resonance imaging (MRI) has demonstrated a high level of sensitivity (96%) and specificity (96%) in diagnosing acute appendicitis [11].

Various scoring systems, such as the Alvarado Score and Appendicitis Inflammatory Response, have been devised to assist clinicians in diagnosing acute appendicitis. However, it is important to note that scoring systems are unable to serve as the sole determining factor for an appendicitis diagnosis [12]. Maybe newer technologies like 99mTc-labeled monoclonal immunoglobulins (LeuTech) will help in the final diagnosis of acute appendicitis. LeuTech is a convenient, safe, rapid, and sensitive imaging test for the diagnosis of appendicitis, which reduces the risk of misdiagnosis and unnecessary appendectomies [13].

The objective of the paper and research was to take a closer look at acute appendicitis, to determine whether hospitalization is the same for all patients, and whether there is any difference in the appearance of postoperative complications, quality of life, and functioning of the gastrointestinal system, and daily activities, and that, because we only performed open appendectomy until 2014 to solve this urgent surgical condition.

Material and Methods

A retrospective survey was conducted in this study by collecting data from a total of 107 patients. The subjects were individuals ranging in age from 4 to 66 who were admitted to the Hospital in Foca between January 2019, and December 2021 with a diagnosis of acute appendicitis (ICD-10 codes from K35 to K35.9) and underwent surgery afterwards. After the surgical procedures, all the removed appendices were examined through pathological analysis to establish the final histological diagnosis. After the pathohistological analysis of the resected appendices, the patients were divided into three groups. The first pathohistological group were patients with normal appendix or catarrhal appendicitis; the second group were patients with uncomplicated appendicitis – phlegmonous appendicitis; while the third group were patients with complicated appendicitis – gangrenous and/or perforated appendicitis.

The observation characteristics in our study encompassed a range of factors, including demographic characteristics such as age and gender. We also assessed the presence of symptoms such as gastric complaints and pain migration. Clinical signs such as an increase in body temperature and pain sensitivity in the RLQ were documented. In order to establish an adequate diagnosis of acute appendicitis and reduce the number of negative appendectomies, different prognostic scores are used for the clinical evaluation of acute appendicitis. In our study, we used the Alvarado Score, a diagnostic scoring system based on the scoring symptoms, physical and laboratory findings, which is suitable for rapid diagnosis in the early stages of inflammation. The Alvarado score has a sensitivity and specificity of 99 and 43% respectively to rule out the diagnosis of AA when <5 and a sensitivity of 82% and specificity of 81% if <7 [14]. Score greater than 6 points indicates acute appendicitis, and less than 6 suggests the absence of appendicitis (1-4 points suspected uncertain diagnosis; 5-6 possible acute appendicitis; 7-9 probable acute appendicitis). There is no sign, symptom, or laboratory test that is 100% reliable in the diagnosis of acute appendicitis.

Laboratory parameters such as absolute and relative leukocyte count, differential blood count, neutrophil-lymphocyte ratio, and CRP concentration were analyzed. Urinalysis was conducted to assess any abnormalities. Additionally, we utilized radiological imaging methods such as US) In situations where the clinical diagnosis was uncertain, or laboratory or ultrasound findings ambiguous, we used CT and MRI. Finally, pathohistological findings were analyzed to determine the degree of inflammation of the appendix.

We used descriptive statistical methods to summarize and present the data. Data is visualized with use of graphs and tables. For numerical data, we calculated mean values, standard deviations, and maximum and minimum values, while frequencies were computed for categorical data. We used the Chi-square test to compare the categorical variables. All of the mentioned tests were two tailed. Statistical significance was set up at $p \leq 0.05$.

Results

In the above analyzed period, 107 patients aged 4 – 66 underwent surgery due to the diagnosis of acute appendicitis. 89 (83.2%) patients were operated with the laparoscopic technique and 18 (16.8%) with the open method. There was no difference between the treated groups in regard to the degree of appendicitis, type and duration of symptoms, the diagnostic procedures and the time that had elapsed from admission to surgery. There was no statistically significant difference in the frequency of the appendicitis type between genders (χ^2=0.47, df=2, $p > 0.05$). The distribution of appendicitis types according to gender is shown in **Graph 1**.

In terms of age and gender distribution, the largest number of operated patients is in the age group 11-60 years, 62 (58%); a slightly smaller number is in the 4-10 years old group, 32 (29.9%); while the fewest patients were in the age group 61-66 years, 13 (12.1%). In all three age groups, there is a slight predominance of male patients, 54 (50.4%) **(Graph 2)**.

Our results show that score 1-4 points (uncertain diagnosis of acute appendicitis) had 32.7% patients. Score of 5-6 points (potential acute appendicitis) had 26.2% patients and the highest percentage of the patients (41.1%) had score of 7-10 points (likely acute appendicitis). Distribution of stages of appendicitis based on the Alvarado Score diagnostic system is presented in **Table 1**.

Palpable pain sensitivity of the right inguinal region was registered in 82 (76.6%) patients while nausea and vomiting were present in 45 (42.1%). Moreover, there was a statistically significant difference in frequencies of these symptoms between different types of appendicitis, (χ^2=29.4, df=2, $p \leq 0.05$ and χ^2=8.93, df=2, $p \leq 0.05$) respectively. There was no statistically significant difference between other mentioned symptoms in patients with appendicitis. The absolute and percentage representation of individual symptoms and clinical signs in the total number of patients by group is shown in **Table 1**.

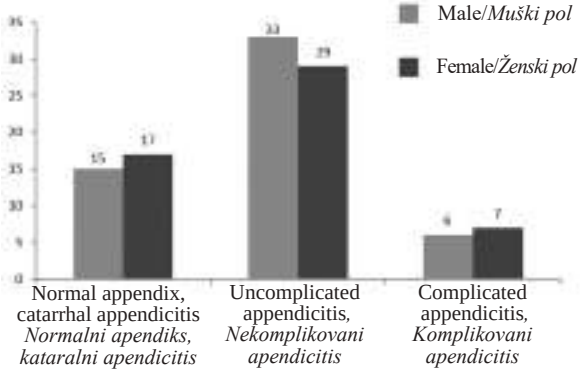
Out of the total of 107 patients, 32 (29.9%) had an intraoperative finding of catarrhal appendicitis. Uncomplicated appendicitis was present in 62 (58%) patients and complicated appendicitis was found in 13 (12.1%). Out of the 107 patients, 27 (25.2%) intraoperative findings did not match the pathohistological findings. Thus, in our study, an unexpectedly large difference in intraoperative and pathohistological findings became the key reason for numerical unevenness. Within the group of catarrhal appendicitis, 11 cases (34.3%) exhibited intraoperative findings that were underestimated in comparison to the group of uncomplicated appendicitis where 4 cases (6.4%) had underestimated intraoperative findings, while in 7 cases (11.3%), the intraoperative findings were overestimated. Among the patients with complicated appendicitis, intraoperative findings were overestimated in 5 cases (38.4%). These findings suggest that there were variations in accurate assessment of the severity of appendicitis during surgery, with both underestimation

Table 1. Representation of symptoms and clinical signs in the formed groups of patients
Tabela 1. *Prikaz simptoma i kliničkih znakova u formiranim grupama pacijenata*

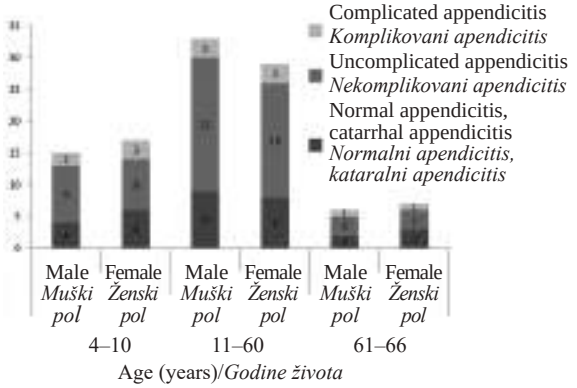
	Catarrhal appendicitis *Kataralni apendicitis* N/*Br.* = 32	Uncomplicated appendicitis *Nekomplikovani apendicitis* N/*Br.* = 62	Complicated appendicitis *Komplikovani apendicitis* N/*Br.* = 13	Chi-square χ^2	p value *p vrednost*
	N/*Br.* (%)	N/*Br.* (%)	N/*Br.* (%)		
Loss of appetite/*Gubitak apetita*	15 (46.9)	24 (38.7)	9 (69.2)	5.625	> 0.05
Nausea and vomiting/*Mučnina i povraćanje*	13 (40.6)	24 (38.7)	8 (61.5)	8.93	≤ 0.05
Migration abdominal pain *Migratorni abdominalni bol*	4 (12.5)	6 (9.7)	2 (15.4)		
Palpable pain sensitivity *Bolna osetljivost na palpaciju*	20 (62.5)	50 (80.6)	12 (92.3)	29.4	≤ 0.05
Increased body temperature *Porast telesne temperature* (> 38° C)	15 (46.9)	14 (22.6)	10 (76.9)	1.08	> 0.05
Sharp pain in the right lower quadrant of the abdomen caused by cough/*Oštar bol u donjem desnom kvadrantu abdomena uzrokovan kašljem*	14 (43.8)	13 (21.0)	7 (53.8)		
Leukocytosis/*Leukocitoza* >10,000	12.6 (6–22)	14.6 (4–26)	15.2 (2–29)		
Neutrophils "turning" left *„Skretanje" neutrofila u levo*	72 (56–92)	82 (51–89)	88 (55–92)		

Table 2. Frequency of operative and pathohistological findings
Tabela 2. *Učestalost operativnog i patohistoloških nalaza*

Findings *Nalazi*	Intraoperative *Intraoperativno*	Pathohistological *Patohistološki*
Catarrhal appendicitis/*Kataralni apendicitis*	32	30
Uncomplicated appendicitis/*Nekomplikovani apendicitis*	62	60
Complicated appendicitis/*Komplikovani apendicitis*	13	17



Graph 1. Distribution of appendicitis types according to gender
Grafikon 1. *Distribucija tipova apendicitisa prema polu*

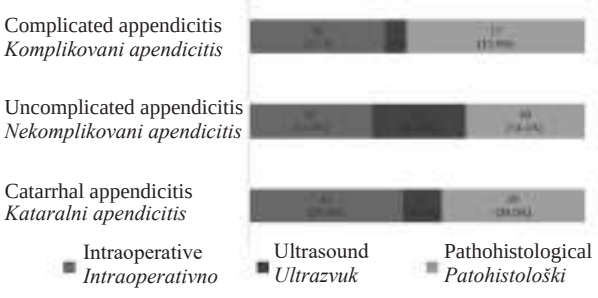


Graph 2. Distribution of appendicitis degree by patients' demographic characteristics
Grafikon 2. *Distribucija stepena apendicitisa prema demografskim karakteristikama pacijenta*

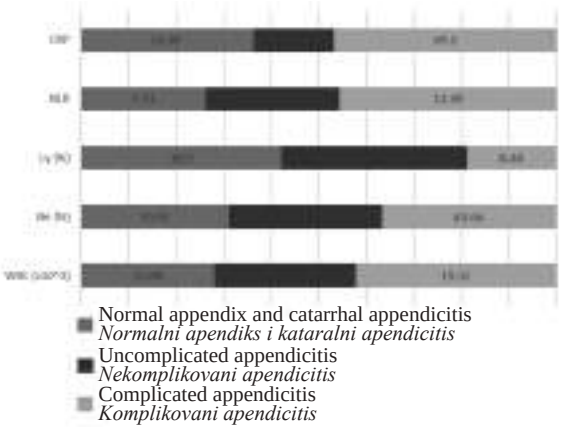
and overestimation occurring in different subgroups of patients **(Table 2)**.

Ultrasonographic examination of the abdomen has proved to be a valuable tool for diagnosing acute appendicitis and ruling out other potential differential diagnoses. It helps decrease the number of negative appendectomies, thus enhancing diagnostic accuracy. An US finding of a normal appendix is sufficient to rule out the diagnosis of appendicitis, and if positive, it should be interpreted with other clinical findings in order to make a decision about the surgery. Over 76.7% were used in the diagnosis of uncomplicated appendicitis, and extremely little in the case of complicated and catarrhal appendicitis. Results of ultrasonographic findings and their correlation with intraoperative and pathohistological findings are shown in **Graph 3**.

Standard laboratory parameters were monitored: absolute number of leukocytes, percentage of neutrophils and lymphocytes, neutrophil-lymphocyte ratio, along with CRP. These parameters were determined from the preoperative venous blood sample. The lowest preoperative values of the neutrophil-lymphocyte ratio were present in the group of catarrhal appendicitis. CRP was performed in 72 (67.3%) operated patients with suspicion of acute appendicitis. The lowest preoperative CRP values were in the uncomplicated appendicitis group (25.11), where they differed only from the complicated appendicitis group (69.50). CRP value in the catarrhal appendicitis group was 53.85. The difference between the groups of catarrhal and complicated appendicitis is shown in **Graph 4**.



Graph 3. Distribution of severity of appendicitis by intraoperative, ultrasound and pathohistological findings
Grafikon 3. *Distribucija stepena apendicitisa prema intraoperativnom, ultrazvučnom i patohistološkom nalazu*



Graph 4. Routine lab tests in the formed pathohistological groups of patients
Grafikon 4. *Rutinske laboratorijske analize u formiranim patohistološkim grupama pacijenata*

Discussion

Acute appendicitis is one of the most common clinical challenges for emergency surgeons, because of its diagnostic processing. The clinical presentation of acute appendicitis may vary a lot, from mild symptoms like moderate abdominal pain or fever, to most severe scenarios, such as diffuse peritonitis and sepsis. The most frequent clinical sign is right lower quadrant abdominal pain. However, these symptoms are not specific for acute appendicitis as they can be present in other septic conditions [15].

Diagnostic and therapy treatment of acute appendicitis have significantly developed in recent years. Laparoscopy, US, CT, MRI and laboratory diagnostics have advanced technically [16]. Our institution`s guidelines do not include abdominal CT and MRI for the diagnosis of acute appendicitis except for unclear pathological conditions. While the clinical diagnosis of appendicitis may be straightforward in patients with common signs and symptoms, atypical presentations can result in delays in treatment, unnecessary hospital admissions for observation, and unnecessary surgery [17].

Timely intervention remains the focus of management in the prevention of progression from uncomplicated to complicated appendicitis. Nonetheless, complications like perforation with intra-abdominal abscess formation, peritonitis, and abdominal sepsis represent severe forms of acute appendicitis. These complications might be associated with severe morbidity or mortality. The probability of perforation has shown to increase after a delayed or missed diagnosis of uncomplicated appendicitis [18].

On the contrary, surgical removal of a normal appendix exposes patients to unnecessary anesthesia and surgical complications. Many diseases resemble acute appendicitis presentations. Therefore, more effort should be made towards decreasing the appendectomy rate and its complications for patients and hospitals. Rather than immediately proceeding with surgery, a more comprehensive evaluation can be pursued, including careful observation of symptoms, running additional diagnostic tests, and considering alternative diagnoses. This approach aims to minimizing the unnecessary removal of a healthy appendix and reducing the associated risks and complications of surgery [19].

Recently published papers report a wide variation in the early appendectomy rate, ranging from 3% to 25%, mostly affecting women [20].

Excision of the appendix not only decreases the risk of life-threatening complications including perforation and sepsis, but also allows for histopathology examination, which is the gold standard for confirming the diagnosis of acute appendicitis, irrespective of the intraoperative findings [21]. The reliability of intraoperative assessment in our study was 74.8%. The dilemma and a question in the case of negative intraoperative finding of appendicitis is whether appendectomy should be performed due to potential inflammation in the future, which is the opinion of some authors [22], or whether the appendix should be left in situ.

From the results of our research, it is possible to see that the neutrophil-to-lymphocyte ratio values are the lowest in catarrhal appendicitis (7.73) while the highest values are found in complicated appendicitis (13.49). Neutrophils play an important role in acute appendicitis, they are the primary responders during acute inflammation, they have the ability to phagocytose and their number increases proportionally to inflammation. During inflammation, the longevity of neutrophils increases significantly by severalfold as they become activated. This ensures the continued presence of primed neutrophils at the site of infection [23]. In a more complicated form of acute appendicitis the appearance of lymphopenia is possible, the pathohistological mechanism of which has not been fully elucidated [24]. According to these facts, an increase in the neutrophil-lymphocyte ratio is expected especially in a complicated form of acute appendicitis as a result of an increase in neutrophils and decrease in the number of lymphocytes.

C-reactive protein is considered one of the most important inflammatory markers [25]. Our patients with complicated forms of the disease had a multiple higher CRP value (48-270 mg/L), though not in the non-perforated form of disease. This speaks of CRP as a good marker of perforation, but not about the form of the disease without perforation. As reported in various studies, white blood cells (WBC) and CRP are the most significant laboratory markers to be considered in the case of acute appendicitis [26]. A WBC cut-off >10.000/ml has sensitivity range between 65 and 85% and specificity range between 32 and 82%, and CRP values >10 mg/L have sensitivity range between 65 and 85% and specificity range between 59 and 73% [27].

Both laparoscopic and open appendectomy are safe and effective techniques for the treatment of suspected acute appendicitis. Both techniques are associated with good clinical outcomes and few complications [28]. The benefits of laparoscopic approach include reduced incidence of surgical site infections, shorter postoperative stay, less pain, reduced incidence of incisional hernias, and faster postoperative recovery and return to everyday activities, along with better cosmesis [29, 30]. In our study, the type of operative technique was determined according to the surgeon`s preference and the patient`s wish. The open technique required hospitalization for six days after the operation, and the laparoscopic appendectomy for three days.

Conclusion

Acute appendicitis is an urgent surgical condition due to its localization in the abdomen, and includes a wide range of differential diseases. The clinical scoring system is not the only clinically reliable indicator of positive findings in acute appendicitis, but it has a high predictive value to negative appendectomies. Despite the high prevalence of acute appendicitis, diagnosis is challenging because many appendicitis symptoms are nonspecific and patients may have atypical clinical presentation. The frequency of minimally invasive surgery in the treatment of acute appendicitis in our coun-

try is 83.2% and it is reflected in the faster establishment of the gastrointestinal tract function, shorter hospitalization, i.e., three days, faster recovery, and return to daily activities and better quality of life.

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INFLUENCE OF THE OUTCOME OF KNEE OSTEOARTHROSIS TREATMENT ON PATIENT

UTICAJ ISHODA LEČENJA OSTEOARTROZE KOLENA NA FUNKCIONALNOST PACIJENTA

Jelena ĐUKIĆ[1, 2], Maja JEVTIĆ[1, 3] and Ksenija BOŠKOVIĆ[1, 4]

Summary

Introduction. The aim of this work is to evaluate the impact of physical procedures on the functional status of patients with gonarthrosis. **Material and Methods.** 30 patients with knee osteoarthrosis were examined (9 male patients, 21 female patients) in the prospective study. All patients were treated on an outpatient basis in the Special Hospital for Rheumatic Diseases in Novi Sad during 2022. Functional status and quality of life were assessed with use of the Western Ontario and McMaster Universities Arthritis Index questionnaire and a specific questionnaire for patients with knee osteoarthrosis. The Western Ontario and McMaster Universities Arthritis Index is a standardized questionnaire used in the assessment of osteoarthrosis of the hip and knee. The specific questionnaire for patients with osteoarthrosis of the knee joint was created by the researchers and contains: general information, a visual-analog pain scale before and after therapy, and a table that monitors the range of motion of the lower extremities during treatment. The results obtained from this kind of research were processed with use of statistical methods. Statistical significance is defined at the probability level of the alternative hypothesis from $p \leq 0.05$ to $p < 0.001$. **Results.** Correlation between the treatment outcome and patients' individual characteristics (gender, age, type of work, time diagnosis) is shown. **Conclusion.** All patients had positive results and improved quality of life, as well as reduced soreness, after two weeks, regardless of their individual characteristics.

Key words. Treatment Outcome; Osteoarthritis, Knee; Pain; Functional Status; Quality of Life; Surveys and Questionnaires

Sažetak

Uvod. Cilj ovog rada jeste procena uticaja fizikalnih procedura na funkcionalni status pacijenata sa gonartrozom. **Materijal i metode.** U prospektivnoj studiji ispitano je 30 pacijenata sa osteoartrozom kolena (devet pacijenata muškog pola, 21 pacijent ženskog pola). Svi pacijenti su ambulantno lečeni u Specijalnoj bolnici za reumatske bolesti Novi Sad tokom 2022. godine. Za procenu funkcionalnog statusa i kvaliteta života korišćeni su upitnici: *The Western Ontario and McMaster Universities Osteoarthritis Index* i specifični upitnik za pacijente sa osteoartrozom kolena. *The Western Ontario and McMaster Universities Osteoarthritis Index* je standardizovan upitnik koji se koristi u proceni osteoartroze kuka i kolena. Specifični upitnik za pacijente sa osteoartrozom zgloba kolena napravili su istraživači i sadrži: generalije, vizuelno-analognu skalu bola pre i posle terapije i tabelu koja prati obim pokreta donjih ekstremiteta u toku lečenja. Rezultati dobijeni ovakvim istraživanjem obrađeni su statističkim metodama. Statistička značajnost je definisana na nivou verovatnoće alternativne hipoteze od $p \leq 0,05$ do $p < ,001$. **Rezultati.** Prikazana je korelacija ishoda lečenja sa individualnim karakteristikama pacijenata (pol, starost, vrsta posla, vreme uspostavljene dijagnoze). **Zaključak.** Svi pacijenti su nakon dve nedelje imali pozitivne rezultate i poboljšan kvalitet života kao i smanjenu bolnost, nezavisno od njihovih individualnih karakteristika.

Ključne reči: ishod lečenja; osteoartritis kolena; bol; funkcionalni status; kvalitet života; ankete i upitnici

Introduction

The aim of the work was to examine the impact of treatment outcome on patient functionality. In the course of the prospective study, we also investigated the relationship between individual characteristics (gender, age, body mass, occupation, type of work) and the level of functional abilities and pain before and after therapy with physical procedures. With the assumptions that the functionality of patients after knee osteoarthrosis (OA) treatment depends on age, gender, the job the person does/has been doing and how long they have been suffering from knee OA. As well as that after the application of physical therapy procedures in patients with osteoarthrosis of the knee, pain is reduced by over 50%.

Material and Methods

The research was approved by the ethics committee of the Special Hospital for Rheumatic Diseases in Novi Sad for the purpose of producing a degree thesis. Subjects examined in the prospective study were 30 patients with a diagnosis of knee OA (9 male patients, 21 female patients) with an average age of 66.3 years. All patients, i.e., research participants were treated at the Special Hospital for Rheumatic Diseases in Novi Sad during August

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Abbreviations
OA – osteoarthritis
WOMAC – The Western Ontario and McMaster Universities Arthritis Index
VAS – visual-analog scale
IBM SPSS – English Statistical Package for the Social Sciences

2022. The survey was conducted in patients with knee OA in terms of their pain, stiffness, body functions, and the mobility of the lower extremities was measured. Participation in the study was voluntary, which the respondents confirmed by their written consent. The research protocol data were collected using the The Western Ontario and McMaster Universities Osteoarthrosis Index (WOMAC) questionnaire and a specific questionnaire for patients with knee osteoarthrosis. The WOMAC is a standardized questionnaire used in the assessment of OA of the hip and knee. It consists of 24 items divided into 3 subscales: pain, stiffness, body function. The first subscale pain subscale includes five items: walking, climbing the stairs, pain at night, pain at rest and weight bearing. The stiffness subscale includes two items: morning stiffness and daytime stiffness. The body functions subscale includes 17 items: going down the stairs, climbing the stairs, getting up from a sitting position, standing, bending forward, walking on a flat surface, getting in/out of a car, going to a store, putting on shoes, lying in bed, undressing, getting out of bed, getting in/out of a bath, sitting, sitting on/getting up from the toilet, heavy housework, light housework. The goal is to rate the activities in each category according to the degree of difficulty, where 0 is nothing, 1 is mild, 2 is moderate, 3 is strong, and 4 is extremely strong. The patient should circle one of the offered numbers for each item. The specific questionnaire for patients with knee OA was made by the researchers and includes: general information (patient's initials, gender, place of residence, age, body weight, body height, occupation, type of work), time of the diagnosis, how often the patient takes analgesics, how many times a year they go to physical therapy, and a visual-analog scale (VAS) for pain assessment before, during and after the therapy. Statistical data processing methods: Statistical analysis and data processing was carried out within the statistical program IBM SPSS ver. 25 (English Statistical Package for the Social Sciences), and within the Microsoft Office package (Word and Excel). The results were presented in tables and graphs. The methods of descriptive statistics were implemented as follows: frequencies (f), percentages (%), range of variability – minimum (Min) and maximum (Max) value, measure of central tendency: M – arithmetic mean, i.e., average value and measure of data variability and SD – standard deviation, i.e., average standard deviation from the arithmetic mean. The t-test for independent samples was used to determine statistically significant differences between the two groups of subjects in the sample. ANOVA test was used to examine differences between three or more groups of subjects. Differences in repeated measurements were tested with the t-test for repeated measurements, while association was determined via Pearson's correlation coefficient. Statistical significance is defined at the probability level of the alternative hypothesis from $p \leq 0.05$ to $p < 0.001$.

The total sample in the study consisted of 30 (N=30) respondents of both genders who were patients at the Special Hospital for Rheumatic Diseas-

Table 1. Average age of the sample and structure of the respondents
Tabela 1. *Prosečna starost i struktura ispitanika*

		Frequency/*Frekvencija*	Percentage/*Procenat*	Min/*Min*	Max/*Maks*	M/*M*	SD/*SD*
Age (years) *Starost u godinama*	40 - 60	5	16.7%	40.00	78.00	66.30	9.10
	61 - 60	13	43.3%				
	61 - 78	12	40%				
	Total (Σ)	30	100%				

Legend: Min - minimum sample value; Max - maximum sample value; M - arithmetic mean; SD - standard deviation
Legenda: *Min – minimalna vrednost uzorka*; *Max – maksimalna vrednost uzorka*; *M – aritmetička sredina*; *SD – standardna devijacija*

Table 2. Structure of the respondents according to BMI categories
Tabela 2. *Struktura ispitanika prema kategorijama BMI*

		Frequency/*Frekvencija*	Percentage/*Procenat*
BMI (kg/m^2)	Malnutrition/*Neuhranjenost*	0	0%
	Normal weight/*Normalna težina*	0	0%
	Overweight/*Prekomerna težina*	18	60%
	Obesity/*Gojaznost*	12	40%
	Severe obesity/*Ozbiljna gojaznost*	0	0%
	Total (Σ)/*Ukupno*	30	100%

Legend: BMI - Body Mass Index/*Legenda*: *BMI - Indeks telesne mase*

Table 3. Structure of the respondents according to type of work
Tabela 3. *Struktura ispitanika prema vrsti posla*

		Frequency/*Frekvencija*	Percentage/*Procenat*
Type of work *Vrsta posla*	Sitting/*Sedeći*	10	33.3%
	Standing/*Stojeći*	20	66.7%
	Hard physical work/*Težak fizički posao*	0	0%
	Kneeling/*Klečeći*	0	0%
	Total (Σ)/*Ukupno*	30	100%

Table 4. Structure of the respondents according to the duration of disease
Tabela 4. *Struktura ispitanika prema trajanju bolesti*

		Frequency/*Frequency*	Percentage/*Procenat*
Duration of the condition (years) *Trajanje bolesti* (*u godinama*)	< 1 y	14	46.7%
	1 - 5 y	12	40%
	5 - 10 y	4	13.3%
	> 10 y	0	0%
	Total (Σ)/*Ukupno*	30	100%

es Novi Sad. Male respondents made up 30% while female respondents made up 70% of the total sample.

36.7% of the total sample reside in a village, while 63.3% respondents live in a city.

The age of patients with knee osteoarthrosis in the total sample (N=30) ranged from a minimum of 40 to a maximum of 78 years, thus, the average age was M=66.30 years. The respondents were divided into three age categories. In the sample, 16.7% respondents aged 40 to 60 years, 43.3% respondents aged 61-60 years, while 40.0% respondents were 61-78 years old **(Table 1)**.

The body mass index (BMI) categories were calculated according to the criteria as follows: < 18.5 – malnutrition, 18.5- < 25 – normal weight, 25- < 30 – overweight, 30- < 40 – obesity and 40+ severe obesity. In the sample, 60% respondents were overweight, while 40% were obese **(Table 2)**.

26.7% of the total sample consisted of employed persons, while 73.3% of respondents were retired.

33.3% of the total sample consisted of persons who work in the sitting position, while 66.7% work while standing. There were no respondents who perform heavy physical work or work in a kneeling position **(Table 3)**.

The duration of the disease was divided into intervals, on which bases four groups were formed. Of the total number of respondents (N=30), 46.7% have been diagnosed with osteoarthrosis less than 1 year ago, 40% have had the condition for 1 - 5 years, while 13.3% of respondents were diagnosed with osteoarthrosis 5 - 10 years ago **(Table 4)**.

Results

Difference in quality of life before and after therapy

After the presented descriptive indicators on the WOMAC questionnaire, we used the t-test for repeated measurements to examine whether there is a statistically significant difference in the quality of life before and after therapy.

There is a statistically significant difference in the achieved average values before and after thera-

Table 5. Difference in quality of life before and after therapy
Tabela 5. *Razlike u kvalitetu života pre i nakon terapije*

	M/*M*	SD/*SD*	t/*t*	df/*df*	p/*p*
Pain, before/*Bol, pre*	6.80	2.83	4.241	29	0.,000
Pain, after/*Bol, posle*	5.37	1.54			
Stiffness, before/*Ukočenost, pre*	0.80	1.35	2.041	29	0.,050
Stiffness, after/*Ukočenost, posle*	0.57	0.86			
Bodily functions, before/*Telesne funkcije, pre*	22.63	10.31	4.639	29	0.,000
Bodily functions, afer/*Telesne funkcije, posle*	19.33	9.39			
WOMAC, before/*pre*	30.23	13.23	5.170	29	0.,000
WOMAC, after/*posle*	24.60	9.42			

Legend: M - arithmetic mean; SD - standard deviation; t - t-test for paired samples; p - statistical significance; df - degrees of freedom
Legenda: *M – aritmetička sredina*; *SD – standardna devijacija*; *t – t-test za uparene uzorke*; *p – statistički značaj*; *df – stepeni slobode*

Table 6. Difference in VAS values before and after therapy
Tabela 6. *Razlike u vrednostima VAS (vizuelno analogne skale) pre i nakon terapije*

	M/*M*	SD/*SD*	t/*t*	df/*df*	p/*p*
VAS before therapy/*Pre terapije*	6.77	1.28	12.624	29	0.000
VAS after therapy/*Posle terapije*	3.97	1.16			

Legend: M - arithmetic mean; SD - standard deviation; t - t-test for paired samples; p - statistical significance; df - degrees of freedom
Legenda: *M – aritmetička sredina*; *SD – standardna devijacija*; *t – t-test za uparene uzorke*; *p – statistički značaj; df – stepeni slobode*

py in all subscales of the WOMAC questionnaire, and in the total score. On the pain subscale, there is a difference in the average values before and after the therapy (t=4.241, p < 0.001), with the finding of reduced pain sensation after the therapy (M=5.37) compared to the initial values (M=6.80). Stiffness after therapy is also less (M=0.57) compared to the period before therapy (M=0.80), t=2.041, p < 0.050. Body functions also improved after therapy (M=19.33) in comparison to the baseline values (M=22.63), t=4.639, p < 0.001. Following the previous findings, the overall quality of life is better after the therapy (M=24.60) than before it (M=30.23), t=5.179, p < 0.001 **(Table 5)**.

Difference in pain intensity before and after therapy

We also examined whether there was a statistically significant change on the VAS scale before and after the therapy. Given that it includes two repeated measurements, we tested the differences with the t-test of paired samples.

The subjects rated the intensity of pain on a scale from 0 to 10, where the higher number indicates greater intensity of pain. Average pain intensity before therapy was M=6.77, and after therapy M=3.97. This difference is statistically significant (t=2.041, p < 0.001) **(Table 6)**.

Respondents' general data and quality of life

After testing the differences in the measured parameters, we proceeded to examine whether there were differences between different categories of respondents, considering the measured subscales of the WOMAC questionnaire.

The t-test for large independent samples examined whether men and women, urban and rural residents, and people working is a standing or sitting position differ statistically significantly on the subscales (pain, stiffness and body functions) and the overall quality of life measured by the WOMAC questionnaire. Statistical significance remained above the limit value of 0.05, and we concluded that the mentioned categories had similar quality of life before and after therapy in the domains: pain, stiffness, physical functioning, but also similar overall quality of life.

The ANOVA test was used to examine whether subjects of different age categories (40 - 60, 61 - 60 and 61 - 78 years) statistically significantly differ on the subscales (pain, stiffness and body functions) and the overall quality of life measured by the WOMAC questionnaire. Statistical significance was above the threshold value of 0.05, and we concluded that respondents of different ages had similar quality of life before and after therapy in the domains of pain, stiffness, physical functioning, but also similar overall quality of life. Also, the ANOVA test was used to examine whether subjects with different durations of the condition (< 1 year, 1 - 5 years, 5 - 10 years) differ statistically significantly on the subscales (pain, stiffness and body functions) and the overall quality of life measured by the WOMAC questionnaire. The statistical significance above is the limit value of 0.05, and we concluded that subjects with different durations of the condition had a similar quality of life before and after therapy in the domains of pain, stiffness, physical functioning, but also a similar overall quality of life.

Discussion

The total sample in our research consisted of 30 respondents with an average age of 66 years. The largest percentage were women (70%), while men made up only 30% of the respondents with knee osteoarthrosis. The age range was from 40 to 78 years. It is stated in researches by other authors that the incidence peaks between the age of 55 to 64 years, more in women than in men [1]. According to O'Connor MI and Hooten EG, one of the reasons why women are more often affected is the way they walk, which is different from the way men walk [2]. Pain was examined before and after therapy in order to see any possible changes and progress. After processing the collected data, we concluded that there is significant progress when it comes to pain. The patients declared after the therapy that there was a reduction in pain. The subjects rated the intensity of pain on a scale from 0 to 10, where a higher number indicates greater intensity of pain. The average pain intensity before the therapy was M=6.77, and after therapy M=3.97. This difference is statistically significant (t=2.041, p < 0.001), but there was no reduction in pain by more than 50%. The two-week therapies that patients underwent when visiting the Special Hospital for Rheumatic Diseases in Novi Sad were enough to change the WOMAC test results significantly, thus, progress was certainly visible. According to the data received after the statistical processing, we concluded that there were significant changes in the WOMAC test results on all subscales of the WOMAC questionnaire, as well as in the total score. There was a sta-

tistically significant difference in the achieved average values before and after therapy. On the pain subscale, there was a difference in the average values before and after the therapy ($t=4.241$, $p < 0.001$), with the finding that pain sensation reduced after the therapy ($M = 5.37$) compared to the initial values ($M = 6.80$). Stiffness after therapy also decreased ($M = 0.57$) compared to the period before therapy ($M = 0.80$), $t=2.041$, $p < 0.050$. Body functions also improved after the therapy ($M = 19.33$) compared to the baseline values ($M = 22.63$), $t=4.639$, $p < 0.001$. Following the previous findings, the overall quality of life was better after the therapy ($M = 24.60$) than before it ($M = 30.23$), $t=5.179$, $p < 0.001$. Osteoarthrosis is the primary cause of pain and disability and represents a significant economic burden on individuals and the society [3]. The latest update from the Global Burden of Disease study estimates that 242 million people worldwide live with symptoms and limitations related to knee or hip OA [4]. In their study on the effect of ozone therapy on knee osteoarthritis, researchers Costa T et al. found that the ozone therapy showed short-term efficacy compared to placebo combined with hyaluronic acid, but was not promising compared to other current treatments [5]. In their 2016 paper, Tang X et al. assessed the prevalence of symptomatic knee OA by gender, age, rural/urban area, socioeconomic status, and geographic location. Among 17.128 subjects, 8.1% had symptomatic knee OA. The prevalence was higher in women (10.3%) compared to men (5.7%). Also, the prevalence increased with age. Symptomatic knee OA was more common in rural than urban areas [6]. In our research, 36.7% of the total sample lived in a village, and 63.3% of respondents lived in a city. One of the risk factors and aggravating circumstances when it comes to OA is obesity. The prevalence of OA is expected to increase gradually with aging of the population and the increasing prevalence of obesity [7]. As obesity affects the entire organism and makes it difficult for all organ systems to work properly, it also has particular effect on bone metabolism, which can be seen in López-Gómez JJ. [8]. In our research, we found that the body mass in the total sample ($N=30$) ranged from a minimum of 68 to a maximum of 105 kilograms, and the average body mass of the entire sample was $M=85.37$. BMI was calculated based on body height and weight. The average BMI in the sample ranged from 25.51 to 35.43, with an average $BMI=29.93$. 60% of respondents in the sample were overweight, while 40% were obese, which shows that the total sample consists of overweight patients and the ones who belong to the obese category, justifying thus the above statement that obesity is an important risk factor for knee OA. Person's occupation can affect the quality of life in many ways, so certain occupations curry higher prevalence of certain diseases. We examined the relationship between the type of work the respondents are engaged with and the results after therapy. 33.3% of the total sample consists of persons who work while sitting, while 66.7% work while standing. There are no respondents doing heavy physical work or working in a kneeling position. As there was no statistically significant difference in the results after therapy in relation to the type of work, we also divided patients according to the time of diagnosis. The duration of the condition was divided into intervals, and four groups were formed on that basis. Out of the total number of respondents ($N = 30$), 46.7% were diagnosed with OA within the past year, 40% have had the condition for 1-5 years, while 13.3% respondents were diagnosed with OA 5-10 years ago. Selten EMH et al. conducted a study on the choice of treatment modality when it comes to knee OA. The aim of the study was to examine whether the theory of expected behavior is related to treatment choices in knee OA. Knee OA patients were randomly selected and filled out a treatment questionnaire where they were offered five treatment modalities - injections, pain medication, physical therapy and arthroplasty. The negative results that were obtained were the treatment choices that came down to painkillers and arthroplasty. Therefore, scientists came to the conclusion that physical agents, as well as physical activity, have a positive effect on the treatment of knee OA [9]. All of our patients were taking certain analgesics, so we examined their status on that topic. How often did they take painkillers? We obtained the following results: Pain-relief medicines were occasionally taken by 46.7% of the respondents, while about half of the respondents (53.3%) avoided taking them, which shows that medications were not the first choice for our patients. In Milenović N et al., we see that people with knee OA take painkillers in most cases and have good or excellent response to therapy [10]. All correlations are positive, indicating that the higher the score on the body function subscale (which represents worse functioning), the higher the values of the mentioned variables that describe the range of knee movements. After statistical data processing, we concluded that the outcome of treatment does not depend on the patient's age, gender, job, or how long they have suffered from knee OA, and that all patients improve to s similar degree after two weeks of therapy at the Special Hospital for Rheumatic Diseases in Novi Sad.

Conclusion

The outcome of the treatment of patients with knee osteoarthrosis does not depend on the patient's gender, age, job or duration of the condition. What is important is that all patients had positive results and improved quality of life after two weeks regardless of their individual characteristics.

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ASSESSMENT OF THE NUTRITIONAL STATUS OF UROLOGY PATIENTS WITH MALIGNANCIES

PROCENA NUTRITIVNOG STATUSA UROLOŠKIH ONKOLOŠKIH BOLESNIKA

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Summary

Introduction. Identifying patients with nutritional risk, nutritive assessment, and individual nutritional support are essential factors for the quality of treatment. Showing the importance of nutritional and clinical parameters as the essential indicators of the need for perioperative nutritional support. Differences in albumin and protein concentrations in the preoperative and postoperative periods of urology patients are directly related to the patients' age. **Material and Methods.** In 130 urological patients with malignancies, nutritional status was evaluated based on preoperative appetite reduction, unintentional body mass loss in the preoperative period, body mass index, the thickness of skin folds, percentage of fat tissue, the difference between normal and measured body weight, the level of albumins and total serum proteins preoperatively and postoperatively and other clinical parameters such as the presence of cardiovascular diseases and according to the classification of the American Society of Anesthesiologists patients status. Interviews, medical history, and anthropometric measurements were used in the research. **Results.** Of the total number of respondents, 81.5% did not have a decreased appetite, and 69.2% did not lose body weight. According to the body mass index, the highest percentage (50.77%) was normally nourished, while the malnourished group only comprised of 0.77%. A decrease in albumin and protein concentration was proven throughout the perioperative period. Older patients had lower concentrations of albumin and protein in this period. **Conclusion.** It is necessary to use several parameters, including body mass index and percentage fat percentage measurement to assess the nutritional status. Adequate perioperative protein nutritional support should be primarily be administered to elderly patients.

Key words: Nutritional Status; Urologic Diseases; Urologic Neoplasms; Serum Albumin; Blood Proteins; Weight Loss; Malnutrition; Body Mass Index; Adipose Tissue

Sažetak

Uvod. Prepoznavanje bolesnika sa nutritivnim rizikom, nutritivna procena i individualna nutritivna potpora značajni su činioci kvaliteta bolničkog lečenja. Prikazivanje značaja nutritivnih i kliničkih parametra kao glavnih pokazatelja potrebe za adekvatnom perioperativnom nutritivnom potporom. Razlike u koncentraciji albumina i proteina u preoperativnom i postoperativnom periodu lečenja uroloških bolesnika direktno su povezane sa starošću bolesnika. **Materijal i metode.** Kod 130 uroloških onkoloških bolesnika procenjivan je nutritivni status na osnovu: preoperativnog smanjenja apetita, nenamernog gubitka telesne mase preoperativno, indeksa telesne mase, debljine kožnih nabora, procenta masnog tkiva, razlika između uobičajene i izmerene telesne mase, nivoa albumina i ukupnih proteina u serumu preoperativno i postoperativno, prisustva kardiovaskularnih oboljenja i procena statusa bolesnika prema klasifikaciji Američkog udruženja anesteziologa. U istraživanju su korišćeni intervju, podaci iz istorije bolesti i antropometrijska merenja. **Rezultati.** Od ukupnog broja ispitanika 81,5% nije imalo smanjenje apetita, gubitak u telesnoj masi nije imalo 69,2%. Prema indeksu telesne mase najveći procenat su činili normalno uhranjeni 50,77%, dok je grupa pothranjenih činila tek 0,77%. Dokazano je smanjenje koncentracije albumina i proteina u čitavom perioperativnom periodu. Stariji bolesnici su imali u ovom periodu niže koncentracije albumina i proteina. **Zaključak**. Za procenu nutritivnog statusa potrebno je koristiti više parametara uključujući indeks telesne mase i merenje procenta masnog tkiva. Starijim bolesnicima potrebno je prevashodno ordinirati adekvatnu perioperativnu proteinsku nutritivnu potporu.

Ključne reči: nutritivni status; urološka oboljenja; urološke neoplazme; serumski albumin; serumski proteini; gubitak telesne težine; malnutricija; indeks telesne mase; masno tkivo

Introduction

The patients' nutritional status significantly affects and improves the outcome of treatment and the recovery of patients after surgery, whether accompanied by malnutrition, overweight, or obesity. Inadequate nutritional support could lead to malnutrition in the perioperative period, adversely affecting the course of surgical treatment, even in patients who were adequately nourished [1]. Malnutrition is a severe condition when your diet does not contain the right amount of nutrients. It can refer to undernutrition – not getting enough nutrients or overnutrition – getting more nutrients than needed [2].

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Abbreviations
BMI – body mass index
ASA – American Society of Anesthesiologists
CVD – cardiovascular disease

Another definition describes malnutrition as a deficiency, excess, or imbalance of a wide range of nutrients, resulting in a measurable adverse effect on body composition and function and a worse clinical outcome, the outcome of the disease [3].

Patients admitted to a health care facility with nutritional status are a challenge to dieticians in providing adequate nutritional care, especially the malnourished ones [4]. Obesity leads to numerous different disorders, both functional and inflammatory [5]. Obese patients undergoing surgery are at greater risk for surgical site infection and slower healing because of reduced blood flow in fat tissue. Extensive cohort studies have shown the association of malnutrition with worse clinical outcomes, slower wound healing, higher incidence of infections, and higher mortality [6]. Assessment of nutritional status in hospital conditions has been examined in different studies, but no specific interest has been devoted to urology patients. Proper evaluation of nutritional status is critical, and it becomes a necessary part of treatment of patients undergoing major surgical interventions. It has been observed that after 12 hours of fasting, there is a reduction of glycogen due to glycogenolysis, that fats and proteins are decomposed, and that endogenous glucose production is enhanced [7]. The stress metabolic response to a stressful situation for the organism, such as a surgical procedure, leads to consumption of the body's energy reserves, protein decomposition, increased inflammation protein synthesis, increased urea formation, and others. Insulin resistance, manifested by glucose intolerance during starvation, is well documented [8]. Malnourished patients or patients with a high risk of developing malnutrition benefit from preoperative nutritional support, which is administered 7 to 14 days before surgery. The best method to improve or maintain nutritional status is oral intake. Nutritional support should be implemented before arrival to the hospital. It must contain all the necessary nutrients and satisfy energy and the body's protein needs [9]. Preoperative nutrition optimization before surgery and maintenance of adequate nutritional status after surgery are the main goals in perioperative nutrition, especially during prolonged starvation or severe catabolism. A short-term period of preoperative fasting (6 hours) is enough to deplete carbohydrate stores, change the patient's metabolic and nutritional status, and increase the risk of dehydration, thus increasing the stress caused by the operation. Similar things and problems are also common in postoperative recovery. The guidelines suggest that early postoperative nutrition should start 6-24 hours after surgery. High-energy concentrated preparations should be used orally as patients cannot take large amounts of food in the early postoperative period. The main benefit of these drinks is that their use satisfies energy and protein needs and shortens the time from the last food consumption to the induction of anesthesia. Early recognition of patients with nutritional risk, adequate nutritional assessment, and individual nutritional support are significant factors in the overall quality of hospital treatment of patients [10].

In addition to insufficient education of general practitioners, there is also the absence of protocols that would introduce screening and assessment of nutritional status as a standard procedure when admitting patients to the hospital.

This research aimed to demonstrate the importance of nutritional and clinical parameters as the leading indicators of the need for a proper perioperative nutritional support. We also evaluated if there was any difference in albumin and protein concentration in preoperative and postoperative period of treatment of urological patients that was directly related to the age of the patients.

Material and Methods

The study included 130 patients hospitalized at the Department of Urology in the University Clinical Center of Vojvodina who underwent surgery due to urologic malignancies. Data were prospectively collected in the period from October 2018 to January 2019.

Patients aged 21 to 85 years. Looking at gender, there were 98 male patients, and 32 female patients.

Nutritional status was assessed based on the nutritional status assessment parameters: preoperative decrease in appetite, unintentional preoperative weight loss, difference between normal and measured body weight, body mass index (BMI), skinfold thickness, percentage of adipose tissue, level of serum albumin preoperatively and postoperatively, level of total protein in serum preoperatively and postoperatively, and clinical parameters such as the presence of cardiovascular diseases (CVD) and the classification of the American Society of Anesthesiologists (ASA) patient status **(Table 1)** [11]. The exclusion criteria were patients classified as ASA grade 5 and the ones who did not speak Serbian language.

Data on preoperative appetite reduction and unintentional weight loss before admission were obtained by interviewing the patients in the preoperative period of surgical treatment, who answered the questionnaire **(Table 2).** The presence of cardiovascular diseases, the patient's ASA, albumin serum level, and total protein serum level preoperative status were obtained from medical history.

Body weight was measured with a calibrated weigh chair, height was measured with a stadiometer attached to the weighing chair, and the BMI was calculated as the body mass/height ratio (kg/m^2). Skinfold thickness was measured on the right side of the patient's body at four standard points (biceps, triceps, lower angle of the scapula, and anterior superior iliac spine) with a Lange-type skin caliper with a standard pressure of 10 g/mm^2. The measurement was repeated three times at each point, and the mean value was calculated from the obtained values. Based on the sum

Table 1. American Society of Anesthesiologists (ASA) classification
Tebela 1. *Klasifikacija Američkog anesteziološkog društva – ASA klasifikacija*

ASA I *ASA I*	Healthy patient without organ disease with a localized pathological process *Zdrav pacijent bez organskog oboljenja sa lokalizovanim patološkim procesom*
ASA II *ASA II*	Patient with mild systemic disease without functional limitations *Pacijent sa blagom sistemskom bolešću bez funkcionalnih ograničenja*
ASA III *ASA III*	Patient with moderate to severe systemic disease causing functional limitations *Pacijent sa umerenom do teškom sistemskom bolešću koja dovodi do funkcionalnih ograničenja*
ASA IV *ASA IV*	Patient with severe systemic disease which is a constant threat to life making life functions difficult- *Pacijent sa teškom sistemskom bolešću koja ugrožava život i otežava životne funkcije*
ASA V *ASA V*	Moribund patient with little possibility for survival with or without surgery *Moribundni pacijent sa malom verovatnoćom za preživljavanje sa operacijom i bez nje*

Table 2. Questionnaire on perioperative appetite reduction and unintentional weight loss
Tabela 2. *Upitnik na koji su ispitanici davali odgovore prilikom intervjua*

Has food intake decreased in recent months due to decreased appetite? *1. Da li se unos hrane tokom poslednjih meseci smanjio zbog smanjenog apetita?* a) Yes/*Da* b) No/*Ne*
Has the patient unintentionally lost weight in the last 3 months? *Da li je bolesnik nenamerno izgubio na telesnoj masi u poslednja tri meseca:* a) No/*Ne* d) Yes, more than 3 kg*/Da, više od 3 kg* g) Yes, more than 15 k g/*Da, više od 15 kg* b) I do not know/*Ne znam* e) Yes, 6 to 10 kg/*Da, 6-10 kg* h) Yes, but I do not know how much*/Da, ne znam koliko* c) Yes, less than 3 kg*/Da, do 3 kg* f) Yes, 11 to 15 kg/D*a, 11-15 kg*

of four skinfolds and using the Durnin and Womersley formula, D = 1.1715 - (0.0779 x log (sum of skinfolds)) for men and D = 1.1339 - (0.0645 x log (sum of skinfolds) folds)) for women, where D is the predicted body density (g/ml), the percentage of fat tissue in the body was calculated based on the formula: percentage of fat tissue = (495/D) - 450.

Similarities and differences were obtained between individual nutritional status assessment parameters that relate to the overall nutritional status assessment results. Data were analyzed with the Statistical Package for Social Sciences, version 23. Descriptive and inferential statistics methods were used for data analysis. Data are presented via arithmetic mean, and standard deviation and categorical variables via frequencies and percentages. Student's t-test was used to assess differences between variables between study groups. Pearson's correlation was used to examine the correlation between the subject's age, serum protein concentration, and serum albumin concentration (preoperatively and postoperatively). A p-value < 0.05 was considered statistically significant. Sampling weights were used (except for the sample description) during the statistical analysis of the data. The results are presented tabularly and graphically.

Results

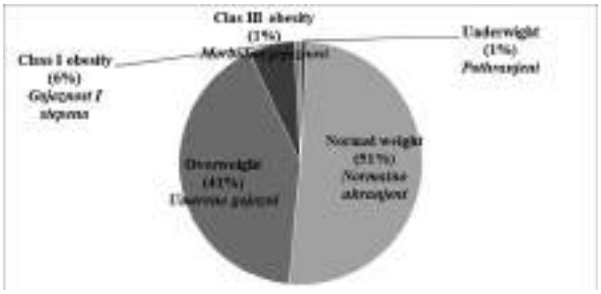
Of the total number of patients, 81.5% did not have a preoperative decrease in appetite, and less than 1/4 (18.5%) had an appetite decrease. Among 130 patients, 47.7% respondents had CVD. According to gender, there is a higher percentage of women (25%) than men (16.3%) who had a preoperative decrease in appetite. In comparison, male respondents (53.1%) had a higher percentage of CVD compared to female respondents (31.3%).

More than 2/3 of the patients (69.2%) had no unintentional weight loss in the preoperative period. 8.5% respondents lost up to 3 kg, 1.5% lost more than 3 kg, 8.5% respondents lost 6-10 kilograms, 5.4% respondents lost body weight but did not know how many kilos, while 4.6% respondents did not know if they had had unintentional weight loss.

Of the total number of women who had unintentional weight loss, the largest number of patients lost between 6-10 kg (15.6%), while the most significant percentage of men lost up to 3 kg (7.1%).

Out of the total number of patients, the largest number (66.2%) had ASA status 3, followed by ASA status 2 (29.2%), while the smallest number of respondents (2.3%) had ASA status 1 or ASA status 4. Observed according to gender, the largest number of both female (50%) and male patients (71.4%) had ASA status 3. No female subjects had ASA status 1. The smallest number of both women (6.3%) and men (1%) had ASA status 4.

The body mass index ranged from 18.8 kg/m^2 to 49.86 kg/m^2, and the average value was 25.07 ± 3.97 kg/m^2. According to the BMI, the patients' nutrition



Graph 1. Percentage of patients' nutrition according to body mass index (BMI) values
Grafikon 1. *Procenat uhranjenosti bolesnika prema vrednostima indeksa telesne mase (ITM)*
BMI categories: BMI< 18.5 – underweight, BMI 18.5-25 – normal weight, BMI 25-30 – overweight, BMI 30-35 – Class I obesity, BMI 35-40 – Class II obesity, BMI > 40 – Class III obesity.
Stepen gojaznosti spram indeksa telesne mase (ITM): ITM < 18,5 – pothranjeni, ITM 18,5 – 25 – normalno uhranjenin, ITM 25-30 - umereno gojazni, ITM 30-35 – gojaznost I stepena, ITM 35 – 40 – gojaznost II stepena, ITM > 40 morbidna gojaznost.

level was distributed so that 0.77% were malnourished and obese (Class 3). The normally nourished made up 50.77%. The pre-obese group made up 41.54%, while the obese (Class 1) made up 6.15% **(Graph 1)**.

The average skinfold thickness in our group of subjects was 42.43 mm ± 12.46 mm, while the average percentage of fat tissue was 25.01 ± 5.52%. The average measured body weight was 76.71±16.08 kg. Men had a statistically significantly higher measured body weight than women (65.34±10.470 vs. 80.42±15.883; t= -5.020; p < 0.05).

The paired samples test evaluated the difference in albumin concentration in the preoperative and postoperative treatment periods. A statistically significant decrease in albumin concentration was found from the preoperative period (49.95±8.52) to the postoperative period (44.83±9.43); t = -9.352; p < 0.005. The average decrease in albumin concentration was 5.11, while the 95% confidence interval extends from -6.20 to -4.03 **(Table 3).**

The paired samples test was used to assess the difference in protein concentration in the preoperative and postoperative treatment periods. A statistically significant decrease in protein concentration was found from the preoperative period (70.30±6.17) to the postoperative period (62.60±8.09); t=-13,553; p < 0.005. The average decrease in protein concen-

Table 3. Preoperative and postoperative comparison of albumin and protein concentrations and comparison of normal and measured body weight
Tabela 3. *Preoperativno i postoperativno poređenje koncentracija albumina i proteina i poređenje uobičajene i izmerene telesne mase*

		N/*Br.*	$\overline{X}$±SD	$\overline{X}$±SD	95% confidence interval *95% Interval poverenja*		t/*t*	p/*p*
					Upper limit *Gornja granica*	Lower limit *Donja granica*		
Albumin concentration *Koncentracija albumina*	Preoperative *Preoperativno*	130	44.83±9.43	5.11±6.24	-6.20	-4.03	-9.352	0.000
	Postoperative *Postoperativno*	130	49.95±8.52					
Protein concentration *Koncentracija proteina*	Postoperative *Postoperativno*	130	62.60±8.09	7.69±6.47	-8.81	-6.57	-13.553	0.000
	Preoperative *Preoperativno*	130	70.30±6.17					
Body weight *Telesna masa*	Normal *Uobičajena*	130	84.35±55.77	7.64±55.5	-1.98	-71.27	1.571	0.119
	Measured *Izmerena*	130	76.71±16.08					

Table 4. Correlation of albumin/protein concentration with the age of subjects
Tabela 4. *Korelacija koncentracije albumina/proteina sa starošću ispitanika*

		Albumin concentration *Koncentracija albumina*		Protein concentration *Koncentracija proteina*	
		Preoperative *Preoperativno*	Postoperative *Postoperativno*	Preoperative *Preoperativno*	Postoperative *Postoperativno*
Patient age *Starost pacijenta*	Pearson Correlation Coefficient *Pirsonov koeficijent korelacije* (r)	-0.098	-0.103	-0.180	-0.201
	p/*p*	0.269	0.242	0.040	0.022
	N/*Br.*	130	130	130	130

tration was 7.69, while the 95% confidence interval extends from -8.8 to -6.57 **(Table 3).**

A paired samples test assessed the difference between normal and measured body weight. No statistically significant difference was found between the normal (84.35±55.77) and measured body weight (76.71±16.08) BMI; t=1.571; p=0.119. The usual body weight was greater than the measured body weight by 7.64 kg on average, while the 95% confidence interval extends from -1.98 to -71.27 **(Table 3).**

There was a weak negative correlation between the patient age and preoperative albumin concentration (r=-0.098; p=0.269) and a weak negative correlation between the patient age and postoperative albumin concentration (r=-0.103; p=0.242), but they were not statistically significant.

There was a statistically significant weak negative correlation between the patient age and the preoperative protein concentration (r=-0.180; p=0.040) and a statistically significant weak negative correlation between the subject's age and the postoperative protein concentration (r=-0.201; p=0.022), which means that younger patients had a statistically significantly higher concentration of both preoperative and postoperative protein values **(Table 4).**

Discussion

Decreased appetite and unintentional weight loss in the preoperative period are additional but not sufficiently sensitive parameters for differentiating malnutrition from normal nutrition [12]. Cardiovascular diseases were present in 47.7% of patients, with a higher percentage in men than women. The association of obesity as a risk factor for the occurrence of various cardiovascular diseases, especially in men, has been shown in various studies [13].

The importance of ASA status as a clinical parameter of the patient's general condition should be considered. La Torre et al. showed that the ASA status alone cannot individually indicate the patient's malnutrition [14]. In our study, there were mainly elderly patients with ASA status III, which indicates adequate application of ASA status and other nutritional assessment parameters. Wolters et al. proved a significant correlation between the classification of ASA status and perioperative risk factors (intraoperative blood loss) and postoperative complications and mortality in a prospective study of 6301 surgical patients. It has been shown that the risk of complications was mainly influenced by ASA status III and IV and that ASA status is a predictor of postoperative outcome [15]. Farrow et al. reported absolute mortality rates of certain classes of ASA status with considerable variation from 0-0.3% for ASA I, 0.3-1.4% for ASA II, 1.8-4.5% for ASA III, 7.8-25.9% for ASA IV and 9.4-57.8% for ASA V. Differences in subjective assessment of physical status, patient population, sample size and duration of postoperative treatment may explain this variability [16].

The frequency of malnutrition at admission in the examined group of urology patients was 0.77% of the BMI. The obtained frequency does not fit in with the results of previous research, according to which malnutrition at admission was in the interval of 3.67–91% [17]. The lower frequency of malnutrition could be explained when BMI is used as an assessment parameter, especially for the elderly population, because of the increase in BMI due to physiological changes occurring in musculoskeletal function [18, 19]. Also, the percentage of customarily nourished patients on admission was 50.78%, and pre-obese 41.54%, which can also be explained by the fact that more than a half of the adult population of Serbia (54%) is overnourished, with 36.7% pre-obese and 17.3% obese [20, 21]. The highest overall prevalence of overweight in our country is recorded in Vojvodina [22]. The average percentage of adipose tissue was 25%, which corresponds to the facts, especially when we considered that the rate of pre-obese subjects in our examined group is 41.54%. Alberino et al. and Caregaro et al. recommend measuring the skin fold thickness above the triceps as the best method of assessing the nutritional status of surgical patients [23, 24]. Several studies have confirmed mutual deviations in fat mass and the degree of nutrition and obesity in normal body mass [25–27]. Marques-Vidal et al. showed the presence of obesity in normal body weight in less than 1% of men, while the frequency of this form of obesity in women was 27.8% and increased with age [25, 28]. Research conducted in our population reveals the presence of obesity in normal body mass in 25.71% of subjects [29]. In comparison, in the general population, 10% of normally nourished men and 13.33% women have borderline increased BMI, and 6.67% of normally fed women have increased fat mass [30]. Similar results of nutritional status assessment using skinfold thickness and percentage of fat tissue are also published by some other authors [31], although there is similarity between nutritional status assessment result using mid-upper arm circumference, on the one hand, and albumin level [32], a body index, loss of body mass [33] and skin folds thickness [34], on the other hand. From the laboratory parameters, a statistically significant decrease in albumin concentration was determined from the preoperative (49.95±8.52) to the postoperative (44.83±9.43) treatment period. Serum albumins are valid parameters of nutritional status because their level reflects the size of the visceral protein composition and is a strong predictor of hospitalization in urology patients. Reduced albumin production due to inflammation, hormonal deficit, redistribution of albumin from vascular to interstitial space during surgery, hyperhydration, and increased losses due to significant proteinuria may contribute to lower serum albumin levels.

A statistically significant decrease in protein concentration was also determined from the preoperative (70.30±6.17 g/l) to the postoperative (62.60±8.09 g/l) treatment period, which can be considered a physiological response of the body to a stressful situation, such as surgery when it comes to increased protein catabolism. There is no clear correlation between the preoperative level of serum proteins and their changes postoperatively [38]. Patients at risk of developing

complications during the postoperative period cannot be identified based on the measurement of preoperative serum protein concentrations. The results of our study show that the usual body mass is greater than the measured body mass of the subjects by 7.64 kg, which was not statistically significant.

This study included only urology patients, while other studies were conducted on patients treated for other surgical diseases. Also, applying different nutritional status assessment parameters and various threshold values for the same parameters further complicates the proper comparison of our results and the results of other studies. In addition, there are no unique recommendations in the literature regarding selecting the optimal parameter for assessing nutritional status at hospital admission. Malnutrition as a nutritional imbalance in urology patients, mostly consisting of an older population with numerous other associated chronic diseases, is not a rare problem, and its frequency can be reduced by proper nutritional status assessment based on various examined parameters, primarily body mass index and skinfold thickness.

Conclusion

To date, there are no agreed positions on the optimal nutritional status assessment parameter for urology patients. However, several parameters should definitely be used, including the body mass index and the measurement of fat tissue percentage. Measuring the percentage of fat tissue with use of calipers is a relatively quick and inexpensive method and can be used for regular assessment of nutritional status. American Society of Anesthesiologists status should be used as a clinical parameter for the nutritional evaluation in elderly patients with American Society of Anesthesiologists status III, together with other parameters. Elderly patients should primarily be prescribed adequate perioperative protein nutritional support in order to prevent complications in the perioperative course of treatment as this study has found that they had significantly lower protein concentrations preoperatively and postoperatively.

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THE SIGNIFICANCE OF VACCINE-INDUCED PROTECTION FROM COAGULATION DISORDERS REPORTED IN COVID-19 PATIENTS WITH A REVIEW OF SEVERITY OF THEIR CLINICAL PRESENTATION

ZNAČAJ VAKCINACIJE U ZAŠTITI OD POREMEĆAJA KOAGULABILNOSTI KOD COVID 19 PACIJENATA SA OSVRTOM NA TEŽINU KLINIČKE SLIKE

Mirjana MILOJEVIĆ ILIĆ

Summary

Introduction. The production and distribution of preventive SARS-CoV-2 vaccines are among the greatest advances that offers protection against severe forms of the disease, including also fatal outcomes. The purpose of our research is to establish the degree to which vaccination contributes to providing protection against coagulation disorder (one of the leading COVID-19 infection complications). Vaccinated patients with COVID-19 breakthrough infections rarely manifest severe clinical presentation with the occurrence of pneumonia. However, the question is whether they are protected against thromboembolic complications irrespective of the occurrence of pneumonia. **Material and Methods.** 132 respondents were divided into 4 groups based on their immunization status (vaccinated V+; unvaccinated V-) and severity of their clinical presentation, the main criterion of which was pneumonia (with pneumonia P+; without pneumonia P-): group 1: V+, P+; group 2: V+, P-; group 3: V-, P+; group 4: V-, P-. All of them tested positive for SARS-CoV-2. The mean values of D-dimer levels were compared to their reference values (0.5 mcg/ml). **Results.** The results indicated elevated D-dimer levels in patients with SARS-CoV-2 pneumonia irrespective of their vaccination status. This refers to both the mean and reference values. The results demonstrated that V+ and P+ had elevated D-dimer levels when compared to V+ and P-, which was not the case with the unvaccinated patients, i.e., V- and P+ had no more significantly higher D-dimer levels when compared to V- and P-. **Conclusion.** Our conclusion is that vaccination has no role in protecting against coagulation disorders irrespective of the occurrence of pneumonia.

Key words: Blood Coagulation Disorders; Thromboembolism; COVID-19 Vaccines; SARS-CoV-2; Fibrin Fibrinogen Degradation Products; Pneumonia; Immunization

Sažetak

Uvod. Najveći napredak do sada u borbi protiv SARS COV-2 pandemije je rana proizvodnja i distribucija vakcina protiv SARS-CoV-2 virusa koje deluju prvenstveno preventivno, a ako i dođe do obolevanja sprečavaju teške forme bolesti i smrtni ishod. Cilj našeg istraživanja jeste da utvrdimo koliko vakcinacija doprinosi zaštiti od poremećaja koagulacije, što je jedna od vodećih komplikacija kod COVID-19 infekcije. Iako se zna da vakcinisani pacijenti ređe obolevaju od teške kliničke slike sa pojavom pneumonije, postavlja se pitanje da li su zaštićeni i od komplikacija u vidu tromboze nezavisno od pojave pneumonije. **Materijal i metode.** U istraživanje su uključena 132 ispitanika, koji su podeljeni u četiri grupe na osnovu statusa imunizacije (vakcinisani V+; nevakcinisani V-) i težine kliničke slike, gde je glavni kriterijum postojanje upale pluća (sa pneumonijom P+; bez pneumonije P-): 1. grupa: V+, P+; 2. grupa: V+, P- ; 3. grupa V-, P+; 4. grupa V-, P-. Svi su imali pozitivan test na SARS-CoV-2 virus. Statistički su poređene prosečne vrednosti D-dimera i vrednosti D-dimera u odnosu na referentne (0,5 mmol/ml) među ovim grupama. **Rezultati.** Rezultati su pokazali da pacijenti sa pneumonijom imaju značajno povišene vrednosti D-dimera bez obzira na status imunizacije. Ovo se odnosi i na prosečne i na referentne vrednosti. Drugi deo rezultata je pokazao da V+, P+ imaju značajno više prosečne vrednosti D-dimera u odnosu na V+, P-, što se nije odnosilo na nevakcinisane, tj. V-, P+, nisu imali značajno više nivoe D-dimera u odnosu na V-, P-. **Zaključak.** Zaključak istraživanja je da vakcinacija nema protektivnu ulogu u zaštiti od poremećaja koagulacije nezavisno od pojave pneumonije.

Ključne reči: poremećaji koagulacije; tromboembolije; COVID-19 vakcine; SARS-CoV-2; D-dimer; pneumonija; imunizacija

Introduction

The COVID-19 pandemic has been a significant global, health, social and economic issue ever since the occurrence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019. Globally, several different types of COVID-19 vaccines have been administered, with various de-

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Abbreviations

SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
V+	– vaccinated
V-	– unvaccinated
P+	– with pneumonia
P-	– without pneumonia
DD	– D-dimer
DIC	– disseminated intravascular coagulation
CT	– computirized tomography
RT-PCR	– real time polymerase chain reaction
EHRs	– electronic health records

grees of efficiency. However, each one of the vaccines significantly reduces the risk of occurrence of severe clinical presentation and fatal outcomes [1–5].

Health risks are primarily associated with respiratory problems and the incidence of severe viral pneumonia, coupled with coagulopathy which eventually leads to thrombosis and embolization of the whole body, disseminated intravascular coagulation (DIC) [6, 7]. Post-Covid patients can suffer from severe complications, such as heart problems, neurological system disorders, problems with the liver, kidneys, skin, etc. [8–10].

The diagnosis of COVID-19 pneumonia is confirmed based on the positive SARS-CoV-2 virus test, clinical symptoms, signs, and objective medical examination, and is verified by the use of diagnostic imaging methods, such as computed tomography (CT) scans and chest X-rays [11]. On the other hand, an elevated D-dimer level is shown to be a sensitive (but not entirely specific) test for detecting coagulopathy [12]. A few sources confirm the correlation between the severity of the clinical presentation and elevation of D-dimer levels, though it is also possible to detect thrombosis in patients with mild upper respiratory tract symptoms [13].

Vaccination primarily focuses on prevention. Furthermore, it reduces the severity of clinical presentation, development of the most severe forms of illness, and fatal outcome as well [14]. No single vaccine can provide full (100%) protection against the SARS-CoV2 virus and that a certain percentage of vaccinated people can also develop viral pneumonia [15]. Pre-existing chronic diseases are the established risk factors for COVID-19 outcomes [16, 17].

As thrombosis is one of the most common causes of death from coronavirus infection, the question is whether vaccination can help reduce the risk of coagulation disorders incidence irrespective of the incidence of pneumonia [18]? Actually, the real question is whether vaccinated patients with pneumonia are less likely to develop coagulation disorder compared to unvaccinated patients with confirmed pneumonia?

Some sources confirm the correlation between the severity of clinical presentation and elevation of D-dimer levels, suggesting that this particular analysis could be used as a predictive factor for the development of severe clinical presentation and adverse course of the disease, but there are reports of COVID-19 cases where patients with mild upper respiratory tract symptoms developed thrombosis, which is a dangerous and potentially fatal condition. The second question is whether correlation between the severity of clinical presentation and elevation of D-dimer levels could be considered statistically significant?

The aim of the research was to show whether there was any difference between the coagulability levels in vaccinated and in unvaccinated patients with pneumonia, taking into account the fact that thrombosis was associated with the severity of clinical presentation that also depends on the vaccination status of the above patients.

Material and Methods

Our research was conducted as a retrospective cohort study that included 132 participants divided into four separate groups. The main variable, which was measured for each participant, referred to the D-dimer levels.

All the participants tested positive for the SARS-CoV-2 virus in the period between April 1, 2021, and June 15, 2021. They were treated (primarily) at the Outpatient Clinic for Respiratory Diseases and Febrile Conditions, Kragujevac Health Center, Kragujevac.

Patients were divided into four separate groups based on the following criteria: patients in whom COVID-19 was confirmed by the real-time RT-PCR test or the rapid SARS-CoV-2 antigen detection test and the severity of clinical presentation (a patient with pneumonia J12, J15 and J18 according to the International Classification of Diseases (ICD)/a patient without pneumonia).

Inspecting the electronic medical records for each individual patient, we checked whether the date of diagnosis met the diagnostic criteria given: 1. Diagnostic vaccination; 2. Minimum 15 days after the vaccination, the diagnosis is confirmed based on the positive result of tests for SARS-CoV-2 virus; 3. Diagnosis of pneumonia during the treatment of COVID-19 infection. Additionally, we checked whether the above diagnosis was verified by chest X-rays.

Having gained insight into the current medical records, we selected 132 patients, i.e., each of the four groups comprised of 33 patients for whom the lab data were collected on D-dimer (DD) levels.-

- Group 1: vaccinated, with pneumonia (V+, P+);
- Group 2: unvaccinated, with pneumonia (V-, P+);
- Group 3: vaccinated, without pneumonia (V+, P-);
- Group 4: unvaccinated, without pneumonia (V-, P-).

Statistical data analysis was performed with use of IBM SPSS® Statistics software.

The obtained data were displayed primarily in a descriptive manner using a combination of tabulated description (i.e., tables) and graphic description (i.e., graphs). Continuous variables, i.e., D-dimer values, were shown using the least and greatest value, the mean value and standard deviation, as well as the median values.

The independent-samples t-test was used for the purpose of analyzing the D-dimer values compared to the immunization status and incidence of pneumonia in the study participants. The above test was used

to compare the mean D-dimer levels between the two examined groups of participants. The analysis was made not only for each participant respectively, but for each of the given groups, and compared again according to their immunization status and the incidence of pneumonia. The results of the analysis were presented graphically in a clustered column graphs.

The results were considered to be statistically significant if the level of statistical significance (the p-value) was less than 0.05 (typically ≤ 0.05).

Results

Out of the total of 132 study participants, 66 participants or 50% of participants were vaccinated, i.e., unvaccinated. Compared to their pneumonia status, there were 66 participants, or 50% of participants with and without pneumonia. The D-dimer levels ranged from 0.01 to 6.20. The mean D-dimer value was 0.69 with a standard deviation of 0.90, whereas the median value was 0.37. Compared to the D-dimer values less than 0.5 and greater than 0.5, there were 86 participants, i.e., 65.6% of participants with D-dimer values less than 0.5, and also, there were 45 participants, i.e., 34.4% of participants with the D-dimer values greater than 0.5.

Using the independent samples t-test, we established that there was no statistically significant difference between D-dimer values in vaccinated participants, i.e., unvaccinated participants (p = 0.356). It referred to both patients with pneumonia (p=0.222) and patients without pneumonia (p=0.671) **(Table 1)**.

For all participants

In V+ group, the mean D-dimer value was 0.76 mcg/ ml. In V- participants, the mean D-dimer value was 0.62 mcg/ml.

For participants with pneumonia

In P+, V+ group, the mean D-dimer value was 1.12 mcg/ml. In P+, V- group, the mean value was 0.79 mcg/ml. The results were presented graphically in **Graph 1**.

For participants without pneumonia

In P-, V+ group, the mean D-dimer value was 0.39 mcg/ml. In P-, V- group, the mean value was 0.44 mcg/ml.

For the purpose of analyzing D-dimer values in comparison to the pneumonia status of the participants, we used the independent samples t-test, comparing thus the mean D-dimer values in participants with, i.e., without pneumonia.

The analysis was supposed to be made not only for all the participants, but for the immunized and non-immunized ones as well **(Table 2)**.

For all participants

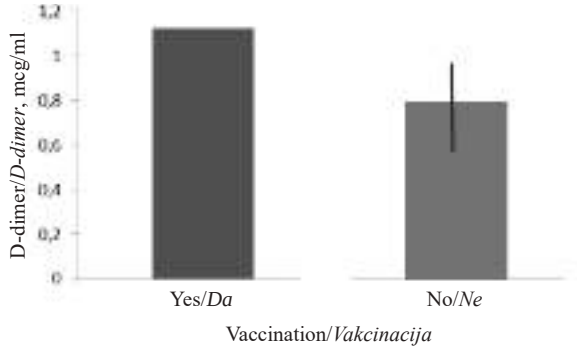
In P+ group, the mean D-dimer value was 0.96 mcg/ml. In P- group, the mean value was 0.41 mcg/ml.

For vaccinated participants

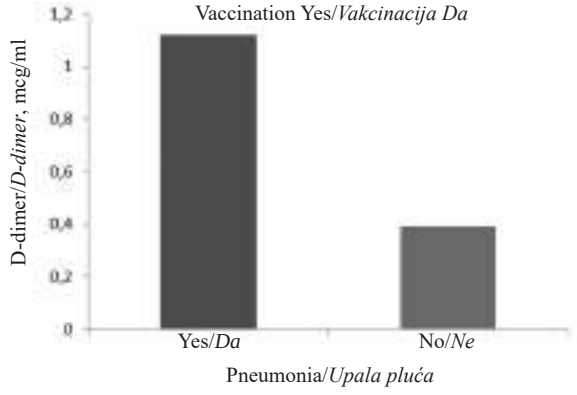
In V+, P- group, the mean value was 0.39 mcg/ml. The results are presented graphically in **Graph 2**. It clearly shows that D-dimer values are signifi-

Table 1. Results of the analysis of D-dimer values compared to the immunization status
Tabela 1. *Rezultati analize vrednosti nivoa D-dimera u odnosu na status imunizacije*

	p/*p*
All participans/*Svi ispitanici*	0.356
Only participans with pneumonia/*Samo ispitanici sa pneumonijom*	0.222
Only participans without pneumonia/*Samo ispitanici bez pneumonije*	0.671



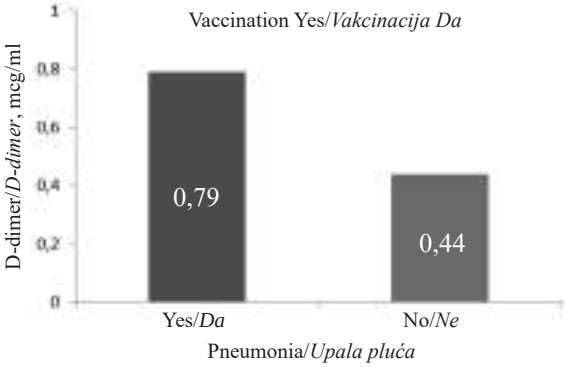
Graph 1. D-dimer values compared to the immunization status of participants with pneumonia
Grafikon 1. *Vrednosti nivoa D-dimera u odnosu na status imunizacije ispitanika koji imaju pneumoniju*



Graph 2. D-dimer values compared to the incidence of pneumonia in immunized participants
Grafikon 2. *Vrednosti nivoa D-dimera u odnosu na prisustvo pneumonije kod imunizovanih ispitanika*

Table 2. The results of the analysis of D-dimer values compared to the incidence of pneumonia
Tabela 2. *Rezultati analize vrednosti nivoa D-dimera u odnosu na prisustvo pneumonije*

	p/*p*
All participants/Svi ispitanici	0.000
Only immunized participants/*Samo imunizovani ispitanici*	0.003
Only non-immunized participants/ *Samo neimunizovani ispitanici*	0.053



Graph 3. D-dimer values compared to the incidence of pneumonia in non-immunized participants
Grafikon 3. *Vrednosti nivoa D-dimera u odnosu na prisustvo pneumonije kod neimunizovanih ispitanika*

cantly higher in the group of immunized participants with pneumonia.

For unvaccinated participants

In V-, P+ group, the mean D-dimer value was 0.79 mcg/ml. In V-, P- group, the mean value was 0.44 mcg/ml. The results are presented graphically in **Graph 3**. D-dimer values in non-immunized patients with pneumonia are not significantly higher than the D-dimer values in non-immunized patients without pneumonia.

There is a moderate positive correlation between D-dimer levels and aging (R=0.265). This result is statistically significant, which means that D-dimer levels increase with age**.**

Discussion

Considering the fact that there has been a rising debate among healthcare workers about the significance of D-dimer levels during the COVID-19 infection, the objective of our research was primarily related to identifying the significance of this particular analysis. The statistical data analysis was made in comparison to mean D-dimer values. The two main research questions were as follows:

1. Are vaccinated patients with COVID-19 pneumonia less likely to show coagulation abnormalities as opposed to unvaccinated patients with confirmed coronavirus pneumonia?

2. Is there a statistically significant correlation between the severity of clinical manifestation and elevation of D-dimer levels considering the existing immunization gap?

The following conclusions were drawn from this particular research:

No statistically significant difference was found between the D-dimer levels in patients with pneumonia compared to the immunization status. Therefore, patients with pneumonia were more frequently reported to have elevated levels of D-dimer, irrespective of whether they were vaccinated or not. In addition, COVID-19 patients without pneumonia were reported to have less mean D-dimer values irrespective of their immunization status. On the basis of our research, it should be emphasized that vaccination had no important role in gaining potentially protective immunity against coagulation abnormalities, irrespective of the lung inflammation occurring during the COVID-19 infection.

Based on the previous experiences not only from clinical practice, but the latest research as well, the increase in D-dimer levels is proportionate to the risk of the development of thrombosis [21]. Our research findings contributed to drawing the three significant conclusions as follows: Firstly, patients with pneumonia had significantly higher D-dimer levels compared to the patients without pneumonia, without considering the vaccination gap (P+: 0.96 mcg/ml compared to P-: 0.41 mcg/ml), which is in accordance with the latest findings of our analysis related to the increase in D-dimer levels during the infection.

However, when all the pneumonia-related findings are examined separately, it can be noted that the results of vaccinated participants contribute significantly to the overall result. This means that vaccinated patients with pneumonia are reported to have significantly higher mean D-dimer values compared to the vaccinated ones without pneumonia (V+, P+: 1.12 mcg/ml compared to V+, P-: 0.39 mcg/ml).

Our previous conclusion confirms the argument on vaccination not being able to offer protection against coagulation abnormalities, irrespective of the incidence of pneumonia.

However, when it comes to the group of unvaccinated patients, our research findings demonstrated that mean D-dimer values do not significantly differ between the patients with mild clinical manifestation without pneumonia and the patients with pneumonia (V-, P-: 0.44 mcg/ml compared to V-, P+: 0.79 mcg/ml).

However, the above levels of D-dimer were lower in comparison to the participants in the vaccinated group, the significance of which lies in the fact that the risk factor for thrombosis development and its growth is proportionate to the increase in D-dimer levels, as mentioned earlier.

Taking into consideration the fact that the study was conducted based on the primary care data ob-

tained from electronic health records (EHRs), there are no data for earlier D-dimer values (if they were checked) based upon which it would have been easy to exclude patients with a previously acquired coagulation disorder.

It should be emphasized that in this particular paper it was not possible to conduct a more thorough and detailed statistical data analysis in regard to the type of vaccines used.

Conclusion

Vaccination offered no protection against coagulation disorder, irrespective of the development of pneumonia. Therefore, regardless of the immunization status, if a more severe clinical presentation involved the development of pneumonia, there would be an increase in the D-dimer levels, which would consequently lead to the increased risk factors for the development of thrombosis.

The vaccinated patients had higher mean D-dimer levels once they developed pneumonia, as opposed to the vaccinated patients with mild clinical manifestation. In the case of unvaccinated patients though, the opposite is true – the mean D-dimer levels of unvaccinated patients with pneumonia are not significantly higher than the levels of unvaccinated patients who showed no evidence of this particular respiratory complication.

Our clinical study is valuable and important to clinical practice as it indicates that the vaccinated patients should receive the same thorough treatment just like the unvaccinated ones. Despite the fact that they rarely develop more severe forms of the disease, they can also develop certain complications that can eventually lead to a lethal outcome.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
Prikaz slučaja
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ELECTROMYONEUROGRAPHY IN THE DIAGNOSTICS OF RARE CAUSES OF CARPAL TUNNEL SYNDROME

ELEKTROMIONEUROGRAFIJA U DIJAGNOSTICI RETKIH UZROKA SINDROMA KARPALNOG TUNELA

Igor DAMJAN[1], Zita JOVIN[2], Željko ŽIVANOVIĆ[2, 3], Saša POPOVIĆ[4] and Vesna NJAGULJ[4]

Summary

Introduction. The paper points to the problem of electromyoneurography of the bifid median nerve as a rare cause of carpal tunnel syndrome. Carpal tunnel syndrome represents a set of symptoms caused by compression of the distal portion of the median nerve. It is important in clinical practice as it significantly effects the functionality and the quality of daily activities. One of the predisposing factors for the carpal tunnel syndrome is the bifid median nerve. Electromyoneurography is still the gold standard for the verification of the carpal tunnel syndrome. **Case Report.** A 48-year-old patient, after a clinical suspicion of carpal tunnel syndrome, has been confirm by ultrasonography to be suffering from moderate carpal tunnel syndrome, with a detection of 'incomplete' bifid median nerve in the carpal tunnel. Electromyoneurography also confirmed a mild level of carpal tunnel syndrome. However, as difficulties were exclusively present in the innervation area of the median nerve internal branch, and there was a possibility of incomplete correlation of electromyoneurography results, the lumbrical muscles and dorsal interossei muscles were examined, and confirmed a moderate degree of carpal tunnel syndrome. **Discussion**. The bifid median nerve can be the cause of the above insufficient sensitivity of this method, which is why it is necessary to apply optional electromyoneurographic techniques. **Conclusion**. The final practical significance lies in the fact that the presence of the diagnosed bifid median nerve could affect the choice and efficiency of certain therapeutical options.

Key words: Carpal Tunnel Syndrome; Electromyography; Diagnosis; Median Nerve; Anatomic Variation; Diagnostic Imaging

Sažetak

Uvod. Rad ukazuje na enigmatičnost elektromioneurografije bifidnog medijalnog nerva kao retkog uzroka sindroma karpalnog tunela. Sindrom karpalnog kanala predstavlja skup simptoma uzrokovanih kompresijom krajnjeg dela središnjeg živca u delu kanala ručja. Svojom učestalošću i fenomenologijom, koja značajno utiče na funkcionalnost i kvalitet dnevne aktivnosti, predstavlja jedan od značajnih entiteta kliničke prakse. Predisponirajući faktor u nastanku ovog sindroma je i bifidni medijalni nerv - anatomska varijacija grananja središnjeg živca već u karpalnom kanalu. Elektromioneurografija predstavlja „zlatni" standard u verifikaciji sindroma karpalnog kanala. Međutim, pored njegove algoritamske značajnosti, mogući su lažno negativni nalazi. **Prikaz slučaja.** Četrdesetosmogodišnjoj pacijenkinji, nakon klinički postavljene sumnje postojanja sindroma karpalnog kanala, ultrasonografski je potvrđeno njegovo postojanje srednjeg stepena, uz detekciju „inkopletnog" bifidnog medijalnog nerva u karpalnom kanalu i elektromioneurografskim pregledom takođe potvđen sindrom karpalnog kanala lakog stepena. Zbog isključive prisutnosti tegoba u inervacionom području unutrašnje grane središnjeg živca i mogućnosti nepotpune korelativnosti elektromioneurografskog nalaza, primenjena je glistasto-međukoštana studija i konstatovan je sindrom karpalnog kanala srednje teškog stepena. **Diskusija.** Bifidni medijalni nerv može biti uzrok navedene nedovoljne senzitivnosti ove metode, te u tim slučajevima pored konvencionalnog, rutinskog i obavezujućeg elektromioneurografskog pregleda potrebna je primena opcionih elektromioneurografskih tehnika. **Zaključak.** Krajnja praktična važnost je u činjenici da prisustvo dijagnostikovanog bifidnog medijalnog nerva može uticati na izbor i uspešnost određenih terapijskih opcija.

Ključne reči: sindrom karpalnog tunela; elektromiografija; dijagnoza; nervus medianus; anatomske varijacije; dijagnostički imidžing

Introduction

Carpal tunnel syndrome represents a set of symptoms and signs caused by compression of the distal portion of the median nerve in the carpal tunnel, defined in 1951 by Brian McArdle [1, 2].

Epidemiological data indicate that carpal tunnel syndrome is the most frequent mononeuropathy, prevalent in 2.7% of general population. Women are three times more likely to develop the carpal tunnel syndrome than men, and it mostly appears in the 5th and 6th decade of life [3]. Carpal tunnel syndrome

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Abbreviations
EMG – electroneurography

has a significant negative effect on the functionality and the quality of daily activities [4].

There is a large number of potential causes of carpal tunnel syndrome. The bifid median nerve, an anatomical variation of the branching of the median nerve happening already in the carpal tunnel, represents one of the rare causes of carpal tunnel syndrome, with frequency from 0.8% to 2.8%; recently, ultrasonographic findings have shown the prevalence of 18.5%. Arbitrarily, the nerve could be "complete" or "incomplete". The "complete" bifid median nerve is rarer, with the prevalence of 5% [1, 3, 5, 6], which affects the nerve and/or its environment by raising the intracanalicular pressure above 30 mm/Hg (normal values being 7 – 8 mm/Hg) and creates disproportion between the nerve volume and the tunnel space resulting in myelin remodeling, damage of axonal transport, the initiation of the cascade of ischemic nerve changes and the creation of intraneural connective tissue. After eliminating the causal factor, nerve remyelination is possible after several weeks [7, 8].

The main symptoms include paresthesia and pain in hands in the area of innervation of the median nerve (except the thenar area), with a possible propagation towards the shoulder, intensifying during the night and when performing certain activities (holding a telephone or a book…). Furthermore, thenar weakness is possible, accompanied by positive pathognomonic test results (Phalen's maneuver, Tinel's sign, carpal-compression test, and rarely used reverse Phalen's maneuver, hand elevation test, tourniquet test, Okutsu test) [1, 9–11]. Sensory symptoms are missing in the case of "pure motor carpal tunnel syndrome" [3].

Possible differential-diagnostic conditions include neuropathy of the median nerve in other locations (entrapment at the level of the Struthers' ligament, pronator syndrome, anterior interosseous nerve syndrome…), damage to the brachial plexus, radiculopathy (primarily of C6 and C7), initial forms of certain polyneuropathies (multifocal motor polyneuropathy, multifocal acquired demyelinating sensorimotor polyneuropathy), as well as migraines, focal epileptic seizures and transient ischemic attacks [1, 7].

Diagnosis of the carpal tunnel syndrome is primarily based on clinical symptoms, whereby electromyoneurography is a diagnostic method of choice. In addition to the confirmation of the diagnosis, information the degree of severity (mild, moderate and severe), the duration (frequently subacute or chronic), and other accompanying conditions. The conventional, routine and mandatory electromyoneurography includes, among others, placing electrodes on the pointer finger in order to register the sensory neurogram, as well as electrodes on the short adductor pollicis muscle in order to register the motor neurogram of the median nerve (external motor branch). Optionally, in case the previous results were in order, examination of lumbrical muscles and dorsal interossei muscles (internal motor branch), or examination of sensory latencies from the first finger of the median and radial nerve (external sensory branch) are also used in addition to other possibilities [3, 12, 13]. Presence of neurophysiological dissociation can be noted in these cases, which may only suggest the presence of the bifid median nerve, but cannot confirm it [5]. In these and other electromyoneurography possibilities, false negative results are found in 16 – 34% examinations [14].

After the examination, it is necessary to do an X–ray of the carpal area and routine lab tests [3, 12]. Ultrasonic examination of peripheral nerves has become a complementary method to electromyography, which not only helps to verify the diagnosis, but also to observe the structure of the median nerve and its environment, and to determine the degree of severity – a diagnostic technique which is used for detecting the bifid median nerve [15–17]. Nuclear magnetic resonance, primarily magnetic neurography, has proven to be a method of similar usefulness, but has not been routinely established yet [18].

Conventional treatment can be non-operative and operative. In the absence of direct external compression, conservative therapy consisting of immobilization and perineural application of corticosteroids are the first choice for the treatment of mild and moderate carpal tunnel syndrome. Immobilization is performed by wearing a special-purpose wrist orthosis during sleep for the period of three weeks. The application of corticosteroid therapy is contraindicated in the case of impaired skin integrity in the carpal tunnel area and in the presence of local infections as is relates to certain side effects –median nerve, ligament or blood vessel injuries. Surgical treatment is performed in cases of unsuccessful conservative treatment for the period of six months with a direct external cause of compression, and in the case of a severe carpal tunnel syndrome [3, 9, 19].

Treatment success rates vary from 40% with conservative therapy to 85% with surgical treatment [20]. The presence of the bifid median nerve poses a risk for the success of surgical approach [5].

Case Report

A 48-year-old patient, after a clinical suspicion of carpal tunnel syndrome (dominant night-time numbness of the second, third and outer half of the fourth finger on the palm side lasting for several months, accompanied by a positive Phalen's maneuver), has been confirmed by ultrasonography to be suffering from moderate carpal tunnel syndrome, with a detection of "incomplete" bifid median nerve in the carpal tunnel. The examination was performed with use of an ultrasound device Samsung Medison Co., LTD (Gangwon-do, Republic of Korea), with high-resolution linear probe 3-16 MHz **(Figure 1A)**. The existing ultrasonography results were afterwards verified on a magnetic resonance device using the 16-channel SENSE neuro-vascular coil, Philips Achieve, 1.5 – T **(Figure 1B).**

Electromyoneurography was performed conventionally and routinely on the median and ulnar nerve system with use of the Neuropack, Nihon Kohden

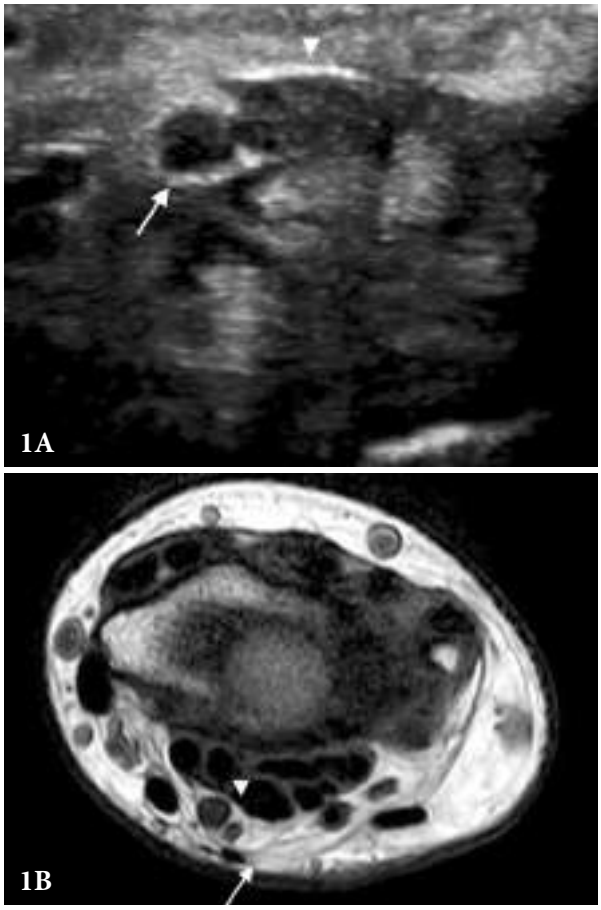

Figure 1A and B. Ultrasound and magnetic resonance of the "incomplete" bifid median nerve in the left-hand area. Asymptomatic external branch of the bifid median nerve, with the cross-sectional area of 6 mm^2 (represented by the arrow); symptomatic internal branch, with the cross-sectional area of 15 mm^2 (represented by the arrowhead).
Slika 1A i B. *Ultrazvuk i magnetna rezonancija "inkompletnog" bifidnog medijalnog nerva u nivou levog ručja. Asimptomatska spoljašnja grana bifidnog medijalnog nerva, površine poprečnog preseka 6 mm^2 (strelica); simptomatska unutrašnja grana, površine poprečnog preseka 15 mm^2 (glava strelice).*

device (Tokyo, Japan). Additionally, the electromyoneurography also confirmed a mild level of carpal tunnel syndrome **(Table 1)**. However, as difficulties were exclusively present in the innervation area of the median nerve internal branch, and due to the encouraging results of the imaging techniques and the possibility of incomplete correlation of electromyoneurography results, the lumbrical muscles and dorsal interossei muscles were examined. A significant difference in distal latencies of the median and ulnar nerve motor neurogram were registered using this technique (median nerve 4.3 ms, ulnar nerve 2.7 ms). The applied method confirmed a moderate degree of carpal tunnel syndrome.

Other potentially predisposing and causative factors were excluded by means of clinical and supplementary diagnostic methods.

The treatment was conducted with conventional approach, night-time immobilization for several months, and physical therapy, after which the patient showed a significant reduction of difficulties, followed by adequate objective findings.

Discussion

After a clinical suspicion of carpal tunnel syndrome, the ultrasonography and magnetic resonance imaging confirmed that the patient suffers from carpal tunnel syndrome and "incomplete" bifid median nerve was also diagnosed. In addition, a high degree of correlation between the clinical and imaging results was noticed – the internal branch of the bifid median nerve was symptomatic.

Conventional electroneurography (EMG) registered a status on the sensory fibers of the bifid median nerve internal branch, where affectedness was detected. Registration of a status on motor fibers of the bifid median nerve internal branch was also conducted at that point, but no damage was detected. It was concluded on the basis on these results that there is a mild degree of carpal tunnel syndrome. However, due to the fact that clinical and supplementary diagnostic findings showed a possibility of lesion on motor fibers of the internal branch (which was not found by the routine EMG), the lumbrical muscles and dorsal interossei muscles were examined, and damage to these fibers was detected. Therefore, the severity of the carpal tunnel syndrome was redefined as moderate.

The above shows that affectedness of exclusively one branch of the bifid median nerve and the application of conventional EMG may only cause a possibi-lity of false negative findings (in cases of damage on sensory fibers of the external branch, as neurography examinations are conducted only on sensory fibers of the internal branch) or insuffi-

Table 1. Electroneurography
Tabela 1. *Elektroneurografsko ispitivanje*

Nerve *Nerv*	Distal latency *Distalna latenca* (ms)	Conduction velocity *Brzina provođenja* (m/sec)	Amplitude *Amplituda*	
Median left side/*Medijanus levostrani*	3.7	57.9	9.3 mV	Motor study
Ulnar left side/*Ulnaris levostrani*	2.3	56.8	7.4 mV	*Motorna studija*
Median left side/*Medijanus levostrani*	3.4	38.5	11.7 μV	Sensor study
Ulnar left side/*Ulnaris levostrani*	2.7	52.2	48.2 μV	*Senzorna studija*

ciently valid findings (like in our case report, or in case of moderate damage to the external branch, when only damage on motor fibers is registered, when a wrong conclusion can be drawn about the pure carpal tunnel syndrome). In these cases, clinical findings can indicate application of an optional technique (examination of lumbrical muscles and dorsal interossei muscles (for motor fibers of the internal branch), i.e., examination of sensory latencies from the first finger of the median and radial nerve (for sensory fibers of the external branch))), which would provide a complete electromyoneurographic definition of these conditions.

Electromyoneurographic examinations that detect damage to exclusively one branch of the median nerve should raise suspicion about the existence of the bifid median nerve as a potential cause of carpal tunnel syndrome. A correct grading system of the severity levels of this syndrome, as well as verification of presence of this anatomical variation of the nerve, should result in a more successful selection of therapeutical options, and reduction of potential risks in case of surgical approach.

Conclusion

In certain cases, including the bifid median nerve, conventional, routine techniques are not completely reliable for establishing the appropriate electromyoneurographic verification and grading of the severity level of the carpal tunnel syndrome.

In case of carpal tunnel syndrome with electromyoneurographic disruption of only sensory or motor pathways of the median nerve, it would be mandatory to use one of the optional techniques, which would ensure getting more valid findings.

Furthermore, if the findings differ from the ones provided by the routine approach, and electromyoneurography was introduced as the initial supplementary diagnostic method, it would be mandatory to perform ultrasonography of peripheral nerves or magnetic resonance neurography as there is a possibility that the carpal tunnel syndrome is caused by the bifid median nerve.

This kind of approach would result in a more successful selection of certain therapeutical modalities and, furthermore, it would cause reduction of risks during the surgical treatment.

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SYNOVIAL SARCOMA OF THE HAND – CASE REPORT AND LITERATURE REVIEW

SINOVIJALNI SARKOM ŠAKE – PRIKAZ SLUČAJA I PREGLED LITERATURE

Sveto BJELAN[1], Mladen JOVANOVIĆ[1, 2], Vanja TATALOVIĆ[1] and Stefan KECMAN[1]

Summary

Introduction. Synovial sarcoma is a rare malignant tumor most often localized on the lower limbs near large joints. Histopathology findings is the gold standard for making the diagnosis. However, due to the similarity with other tumors, the findings can be misinterpreted and the correct diagnosis often delayed, and the treatment is inadequate in the early stages of the disease inadequate. **Case Report.** A 15-year-old female patient came for an examination due to subcutaneous lesion in her hand. The lesion was excised on three occasions due to recurrence, and each time the histopathology findings showed a dermatofibroma. After five years, the patient returned due to the changes under the scar and unpleasant sensations. A surgical excision was performed when dermatofibroma was verified. Two years later, the patient developed necrosis of the entire finger. The finger was amputated, and synovial sarcoma was verified. The patient underwent 25 cycles of radiotherapy. In the following year and a half, the tumor developed metastases, first locoregional and then distant, in the region of the left shoulder joint and the left lung. **Conclusion.** The histopathological similarity of this tumor with other benign changes indicates the need for further evaluation and differentiation of the pathohistological characteristics from tumors with similar characteristics. Early detection of this type of tumor enables a more favorable course and outcome of the treatment of these patients. Initial radical surgical treatment of this type of tumor is necessary due to the aggressiveness they show and the high frequency of local recurrence.

Key words: Sarcoma, Synovial; Hand; Soft Tissue Neoplasms; Diagnosis, Differential; Diagnostic Errors; Neoplasms; Recurrence

Sažetak

Uvod. Sinovijalni sarkom je redak maligni tumor najčešće lokalizovan na donjim ekstremitetima u okolini velikih zglobova. Zlatni standard za postavljanje dijagnoze je patohistološki nalaz. Međutim, zbog sličnosti sa drugim tumorskim promenama, nalaz se može pogrešno protumačiti te je postavljanje prave dijagnoze često odloženo, a lečenje neadekvatno u ranim fazama bolesti. **Prikaz slučaja.** Petnaestogodišnja pacijentkinja se javila na pregled zbog promene na šaci. Promena je ekscidirana u tri navrata zbog recidiviranja i sva tri puta je patohistološki nalaz ukazivao na dermatofibrom. Nakon pet godina pacijentkinja se javlja zbog promene ispod ožiljka i neprijatnih senzacija. Urađena je hirurška ekscizija kada je patohistološkim nalazom verifikovan dermatofibrom. Dve godine kasnije kod pacijentkinje se razvila nekroza celog prsta, zbog čega se javila na kontrolni pregled. Prst je amputiran, a patohistološkom analizom je verifikovan sinovijalni sarkom. Kod pacijentkinje je potom sprovedeno 25 ciklusa radioterapije. U narednih godinu i po dana je ovaj tumor dao metastaze, prvo lokoregionalne, a potom i udaljene, u predelu zgloba levog ramena i levog plućnog krila. **Zaključak.** Patohistološka sličnost ovog tumora sa drugim benignim promenama ukazuje na potrebu za daljom evaluacijom i diferencijacijom patohistoloških karakteristika od tumora srodnih karakteristika. Rano otkrivanje ove vrste tumora omogućava povoljniji tok i ishod lečenja ovih pacijenata. Neophodno je inicijalno radikalno hirurško lečenje ove vrste tumora zbog agresivnosti koju pokazuju kao i velike učestalosti lokalnog recidiva.

Ključne reči: sinovijalni sarkom; šaka; neoplazme mekog tkiva; diferencijalna dijagnoza; dijagnostičke greške; metastaze; recidivi

Introduction

Synovial sarcoma is a relatively rare malignant tumor, most often localized around joints, tendons or bursae, but can also be found outside these areas. The prevalence of this tumor is high in patients between 10 and 40 years [1]. It is usually localized near the large joints of the extremities, especially around the knee and ankle [2,3], while localization on the hand is less common. Tumor manifestation on fingers, in contrast to the carpal region, is extremely rare, which is the case here. Diagnosing synovial sarcoma can be extremely exhausting and time-consuming. Studies show that the average period from the appearance of the first symptoms to the correct diagnosis is 2 to 5, and sometimes even up to 20 years [1, 4]. The main symptom is a slow-growing subcutaneous tumor, and in addition, there is a pulsating pain that is also insufficiently specific for making the diagnosis [1, 3]. Histopathological verification is the gold standard for determining the diagnosis. A tumoral change can rarely be seen on an X-ray image. Magnetic resonance imaging (MRI) can be used as an important tool in establishing the diagnosis, but also in determining the limits of the change and the margins of the sur-

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Abbreviations
MRI – magnetic resonance imaging
HP – histopathology

gical resection. Current therapy consists of multimodal treatment that includes radical surgical excision, systemic and perfusion chemotherapy, as well as radiotherapy [3,6]. This case report has a long and unusual path to the accurate diagnosis, as well as the unusual localization, and unfortunately unfavorable course too. It aims to draw the attention of clinical doctors and pathologists, to facilitate faster diagnosis of synovial sarcoma, and to make the relevant data available that could possibly be used in setting guidelines for the diagnosis and surgical resection.

Case report

A 20-year-old female patient came the first time to the outpatient department of the Clinic for Plastic and Reconstructive Surgery of the University Clinical Center of Vojvodina due to subcutaneous tumor and thickening of palmar skin at the level of the proximal interphalangeal joint of the index finger. Inspection of the medical documents revealed that the symptoms such as hardening and unusual feeling dated back 5 years, when excision with histopathology (HP) verification was performed on several occasions. Each time, the findings indicated a benign change - cutaneous fibrous histiocytoma (CFH). Re-excision of the change with HP verification was indicated in our facility, when the histopathology findings showed a dermatofibroma (plaque-like CD34+ dermatofibroma). During further treatment, the patient had complications such as wound dehiscence and infection, which were treated with local and systemic antibiotic therapy, to which an adequate response was obtained. After the wound complete healed, the patient was referred for physical therapy. A control X-ray examination of the hand and an ultrasound of the soft tissues in the scar area were advised in further follow-up. The patient failed to appear for the scheduled follow-up examination.

Two years later, the patient came for examination due to pain, with severe necrosis of the index finger and signs of local infection – purulent discharge and complete stiffness of the second finger. Active mobility in any of the three index joints was impossible **(Figures 1 and 2)**. After the examination, a decision was made to amputate the patient's index finger under general anesthesia. Intraoperative observation showed that the metacarpophalangeal joint was also affected by necrosis, and the index finger was amputated with partial resection of the head of the second metacarpal bone. The resected part was sent for HP verification, when the diagnosis of synovial sarcoma was obtained after several revisions and mutual consultations of several pathologists **(Figure 3)**, although it was initially described as a benign tumor (histiocytoma, dermatofibroma). The histopathology description read: "Tumor cells are spindle-shaped and arranged in bundles, bands and smaller swirls. Blood vessels are irregularly shaped, branched in places. The tumor tissue spreads along the hypocellular c+ connective tissue in the tendon. Immunohistochemical tissue is positive for vimentin, CKAE1/AE3, EMA and focally for CD56. Negative for SMA, S100 and CD31. The finding is in favor of a synovial sarcoma." Macroscopically, the color of the tumor was black-grey. The bone marrow of the second metacarpal bone was free of tumor elements. The free tumor margin was at least 1.5 cm. The postoperative period passed without complications. The patient

Figures 1 and 2. Index finger necrosis
Slike 1 i 2. *Nekroza kažiprsta*

Figure 3. Low magnification (10x) photomicrographs of hematoxylin and eosin-stained sections showing numerous cells packed in bundles and whorls
Slika 3. *Mikrofotografije niskog uvećanja (10x) hematoksilin i eosin obojeni delovi pokazuju brojne ćelije upakovane u vijuge i snopove*

was then presented to the Oncology Committee for Soft Tissue Tumors of the Institute of Oncology of Vojvodina, which indicated further follow-up.

Less than a year after the last operation, the patient noticed hardening in the scar area and felt pain. She was referred for an MRI, which showed a vaguely limited signal characteristic of pathologically altered tissue with propagation through the distal parts of the second metacarpal bone **(Figure 4)**, and further operative treatment was indicated. The patient underwent reamputation of the second metacarpal bone and capsulectomy of the third metacarpophalangeal joint under general anesthesia **(Figure 5)**. The wound healed properly. The patient underwent physical therapy, and disease propagation was obtained as a HP finding, with clear margins again. In the course of further diagnostics, there were no signs of dissemination of the underlying disease on the computed tomography of the chest, abdomen and pelvis, which were performed after the operation. The patient was presented again

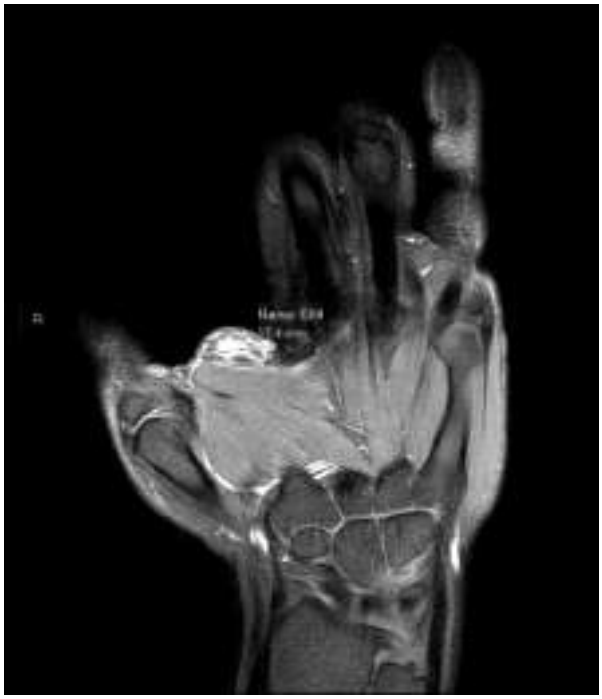

Figure 4. Disease propagation on the second metacarpal bone
Slika 4. *Propagacija bolesti na drugu metakarpalnu kost*

to the Oncology Committee for Soft Tissue Tumors, which indicated 25 cycles of radiotherapy that were fully implemented. No local recurrence or systemic dissemination of the disease was recorded in further control examinations and repeated diagnostics, and further follow-up was indicated.

Over a year after the second operation, during the control examination, small multiple skin lesions were

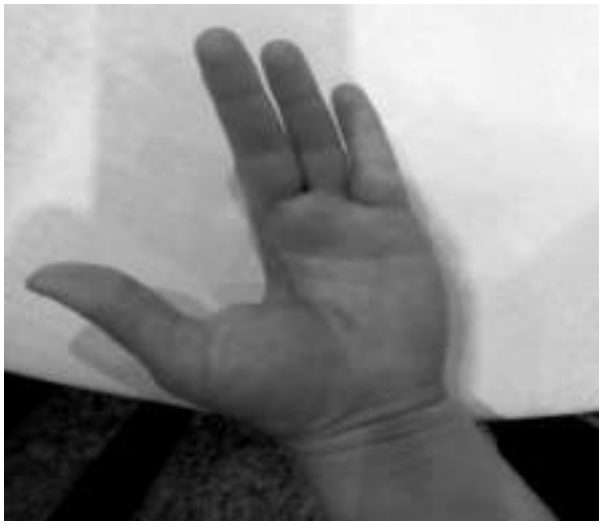

Figure 5. Condition after amputation of the second metacarpal bone and partial capsulectomy of the third metacarpophalangeal joint
Slika 5. *Stanje nakon amputacije druge metakarpalne kosti i parcijalne kapsulektomije trećeg metakarpofalangealnog zgloba*

found on the palm in the projection of the first metacarpal bone with a diameter of up to 5 mm. Similar changes were observed in the area of the left axillary region. Enlarged lymph nodes in the axilla were not observed. Biopsy of the changes under local anesthesia with HP verification was recommended, which the patient refused due to her early pregnancy. A delayed biopsy was performed three months later, and the HP showed a ring granuloma, DDx necrobiotic interstitial granulomatous dermatitis, without signs of the previously diagnosed tumor elements. Enlargement of the regional lymph nodes of the axilla was observed during the control examination. The Council of Gynecology Specialists made a decision to terminate the pregnancy due to high possibility of the paraneoplastic syndrome, which is why the patient was hospitalized at the Clinic of Gynecology and Obstetrics, University Clinical Center of Vojvodina. During her stay at the Clinic, the patient developed left arm swelling with severe pain in the shoulder joint area and a urinary infection, accompanied by high values of laboratory markers of inflammation. After discharge, an MRI of the chest with the shoulder joint was performed, where a massive tumor bony infiltration of the glenoid, the proximal humerus, clavicle, acromion and the left sternoclavicular joint was observed **(Figure 6)**. The MRI also showed ipsilateral infiltration of the lung parenchyma, as well as pathological changes and enlargement of the left axillary lymph nodes. The patient was again referred to the Oncology Committee that will decide on further systemic treatment, given that further surgical treatment is not indicated at this time.

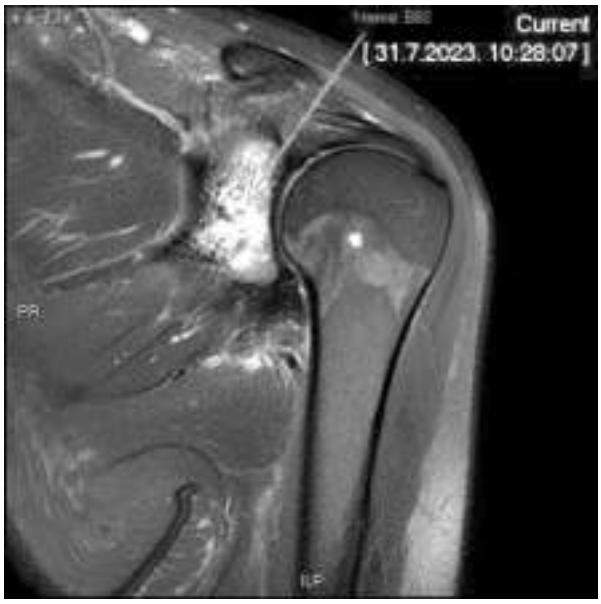

Figure 6. Massive bony infiltration of the glenoid, proximal part of the humerus, clavicle, acromion and the left sternoclavicular joint.
Slika 6. *Masivna koštana infiltracija glenoida, proksimalnog dela humerusa, klavikule, akromiona i levog sternoklavikularnog zgloba*

Discussion

Synovial sarcoma is a highly malignant tumor, rarely occurring in clinical practice, with an incidence of 1.42 per million adults in the United States [7]. Synovial sarcomas in the hand region have a very low incidence compared to other localizations, with a frequency of 4-8.5% in different studies [2, 8, 9], while fingers are affected less often than hands [10]. However, in a Serinelli S, et al. study, there was an increase in the number of synovial sarcomas of the hand, especially on the palmar side of the fingers [1]. It can be seen in the above case that the tumor was not recognized for a long time, and that the histopathology diagnosis of benign lesions combined with the patient's lack of motivation affected the unfavorable course of the disease. This case is extremely unusual given that the diagnosis of the malignant disease was made by at least three different pathologists after four histopathology analysis that showed the benignity, which can be explained by the histopathological similarity of this malignant tumor with benign changes. Benign lesions such as histiocytoma, dermatofibroma or annular granuloma may correspond to this tumor according to the pathohistological characteristics. Therefore, it is sometimes necessary to perform additional diagnostic methods, primarily immunohistochemical analysis, especially for the recurring changes, in order to establish a differential diagnosis. The study by Serinelli also shows that the tumor was initially misrecognized as a benign change such as abscess and arthritis in about 30% cases [1]. Despite their name, synovial sarcomas do not arise from synovium, their histogenesis is still unclear [11, 12]. The Naka N, et al. study suggests that the origin of this tumor may be from a multipotent mesenchymal stem cell [13].

During the excision of the change, one should consider the specificity of localization and the fact that fingers, being a functionally extremely important part of the body, have limited possibilities for skin and soft tissue reconstruction, which makes it difficult to achieve wide surgical margins [14]. Radical surgical excision was the treatment of choice in most studies. However, adjuvant radiotherapy and chemotherapy were used in 50% of cases [1], while in another study, 30% of patients received radiotherapy and only 5% received immunotherapy [8], which indicates the increasingly widespread use of adjuvant chemo- and radiotherapy after surgical excision of such changes. Damron et al. believe that standard therapy, in addition to radical excision, should always include adjuvant radiotherapy or chemotherapy [15]. Radiation therapy can improve local disease control [16]. Davis et al. observed that the choice of initial treatment affects the final oncological outcome of the disease [17]. The recurrence rate in the studies was from 33 to 80% of cases, depending on the literature [1, 6], which indicates a high degree of malignancy of this type of tumor.

Conclusion

After analyzing the clinical course of this case, it is necessary to emphasize that synovial sarcoma is very difficult to recognize in the early stages of the disease and that pathologists and clinical doctors should always suspect this type of tumor, which often gives unfavorable outcomes due to late detection. Examples from this and other mentioned papers indicate that one cannot always fully rely on histopathology verification and that the clinical course is also an important part, especially in the cases where changes recur. Early detection of this type of tumor enables a more favorable course and outcome of the treatment of these patients. It is necessary to consider the initially more radical treatment of such tumors due to the aggressiveness they show. Further evaluation and differentiation of the pathohistological characteristics of synovial sarcoma from tumors with similar characteristics and appearance in the clearest cases will allow for easier recognition of this type of malignant mesenchymal tumor in the initial stages of the disease, which will significantly affect the treatment prognosis. Also, it is necessary to emphasize the importance of health education of the general population, which could improve compliance.

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THE IMPORTANCE OF EARLY DIAGNOSIS AND TREATMENT IN PATIENTS WITH ANKYLOSING SPONDYLITIS – CASE REPORT

ZNAČAJ RANOG OTKRIVANJA I LEČENJA BOLESNIKA SA ANKILOZIRAJUĆIM SPONDILITISOM − PRIKAZ SLUČAJA

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Summary

Introduction. Ankylosing spondylitis is a common, chronic musculoskeletal condition associated with substantial functional limitations. Inflammation in later phases of the disease may lead to fibrosis and calcification of the spine, causing poor quality of life. This case report emphasizes the importance of early diagnosis of ankylosing spondylitis as one of the major factors in further course of the disease. **Case report.** A 27-year-old man was diagnosed with ankylosing spondylitis in 2019. He was first time examined in 2005 because of joint pain which was then characterized as growing pains. Symptoms of joint pain reappeared approximately 10 years later, and were present in lumbar and thoracic spine accompanied by morning stiffness. New pain spots also appeared, as well as positive laboratory results regarding inflammation. Despite the lasting diarrhea, additional tests such as anti-smooth muscle and anti-mitochondrial antibody, Hepatitis B surface Antigen and anti-Hepatitis C virus antibody test as well as stool test results all turned out to be negative. The magnetic resonance imaging showed edema of lower edges of the lumbosacral corpus, most likely as part of spondylitis, changes to the sacroiliac joints in terms of chronic phase of sacroiliitis with discrete activity, and right shoulder active synovitis. The human lymphocyte antigen B27 testing showed positive results. Despite the prescribed medical therapy, the disease activity remained high with positive clinical presentation. This patient may be a candidate for biological therapy. **Conclusion.** Early diagnosis and effective treatment provide reduction of pain, fatigue and disease activity and also prevent functional limitations, therefore improving the quality of life.

Key words: Spondylitis, Ankylosing; Early Diagnosis; Risk Factors; Treatment Outcome; Pain; Quality of Life

Sažetak

Uvod. Ankilozirajući spondilitis predstavlja hronično muskuloskeletno oboljenje praćeno postepenom funkcionalnom onesposobljenošću. U kasnijim fazama inflamacija u sklopu ovog oboljenja može dovesti do fibroze i kalcifikacije kičme sa posledičnim smanjenjem kvaliteta života. Ovaj prikaz slučaja naglašava značaj ranog dijagnostikovanja ankilozirajućeg spondilitisa kao jednog od bitnih faktora u daljem toku same bolesti. **Prikaz slučaja.** Dvadesetsedmogodišnjem bolesniku je ankilozirajući spondilitis dijagnostikovan 2019. godine. Bolesnik je prvi put pregledan zbog bolova u zglobovima 2005. godine, kada je bol povezan sa rastom i razvojem. Međutim nakon deset godina javili su se bolovi u području slabinskog i grudnog dela kičme praćeni jutarnjom ukočenošću. Takođe, javila su se i nova bolna mesta uz pozitivne laboratorijske nalaze u pravcu inflamacije. Uprkos perzistentnim dijarejama dodatna ispitivanja koprokulture, antiglatkomišićna i antimitohondrijalna antitela kao i antihepatitis B površni antigen i antihepatitis C virus antitela su pokazala negativan rezultat. Magnetnorezonantnom tehnikom prikazan je otok donjih delova tela slabinsko-trtičnih pršljenova najpre u sklopu spondilitisa, promene u sakroilijačnom zglobu u pravcu hroničnog sakroiliitisa sa diskretnom aktivnosti kao i sinovitis desnog ramena. Nalaz humanog leukocitnog antigena B27 pokazao je pozitivan rezultat. Uprkos prepisanoj medikamentnoj terapiji registruje se visoka aktivnost bolesti praćena pozitivnim kliničkim nalazom. Prikazani bolesnik je potencijalno kandidat za biološku terapiju. **Zaključak.** Rano postavljena dijagnoza ankilozirajućeg spondilitisa kao i efektivna terapija omogućavaju smanjenje intenziteta bola, napora, aktivnosti bolesti i preveniraju funkcionalna ograničenja, a time poboljšavaju kvalitet života pacijenata obolelih od ankilozirajućeg spondilitisa.

Ključne reči: ankilozirajući spondilitis; rana dijagnoza; faktori rizika; ishod lečenja; bol; kvalitet života

Introduction

Ankylosing spondylitis (AS) is an autoimmune disease that mainly involves spine joints, sacroiliac joints (SIJs) and their adjacent soft tissues, such as tendons and ligaments [1].

In more advanced cases, it can cause immobile position due to fibrosis and calcification. AS primarily manifests with back pain, spinal rigidity, and inflammation in the joints, fingers or toes. However, extra-articular manifestations such as acute anterior uveitis and inflammatory bowel disease (IBD) can

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Abbreviations

AS – ankylosing spondylitis
SIJs – sacroiliac joints
IBD – inflammatory bowel disease
HLA B27 – human lymphocyte antigen B27
NSAIDs – anti-inflammatory drugs
MRI – magnetic resonance imaging
BASMI – Bath Ankylosing Spondylitis Metrology Index
BASDAI – Bath Ankylosing Spondylitis Disease Activity Index
BASFI – Bath Ankylosing Spondylitis Functional Index
ASDAS – Ankylosing Spondylitis Disease Activity Score
CD – Crohn's disease
SpA – axial spondyloarthritis

also occur [2]. Crohn's disease (CD) and ulcerative colitis occur in 5-10% of patients with AS due to genetic, clinical, immunological, and microbial connections between AS and CD [3, 4].

The prevalence of AS is generally believed to be between 0.1% and 1.4% globally [5].

It is important to note that the human lymphocyte antigen B27 (HLA B27) gene is present in approximately 90% of individuals with Ankylosing Spondylitis (AS), while it is found in less than 8% of the general population. However, the exact mechanism by which this gene contributes to the development of AS remains uncertain [6]. HLA B27 also plays a crucial role in the diagnosis, classification, and severity of axial spondyloarthritis (SpA) [7].

This case report emphasizes the importance of early diagnosis of ankylosing spondylitis as one of the major factors in further course of the disease.

Case report

A 27-year-old man, was diagnosed with ankylosing spondylitis in 2019. The patient did not have any underlaying comorbidities. He was first examined in 2005 because of joint pain that was then characterized as growth pains. The symptoms of joint pain reoccurred approximately 10 years later and were present in lumbar and thoracic spine accompanied by morning stiffness. He was treated by a physiatrist only with nonsteroidal anti-inflammatory drugs (NSAIDs) with transient improving effect. Looking at the chronicity of his problem, especially with minimal improvement and new pain spots, he was suggested to an X-ray of the right shoulder in regard to the newly onset symptoms. Meanwhile he had episodes of one-month lasting diarrheas without increased body temperature. Laboratory findings showed a confirmed inflammatory syndrome (sedimentation-SE 90 mm/h and C reactive protein - CRP 150 mg/l) followed by the increased level of transaminases. He underwent additional testing such as anti-smooth muscle antibody (ASMA) and anti-mitochondrial antibody (AMA), Hepatitis B surface Antigen (HBsAg) and anti-hepatitis C virus antibody (HCV), as well as a stool test, which all turned out to be negative. As the right shoulder X-ray showed deformity of the humerus head and reverse cervical lordosis, he was referred for further testing. The magnetic resonance imaging (MRI) showed edema of lower edges of the lumbosacral corpus, most likely as part of spondylitis, changes in the sacroiliac joints (SIJs) in terms of chronic phase of sacroiliitis with discrete activity and right shoulder active synovitis. HLA testing showed HLAB27 positivity. The patient was diagnosed with ankylosing spondylitis and started sulfasalazine and methylprednisolone therapy. Methylprednisolone therapy was soon discontinued. Furthermore, the patient was eligible for biological therapy, but was rejected as his condition got complicated by a urogenital infection. Since his condition did not improve (Bath Ankylosing Spondylitis Metrology Index- BASMI 6.8, Bath Ankylosing Spondylitis Disease Activity Index – BASDAI 6.1, Bath Ankylosing Spondylitis Functional Index – BASFI 5.8, Ankylosing Spondylitis Disease Activity Score – ASDAS 5.06) the sulfasalazine doses accompanied with NSAIDs were increased and he was advised to do a new MRI scan of spine and shoulder in the next three months. His latest results of the MRI scans showed the already seen signs of spondylitis and synovitis followed with high disease activity (BASDAI 4.95, BASFI 7.0, ASDAS 5.48) and positive inflammatory results. Bone density scan (DEXA) was referent. Clinical presentation showed positive Mennell's sign, thoracic kyphosis, Schober test 1 cm, tragus to wall test 20 cm, Thomayer distance 40 cm, respiratory index 4 cm, lateral flexion 4 cm and cervical rotation 10 cm. Finally, after the urogenital infection healed, he was approved to take the biological drugs.

Discussion

The prognosis of patients with AS varies depending on the presence of extraspinal manifestations (i.e. uveitis, psoriasis, and IBD), age at diagnosis and the treatment received [8, 9]. AS usually initially appears during the third decade of life, and rarely after the age of 45 [5]. However, diagnosis of AS is often delayed. Since AS is a rare condition, both medical professionals and patients are less familiar with it compared to the more common back disorders [10–12]. Compared to other rheumatic diseases, patients usually experience a delay between symptoms and diagnosis [13]. European data indicate an average time from symptom onset to diagnosis of between 8.5 and 11 years [14, 15]. A key reason for the delay in AS diagnosis is the requirement for radiographic evidence of sacroiliitis [16]. Radiographic changes develop slowly, with only 70% of AS patients fulfilling these diagnostic criteria after 5 years of symptoms [17]. Even though it has been reported that onset before the age of 10 or after the age of 45 is rare, approximately 15% of patients have onset of their disease in childhood (before the age of 16), but this percentage may be as high as 40% in some developing countries [18, 19].

Various studies conducted in China, Taiwan, and India have revealed that juvenile-onset AS patients are more prone to experiencing hip involvement than those with adult-onset AS. Due to substantial individual differences in clinical manifestations and the developmental stage of sacroiliac joints in children,

imaging diagnoses are limited, potentially leading to delayed diagnosis. Within 10 to 15 years, approximately 40% of juvenile spondyloarthropathy patients progress to functional disability, and hip involvement has been closely linked to a poor prognosis [20]. Considering all these facts, there is a need to develop a distinct strategy for children and adolescents with SpA.

Early diagnosis of spondylitis of any cause can significantly affect the patients' quality of life, but also reduce treatment costs before any accompanying complications occur [21].

Conclusion

Early diagnosis and effective treatment provide reduction of pain, fatigue and disease activity and also prevent functional limitations, therefore improving the quality of life.

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DO NOT ATTEMPT CARDIOPULMONARY RESUSCITATION – ETHICAL ASPECTS

ODLUKA O NEZAPOČINJANJU KARDIOPULMONALNE REANIMACIJE – ETIČKI ASPEKTI

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Summary

Introduction. "Do Not Attempt Cardiopulmonary Resuscitation" is a clear decision not to initiate resuscitation in the final stages of the disease. This decision shall be made if it is assessed that health will not be improved after resuscitation, and it can be made by the patient, family, or the medical team. **Informed patient consent - "Code status".** Informed patient consent or "Code status" refers to the type of medical treatment the patient wants medical personnel to apply or not to apply in case of cardiac arrest. Patients make a decision about no resuscitated while they are in a situation to consciously make decisions, or authorize family members or guardians to make and implement such a decision for them. There might be a problem with patients and their families not fully understanding the meaning and the process of resuscitation, the prognosis, risks, and consequences. They do not understand the terms of short-term and long-term survival rates and post-resuscitation quality of life. **Do not attempt Cardiopulmonary Resuscitation.** According to the current guidelines from the European Resuscitation Council, a joint decision on cardiopulmonary resuscitation planned in advance should be the first priority from the ethical standpoint. The decision-making team should take into account the patient's wishes when making the decision about cardiopulmonary resuscitation, thus, the end-of-life discussions with patients are necessary. **The practice of ethics.** It is necessary to know when to start and when to stop with cardiopulmonary resuscitation. Several criteria need to be taken into account when making a decision not to initiate cardiopulmonary resuscitation. One unambiguous criterion is the safety of the rescuer. **Conclusion**. Continuous research is also needed to improve knowledge in this area and facilitate decision-making and improve post-resuscitation survival and quality of life for these patients.

Key words: Cardiopulmonary Resuscitation; Ethics; Decision Making; Resuscitation Orders; Death; Critical Illness

Sažetak

Uvod. *Do not attempt Cardiopulmonary Resuscitation* predstavlja jasnu odluku o nezapočinjanju reanimacije. Ta odluka se donosi ukoliko je procena da nakon reanimacionog postupka neće doći do unapređenja zdravlja; mogu je doneti pacijent, porodica ili medicinski tim. **Informativni pristanak pacijenata.** Informativni pristanak pacijenta ili *Code status* podrazumeva vrstu medicinskog tretmana koju pacijent želi da medicinsko osoblje primeni ili ne primeni u slučaju srčanog zastoja. Pacijenti donose odluku o nereanimiranju dok su u situaciji da svesno donose odluke ili daju ovlašćenje članovima porodice ili starateljima da umesto njih donesu i sprovedu tu odluku. Problem može biti to što pacijenti, kao i njihove porodice ne razumeju u potpunosti značenje i postupak reanimacije, prognozu, rizik i posledice. Ne razumeju termine kratkoročnih i dugoročnih stopa preživljavanja i postreanimacionog kvaliteta života. **Odluka o nezapočinjanju resustitucije.** Prema trenutnim smernicama Evropskog saveta za reanimaciju (*European Resustitation Council*), sa etičkog aspekta, na prvom mestu treba da postoji unapred isplanirana zajednjička odluka o kardiopulmonalnoj reanimaciji. Tim koji odlučuje treba prilikom donošenja odluke o kardiopulmonalnoj reanimaciji da uzme u obzir želje pacijenta, stoga je potrebno sa pacijentima blagovremeno razgovarati (*end-of-life-discussions*). **Etička praksa.** Potrebno je znati kada započeti i kada prestati sa kardiopulmonalnom reanimacijom. Prilikom donošenja odluke da se ne započne kardiopulmonalna reanimacija potrebno je uzeti u obzir nekoliko kriterijuma. Jedan nedvosmislen kriterijum je bezbednost spasioca. **Zaključak**. Potrebna su stalna istraživanja kako bi poboljšali saznanja na ovu temu radi lakšeg donošenja odluke i boljeg postreanimacionog preživljavanja i kvaliteta života ovih pacijenata.

Ključne reči: kardiopulmonalna resuscitacija; etika; odlučivanje; instrukcije za reanimaciju; smrt; kritično oboleli

Introduction

Cardiopulmonary resuscitation (CPR) is a life-saving technique that consists of a series of procedures performed during cardiac arrest of various causes [1, 2]. Cardiac arrest can be sudden, reversible, and requires all resuscitative measures, and should be distinguished from cardiac arrest that occurs in the terminal stages of chronic diseases. In these situations, a positive outcome and adequate quality of life after resuscitation are usually not expected [3–5].

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Abbreviations

CPR – cardiopulmonary resuscitation
DNACPR – Do Not Attempt Cardiopulmonary Resuscitation
ERC – European Resuscitation Council
ALS – advanced life support

Chronic illnesses associated with low resuscitation success or poor post-resuscitation quality of life are terminal stages of cancer, multiple organ dysfunction involving three or more organ systems, severe kidney and liver failure, and terminal stages of Aquired imunodeficiency syndrome [6]. There is a significant controversy surrounding resuscitation of patients after suicide attempts and resuscitation of COVID-positive patients in the terminal stages of the disease [7–9]. Nevertheless, from both medical and ethical points of view, the only justified decision not to initiate CPR is the assessment that resuscitation will not benefit the patient.

Cardiopulmonary resuscitation aims to preserve life, improve health, and reduce suffering [10]. Therefore, the most important thing in the terminal stages of these diseases is to assess the post-resuscitation quality of life [11]. Advanced medical techniques enable life extension at any cost, even at the cost of a poor quality of life [12]. Quality of life can be assessed based on five components: 1) assessment of mental status; 2) assessment of physical status (independent, moderately dependent, fully dependent); 3) assessment of socialization (integrated, isolated); 4) assessment of pain intensity (no pain, minimal pain, moderate, severe pain); 5) assessment of depressive behavior (no depression, moderate, or severe depression) [11, 12].

In many Western countries, there is a clear decision not to initiate resuscitation in the final stages of the disease, known as "Do Not Attempt Cardiopulmonary Resuscitation – DNACPR". This decision is made if it is assessed that health will not be improved after resuscitation. It can be made by the patient, family, or medical team [13–15].

Informed Patient Consent – "Code status"

Informed patient consent or "Code status" refers to the type of medical treatment that the patient wants medical personnel to apply or not to apply in case of cardiac arrest. As the patient cannot make this decision if there is a cardiac arrest, it should be made in a timely manner, in patients in the terminal stages of the disease, while they are still in a situation to make the decision independently and wisely [16, 17].

In 1974, the American Medical Association first recommended the existence of a document where patients would state whether they wanted to be resuscitated in the terminal stage of a chronic illness. The DNACPR became hospital practice for the first time in 1976, changing the previous policy that CPR must be routine practice after every cardiac arrest, regardless of cause and consequences [18, 19]. Patients make the decision about not being resuscitated while they are in a situation to consciously make decisions, or authorize family members or guardians to make and implement such decision for them [1, 18, 19].

The problem may be that patients, as well as their families, do not fully understand the meaning and the process of resuscitation, the prognosis, risks, and consequences. They do not understand the terms of short-term and long-term survival rates, post-resuscitation quality of life, and how survival from resuscitation measures would affect the patient's functional status [16, 20, 21]. Therefore, the responsible healthcare worker must explain to the patient the consequences of refusing the proposed medical measure, and require from the patient a written statement about it, which must be kept in medical documentation [1, 21].

The Patient Rights Act of the Ministry of Health of the Republic of Serbia allows for the possibility that patients with cancer or another chronic disease can express their opinions on therapeutic measures to be taken in the event of cardiac arrest during treatment, but this is not the practice in most healthcare facilities [22]. Also, in addition to legal acts, the doctor is obliged to adhere to the Code of Professional Ethics of the Serbian Medical Chamber, which deals with the doctor's relationship to the expressed will of the dying person [23].

Do Not Attempt Cardiopulmonary Resuscitation

Do-Not-Attempt-Cardiopulmonary-Resuscitation refers to a pre-planned decision not to initiate CPR in order to align the patient's wishes with their treatment. The general recommendation is that not all patients should be resuscitated, and this recommendation considers both the ethical and medical perspectives [24]. From the medical perspective, the possibility of poor outcome and poor post-resuscitation quality of life in certain patients is taken into account, which outweighs the benefit of resuscitation for that patient [25, 26]. From the ethical perspective, many authors argue for the individual's right to die. However, in practice, it is difficult to know which individual will have severe consequences from CPR that will affect their quality of life.

Assessment of each individual is subjective, and there is often disagreement among team members about the outcome assessment [1, 12]. The patient and their family can also define futility of resuscitation quite differently from medical staff. Besides professional and moral responsibility, bias, fear, guilt, demographic and religious beliefs can also influence the decision. Due to all of these factors, is extremely difficult in some situations to make the decision about not initiating the resuscitation and the futility thereof [27].

In any case, the medical act must be a combination of the patient's free will, ethical norms, and legal acts [25, 27]. In the current guidelines of the European Resuscitation Council (ERC) from 2021, there is an entire chapter on the ethical aspects of resuscitation. Their purpose is to provide ethically correct evidence-based recommendations on the decision not to initiate resuscitation, as well as the decision to stop

Table 1. Key ethical messages for resuscitation according to European Resuscitation Council guidelines 2021 [1]
Tabela 1. *Ključne etičke poruke za reanimaciju prema vodiču Evropskog saveta za reanimaciju 2021 [1]*

1. Pre-planned care – Help patients and families achieve outcomes that are important for them – Allow clinicians and patients to participate in shared decision making – Integrate DNACPR decisions with emergency care treatment plans *1. Unapred isplanirana nega* *– Pomoći porodicama pacijenata da postignu ishode koji su važni za njih* *– Omogućiti kliničarima i pacijentima da učestvuju u zajedničkom donošenju odluka* *– Integrisati odluke o nezapočinjanju kardiopulmonalne reanimacije sa planovima lečenja urgentne nege*
2. Educating patients and general public – What does resuscitation include and what are the outcomes after resuscitation – How to inform clinicians about the outcomes that are important to them *2. Edukacija pacijenata i javnosti* *– Šta resuscitacija obuhvata i koji su ishodi nakon resuscitacije* *– Kako da obaveste kliničare o ishodima koji su njima važni*
3. Educating healthcare professionals – About the importance of pre-planned care – What does shared decision making include – How to properly discuss the pre-planned care with the patient's family *3. Edukacija zdravstvenih radnika* *– O važnosti unapred isplanirane nege* *– Šta obuhvata zajedničko donošenje odluka* *– Kako adekvatno razmatrati unapred isplaniranu negu sa porodicom pacijenta*
4. When to initiate and discontinue resuscitation – Use clearly specified criteria for suspending and terminating CPR – Do not base the decisions on isolated clinical signs or markers of poor prognosis – Document the reasons for decision- making regarding CPR *4. Kada započeti i prekinuti resuscitaciju* *– Koristiti unapred definisane kriterijume za obustavljanje i prekidanje kardiopulmonalne reanimacije* *– Ne bazirati odluke na izolovanim kliničkim znacima ili markerima loše prognose* *– Dokumentovati razloge za donošenja odluka u vezai sa kardiopulmonalnom reanimacijom*
5. Research – Involve patients and public in the design, implementation and interpretation of research – Respect the dignity and privacy of research subjects – Comply with recommendations during research implementation *5. Istraživanje* *– Uključiti pacijente i javnost u dizajniranje, sprovođenje i tumačenje istraživanja* *– Poštovati ugled i privatnost ispitanika* *– Poštovati preporuke tokom sporvođenja istraživanja*

it. As already mentioned, the ethical approach to resuscitation should certainly be based on the assessment of balance between benefits and harms. It also promotes an equitable approach to all patients, regardless of the routine practice of the institution where the patient is located [1, 27].

The Practice of Ethics

According to current ERC guidelines, from the ethical standpoint, the first priority for patients suffering from life-limiting illness should be a pre-planned joint decision on CPR in case of cardiac arrest. A life-limiting illness is an active, progressive, or advanced disease, that has little or no prospect of cure and that one is likely to die from at some point. The decision-making team should take into account the patient's wishes when making a decision about CPR, so timely discussions with patients (end-of-life discussions) are necessary [1, 20].

To make an adequate decision, patients and families need to be educated about the indications for CPR, the procedure, and potential outcomes. In addition, appropriate education of medical staff is necessary [28]. According to the above guidelines, it is necessary to know when to start and stop CPR. This, among other things, involves predetermined criteria for stopping CPR **(Table 1)** [1, 21, 27].

Several criteria need to be taken into account when making a decision not to initiate CPR, whether in-hospital or out-of-hospital [2]. One unambiguous criterion is the safety of the rescuer. If endangered, CPR should not be initiated. Also, CPR should not be initiated if there is obvious fatal injury or irreversible death, and the third unambiguous criterion is an order from a superior team member not to initiate or discontinue CPR. Other additional criteria considered when deciding not to initiate or discontinue CPR include the duration of CPR – if asystole is present for more than 20 minutes despite all the ad-

vanced CPR measures (Advanced Life Support – ALS). Another criterion is the presumption that further resuscitation will lead to harmful consequences for the patient that outweigh the benefits the patient would have had from resuscitation [2, 27].

Conclusion

Continuous research is needed to improve knowledge in this area in order to facilitate decision-making and improve post-resuscitation survival and quality of life for these patients.

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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

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∗ Organizacija kao autor

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Knjige i druge monografije

∗ Jedan ili više autora

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∗ Disertacija

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Elektronski materijal

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

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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.