ISSN 2737-971X
eISSN 2737-9752

SERBIAN JOURNAL OF THE MEDICAL CHAMBER

SRPSKI MEDICINSKI ČASOPIS LEKARSKE KOMORE

VOLUMEN 4 • BROJ 4 • DECEMBAR 2023.
VOLUME 4 • NUMBER 4 • DECEMBER 2023

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OSNIVAČ, VLASNIK, IZDAVAČ

Lekarska komora Srbije
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Institut za medicinska istraživanja, Univerzitet u Beogradu
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FOUNDER, OWNER & PUBLISHER

Serbian Medical Chamber
1-3 Kraljice Natalije Street, 11000 Belgrade, Serbia
CO-PUBLISHER
Institute for Medical Research, University of Belgrade
4 Dr Subotića Street, P.O. Box 102, 11129 Belgrade, Serbia

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ŠTAMPA: SAJNOS, Novi Sad

TIRAŽ: 200 primeraka
Časopis izlazi 4 puta godišnje

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PRINTED BY: SAJNOS, Novi Sad

CIRCULATION: 200 copies
The Journal is published quarterly

EDITORIJAL

„Svako ko prestane učiti je star, bilo da ima dvadeset ili osamdeset godina“
Henri Ford

Poštovane koleginice i kolege,

Jako sam ponosan na činjenicu što pišem editorijal za nacionalni časopis, za časopis koji je krenuo u svoj život i svoje postojanje; što pišem ispred Uredništva u ime Instituta za medicinska istraživanja Univerziteta u Beogradu, kao suizdavača ovog časopisa; i što pišem za broj koji će zatvoriti ovu, 2023. godinu, po mnogo čemu bolju od prethodnih, što se tiče zdravstvenog stanja nacije, posle kolektivno preležanog KOVID-a. Duboko verujem da ovim časopisom, i kroz njega svi mi pojedinačno, doprinosimo daljem razvoju i struke i nauke kod nas. Ambicije su naravno mnogo šire.

Upoznajem ovaj, sada naš zajednički časopis, već prepoznat i klasifikovan kao časopis nacionalnog značaja, i vidim u njemu članke, stavove i tumačenja koji nam svima mogu pomoći – i kliničarima, i istraživačima, i nastavnicima. Svaka od ovih pojedinačnih struka i profesija ne može stajati i postojati sama, već se moraju prožimati, dopunjavati i sarađivati. Tu ja vidim našu zajedničku, ali i svoju pojedinačnu ulogu i mogući doprinos. Naime, pomenute komponente čine naše zajedničke pilone, pilone koji nas drže i pomažu nam da i mi potom dalje pomažemo. To je zdravlje, to je nauka, i to je obrazovanje. To je suština, i toga se moramo držati, jer svaka od ovih komponenti sama za sebe nije dovoljna. Moramo se udruživati, gde god možemo, tako smo jači i značajniji.

Uz veliko poštovanje, ali i čast, predstavljam ovaj broj Srpskog medicinskog časopisa Lekarske komore, nastao zajedničkim naporima i Uredništva, i saradnika, i autora, i recenzenata.

Ovaj broj Časopisa otvara rad po pozivu, rad dvoje inostranih kolega, Iversena i Plesnera, koji razmatraju ulogu daratumumaba u lečenju multiplog mijeloma. Autori opisuju efekat produženog preživljavanja kroz modulaciju imunskog sistema ili mikrookruženja koštane srži. Zaključuju da primena daratumumaba, samog ili u kombinaciji sa drugim lekovima, poboljšava ishod lečenja pacijenata sa mijelomom, bez značajnog povećanja toksičnosti.

Sledi nekoliko originalnih radova.

Prvi je rad koleginice Životić i saradnika, koji se bavi efektom koekspresije određenih molekula i njihovim uticajem na karcinom bubrežnih ćelija. U radu se navodi da biološko ponašanje i karakteristike tumora bubrega zavise od ekspresije ispitivanih molekula, uz određene ograde u zaključku.

Sledeći je rad koleginice Mioljević i saradnika, koji se takođe bavi bubrežnim oboljenjima, odnosno zahvaćenošću bubrega fibrozom i ekspresijom neuralnog ćelijskog adhezionog molekula u intersticijumu bubrega. Autori zaključuju da je prisustvo ovakvih ćelija u intersticijumu bubrega karakteristika ranih faza hroničnih bolesti bubrega.

EDITORIAL

"Anyone who stops learning is old, whether at twenty or eighty."
Henry Ford

Dear colleagues,

I am very proud of the fact that I am writing an editorial for a national journal, for a journal that has taken on its own life and existence; that I am writing in front of the Editorial Board on behalf of the Institute for Medical Research, University of Belgrade, which is a co-publisher of this journal; and that I'm writing for the issue that will close the year 2023, which was in so many ways better than the previous ones, as far as the health of the nation is concerned, after the collective COVID affliction. I deeply believe that this journal, and through it all of us individually, are contributing to the further development of our profession and of medical science. Ambitions are, of course, much higher.

I am now becoming familiar with this publication, now our joint journal, which has already been recognized and classified as a journal of national significance, and in it I see articles, views and interpretations that can help us all – clinicians, researchers, and teachers alike. Each of these individual occupations and professions cannot stand and exist alone, rather they must be synergistic, they must complement each other, and collaborate. This is where I see both our common and my own individual role and possible contribution. Namely, the abovementioned components make up our common pylons, the pylons that hold us up and help us, so that we can help further. This is health, this is science, and this is education. This is the essence which we must persevere in, as each of these components alone is not sufficient. We must come together, wherever we can, as this is how we gain strength and significance.

With great respect and honor, I present this issue of the Serbian Journal of the Medical Chamber – the result of the joint effort of the Editorial Board, our associates, the authors of the articles, and the reviewers.

This issue of the Journal opens with an invited paper, an article written by two colleagues from abroad, Iversen and Plesner. The article analyzes the role of daratumumab in the treatment of multiple myeloma. The authors describe the effect of prolonged survival through the modulation of the immune system or of the bone marrow microenvironment. They conclude that the use of daratumumab, alone or in combination with other drugs, improves the treatment outcome in patients with myeloma, without a significant increase in toxicity.

This issue of the Journal also presents several original articles.

The first among them is an article by Životić et al., which analyzes the effect of the co-expression of certain molecules and their influence on renal cell carcinoma. The study stipulates that the biological behavior and characteristics of renal tumors depend on the expression of the studied molecules. However, certain limitations to this effect are stated in the conclusion.

The following article is a study by our colleague Mioljević and associates, which also deals with kidney diseases, i.e., the degree of fibrosis in the kidney and the expression of the neural cell adhesion molecule in the renal

Koleginice Dejanović i Jovanović su ispitivale povezanost citokina u plazmi sa apoptozom limfocita pacijenata obolelih od hronične limfocitne leukemije. Opšti zaključak je da nema korelacije, uz opis da interleukin-12 ipak pokazuje pozitivnu korelaciju kod uznapredovale bolesti.

Sledeći rad nam govori nešto drugo – o obezbeđenosti Crne Gore lekarima specijalistima medicine. Autori razmatraju lekare poredeći vrste specijalizacija, ali i njihovu starosnu i polnu strukturu u odnosu na druge zemlje Evropskog regiona. Studija ukazuje na značajni manjak ovako definisanih grupa lekara u Crnoj Gori, u odnosu na većinu zemalja Evropskog regiona, kao i na neadekvatnu starosnu strukturu.

Regionalno razmatranje je prisutno i u sledećem radu, ovog puta je u pitanju obuhvat obaveznom vakcinacijom na teritoriji Mačvanskog okruga, u jedanaestogodišnjem periodu. Autorka Pajičić sa saradnicima analizira podatke iz domova zdravlja i zaključuje da obuhvat vakcinacijom tokom posmatranog perioda opada, te ukazuje na potrebu promovisanja vakcinacije.

Analiza Službe za hitnu medicinsku pomoć Pančevo, koja je posmatrala vanbolnički srčani zastoj i mere kardiopulmonalne reanimacije, ukazuje na mali broj započetih mera, kao i na značajni deo neprepoznatih vanbolničkih srčanih zastoja od strane dispečera, te autori smatraju da je neophodno edukovati stanovništvo i ukazuju na potrebu uvođenja jedinstvenog protokola za dispečere.

Uticaj perioperativnih faktora na ishod kod pacijenata sa rupturiranom aneurizmom abdominalne aorte, Čović i saradnika, jeste retrospektivna studija zasnovana na medicinskoj dokumentaciji za dvogodišnji period, koja pokazuje značajni i nepredvidljivi uticaj ovih faktora na ishod kod pacijenata operisanih u Kliničkom centru Vojvodine zbog rupture aneurizme abdominalne aorte.

Časopis dalje uključuje i serije slučajeva.

Autori Zečić i Zečić razmatraju primenu intraoperativnog ultrazvuka u lokalizovanju nepalpabilnih lezija dojke, te kroz veliku retrospektivnu studiju sa velikim brojem operisanih pacijentkinja, zaključuju, na osnovu operativnih nalaza, da su sve nepalpabilne lezije u dojkama uspešno lokalizovane intraoperativnim ultrazvukom, a potom i ekscidirane.

U svom radu, koautori Maljković i Matić razmatraju funkcionalne rezultate lečenja pacijenata sa povredom mekih tkiva ručnog zgloba. Analiza funkcionalnih testova i upitnika ukazuje na značaj blagovremenog lečenja.

Prikazi slučajeva počinju grupom autora okupljenih oko koleginice Pavlović Stojanović, koji opisuju situs inversus stanje unutrašnjih organa pacijentkinje, a kroz koje ukazuju na značaj identifikacije ovakvih osoba pri dijagnostici pojedinih oboljenja.

Autori predvođeni dr Inić opisuju gigantski filodni tumor, koji zbog svoje retkosti predstavlja dilemu i zahteva tačnu preoperativnu dijagnozu.

Krivokapić i saradnici predstavljaju izveštaj o slučaju devetnaestogodišnjaka sa dugom istorijom Leg-Kalve-Pertesove bolesti, relativno česte bolesti kuka dečijeg doba. Opisana, relativno zahtevna procedura, rezultira kraćim periodom hospitalizacije, smanjenim rizikom od komplikacija i manjim troškovima, u poređenju sa karličnom i butnom osteotomijom.

Kolege Dimitrijević i saradnici opisuju neuropsihijatrijski lupus kod dve pacijentkinje, sa različitim kliničkim manifestacijama bolesti, te ukazuju na neophodnost dodatnih kliničkih ispitivanja koja bi dovela do novih terapijskih opcija.

Na kraju mi preostaje da pozovem kolege – i kliničare, i istraživače, i nastavnike, da nam se pridruže kako bismo svi zajedno obogatili ovaj naš časopis i učinili ga neizbežnim u daljem profesionalnom radu svih nas.

S poštovanjem,

Dr Saša Radovanović, Naučni savetnik

Institut za medicinska istraživanja, Univerzitet u Beogradu

interstitium. The authors conclude that the presence of these cells in the renal interstitium are a characteristic of the early stages of chronic kidney disease.

Our colleagues Dejanović and Jovanović examined the relationship between cytokines in the plasma and lymphocyte apoptosis, in patients with chronic lymphocytic leukemia. The general conclusion is that there is no correlation, however, it is noted that interleukin-12 does demonstrate a positive correlation in advanced stages of disease.

The next paper is about something different - the availability of specialist medical doctors in Montenegro. The authors observe doctors by comparing the types of specializations, but also their age and gender structure, in relation to other countries in the European Region. The study reports a significant shortage of groups of doctors defined in this way in Montenegro, as compared to most countries in the European Region, as well as an inadequate age structure.

The regional level is also examined in the next paper, this time concerning mandatory vaccination coverage in the territory of the Mačva District, during an eleven-year period. Pajičić et al. analyzed data from community health centers concluding that vaccination coverage during the observed period decreased, pointing out the need for promoting vaccination.

Analysis of the Emergency Medical Service Pančevo, which observed out-of-hospital cardiac arrest and measures of cardiopulmonary resuscitation, indicates a small number of initiated measures, as well as a significant portion of unrecognized out-of-hospital cardiac arrests by dispatchers. The authors believe that it is necessary to educate the population and indicate the need to introduce a uniform protocol for dispatchers.

The impact of perioperative factors on the outcome in patients with ruptured abdominal aortic aneurysm, by Čović et al., is a retrospective study based on medical records covering a two-year period. This study demonstrates the significant and unpredictable impact of these factors on the outcome in patients surgically treated at the Clinical Center of Vojvodina, due to ruptured abdominal aortic aneurysm.

The Journal further introduces case series.

Coauthors Zečić and Zečić discuss the application of intraoperative ultrasound in the localization of non-palpable breast lesions, and in a large retrospective study which included many surgically treated patients, they conclude, based on the surgical findings, that all non-palpable lesions in the breasts were successfully localized by intraoperative ultrasound, and then excised.

In their study, co-authors Maljković and Matić consider the functional results of the treatment of patients with soft tissue injuries of the wrist. Analysis of functional tests and questionnaires indicates the importance of timely treatment.

The first case report in this issue of the Journal was written by a group of authors gathered around our colleague Pavlović Stojanović, who describe the situs inversus condition of their female patient's internal organs. In this case report they indicate the importance of identifying such persons when diagnosing certain diseases.

Inić et al. describe a giant phyllodes tumor, which, due to its rarity, presents a dilemma and requires an accurate preoperative diagnosis.

Krivokapić et al. present a case report of a nineteen-year-old patient with a long history of Legg-Calve-Perthes disease, a relatively common childhood hip disease. The relatively demanding procedure described in the article results in shorter hospital stay, reduced risk of complications, and lower costs, as compared to pelvic and femoral osteotomy.

Our colleagues Dimitrijević et al. describe neuropsychiatric lupus in two patients, with different clinical manifestations of the disease, and emphasize the necessity of additional clinical trials that would lead to new therapeutic options.

Finally, I would like to invite my colleagues – clinicians, researchers, and teachers alike, to join us so that we can contribute to the Journal together and make it an integral part of our further professional work.

Sincerely,

Dr Saša Radovanović, Research Professor
Institute for Medical Research, University of Belgrade

SADRŽAJ

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ULOGA DARATUMUMABA U LEČENJU MULTIPLOG MIJELOMA

RAD PO POZIVU

INVITED PAPER

DARATUMUMAB FOR THE TREATMENT OF MULTIPLE MYELOMA

Katrine Fladeland Iversen[1], Torben Plesner[1]

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SAŽETAK

Daratumumab je prvo odobreno monoklonsko antitelo koje se vezuje za CD38 protein na površini ćelija mijeloma. Istorijski gledano, standardni antimijelomski protokol bio je oralni melfalan uz prednizolon. Nešto više od dve decenije nakon toga počinje primena visokodoznog melfalana praćenog autolognom transplantacijom matičnih ćelija, što postaje standard lečenja mlađih pacijenata sa mijelomom. Istovremeno, sprovodi se profilaksa čestih i razornih skeletnih komplikacija intravenskom primenom bisfosfonata. U narednim godinama počela je nova era značajnih poboljšanja u terapiji mijeloma sa uticajem na preživljavanje starijih i/ili "frail" pacijenata imunomodulatornim lekom talidomidom, što je nastavljeno primenom njegovog manje toksičnog i efikasnijeg analoga lenalidomida. Istovremeno je u terapijske protokole uveden bortezomib, prvi u klasi inhibitora proteazoma. Uprkos poboljšanju u preživljavanju, prognoza je ostala loša za pacijente sa relapsom nakon terapije bortezomibom i lenalidomidom sa srednjim ukupnim preživljavanjem od samo 9 meseci.

Zatim se nakon početnih dozno eskalacionih studija, utvrđuje da daratumumab dovodi do produženog preživljavanja u odsustvu značajnog "ubijanja" tumorskih ćelija kroz modulaciju imunskog sistema ili mikrookruženja koštane srži. Primena daratumumaba samog ili u kombinaciji poboljšala je ishod lečenja svih pacijenata sa mijelomom bez značajnog povećanja toksičnosti. Zahvaljujući ovakvom pristupu, pacijenti sa mijelomom žive duže i imaju bolji kvalitet života. uz dalje napore za njihovo izlečenje, što predstavlja glavni terapijski cilj.

Ključne reči: daratumumab, multipli mijelom, terapija, prognoza

ABSTRACT

Daratumumab is the first approved monoclonal antibody that targets the CD38 protein on the surface of myeloma cells. Historically, a well-established anti-myeloma protocol included oral melphalan and prednisolone as the standard of care. Apart from this, in a bit longer than two decades the high dose of melphalan followed by autologous stem cell transplantation became the standard for young and fit myeloma patients. Simultaneously, the prophylactic treatment of frequent and devastating skeletal complications was improved using intravenous bisphosphonate. In the following years, there came an era of significant improvements in anti-myeloma treatment that had an impact on survival rate of elderly and/or frail myeloma patients. The treatment included immunomodulatory drug thalidomide followed by the development of a less toxic and more effective analogue lenalidomide. At the same time, bortezomib, a first-in-class proteasome inhibitor, was introduced in the therapeutic protocols. Despite these improvements in survival, the prognosis remained poor for patients relapsing after treatment with bortezomib and lenalidomide with a median overall survival of only 9 months.

After the initial dose escalation studies daratumumab resulted in a prolonged survival in the absence of significant killing of tumor cells through modulation of the immune system or the bone marrow microenvironment. The emerging picture showed that the addition of daratumumab alone or in combination improved the outcome in all myeloma patients without adding significantly to toxicity. Owing to this approach, myeloma patients live longer and have a better quality of life and there are further efforts to cure them which represents the main therapeutic goal.

Key words: daratumumab, multiple myeloma, therapy, prognosis

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Primljeno • *Received*: November 10, 2023; **Revidirano • *Revised*:** November 20, 2023; **Prihvaćeno • *Accepted*:** November 20, 2023; ***Online first*:** December 25, 2023

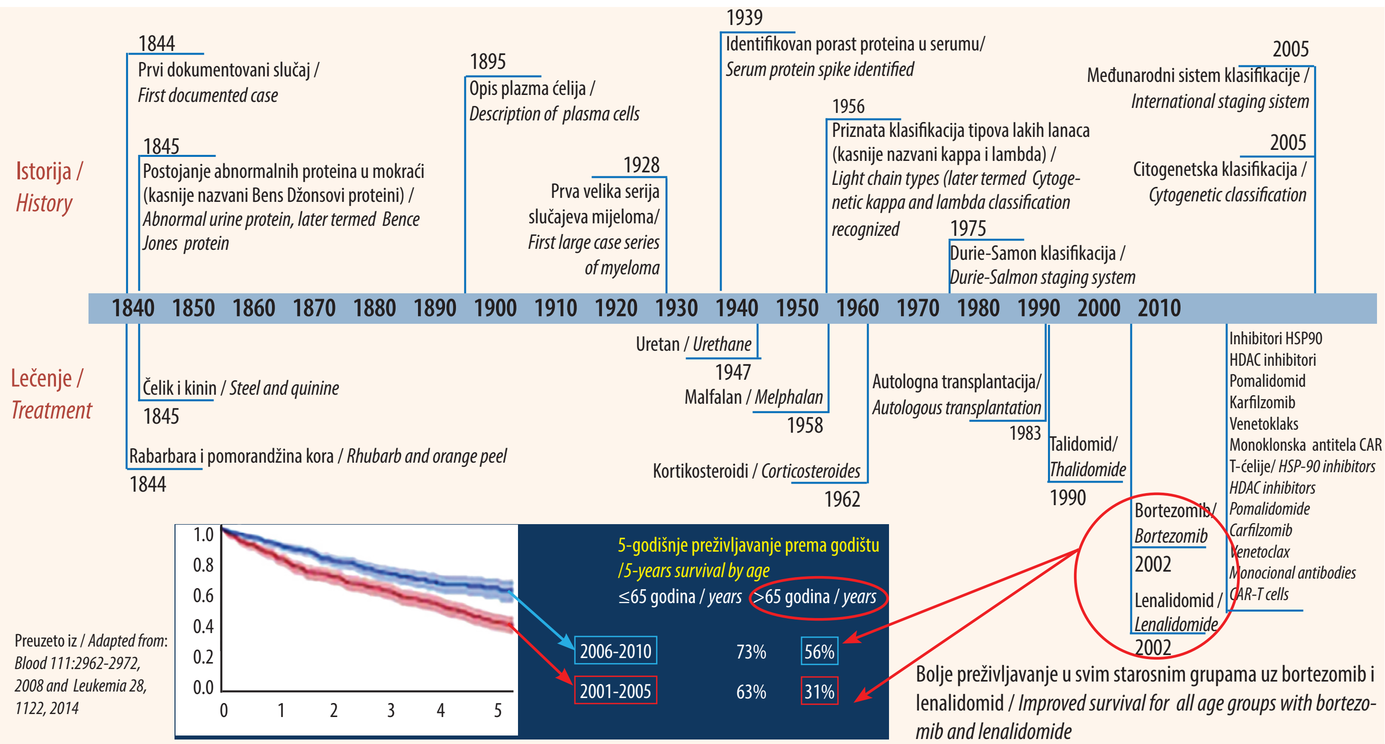
DOI: 10.5937/smclk4-47645

Tokom nešto više od dve decenije svedočimo velikoj promeni u lečenju multiplog mijeloma. Naslanjajući se na dobro uspostavljen režim koji podrazumeva korišćenje melfalana i prednizolona, *InterGroup Francophone du Myelome* je poboljšala ishode kod mladih i fizički zdravih pacijenata sa mijelomom koji su dobro podnosili toksičnost velikih doza melfalana [1,2]. Istovremeno, profilaktička terapija čestih i razarajućih koštanih komplikacija koje nastaju usled multioplog mijeloma unapređena je intravenskom upotrebom bisfosfonata [3]. Naredne prekretnice u unapređenju lečenja mijeloma koje bi imale uticaja na preživljavanje starijih i/ili slabih pacijenata koji boluju od mijeloma (Slika 1) najavljene su posmatranjem efekta koji je talidomid imao na lečenje mijeloma nakon čega je usledio razvoj njemu analognog lenalidomida koji je manje toksičan i efikasniji [4,5]. Istovremeno je bortezomib, prvi proteazomni inhibitor, pokazao obećavajući učinak u lečenju mijeloma [6,7].

Uprkos napretku u preživljavanju, prognoza je ostala loša za pacijente kod kojih dolazi do relapsa nakon lečenja bortezomibom i lenalidomidom, pri čemu njihovo srednje preživljavanje iznosi svega 9 meseca [8]. Lekari koji su se bavili lečenjem mijeloma sanjali su o pronalaženju antitela koje bi u potpunosti promenilo ishod kod pacijenata koji boluju od mijeloma, slično onome što je rituksimab učinio za pacijente obolele od malignog limfoma. Jedna mala dansko-holandska biotehnološka kompanija, Genmab, 2006. godine je predložila kliničko testiranje antitela CD38 (daratumu-

In a matter of a little more than two decades, we have witnessed a tremendous change in the treatment of multiple myeloma. Building on the well-established regimen of oral melphalan and prednisolone the *InterGroup Francophone du Myelome* improved the outcomes of young and fit myeloma patients that could tolerate the toxicity of high-dose melphalan [1,2]. At the same time, prophylactic treatment of frequent and devastating skeletal complications of multiple myeloma was improved by the use of intravenous bisphosphonate [3]. The next milestones of improvements of anti-myeloma treatment that would also have impact on the survival of elderly and/or frail myeloma patients (Figure 1) was heralded by the observation of anti-myeloma activity of thalidomide followed by the development of less toxic and more effective analog lenalidomide [4,5]. Simultaneously bortezomib, a first-in-class proteasome inhibitor, showed promising activity in myeloma [6,7].

Despite these improvements in survival, prognosis remained poor for patients relapsing after the treatment with bortezomib and lenalidomide with a median overall survival of only 9 months [8]. Myeloma doctors were dreaming of an antibody that could transform the outcomes for myeloma patients in a manner similar to what rituximab had accomplished for patients with malignant lymphomas. In 2006 Genmab, a small Danish-Dutch biotech company, came forward with a proposal to test a CD38 antibody (daratumumab) clinically in relapsed-refractory myeloma. The ra-



Slika 1. Istorijat i lečenje multiplog mijeloma od 1844. godine do danas

Figure 1. History and treatment of multiple myeloma from1844 to the present

maba) kod relapsirajućeg refraktornog mijeloma. To su obrazložili postojanjem jake ekspresije CD38 u ćelijama mijeloma i dokazane sposobnosti ovog antitela da *in vitro* ubije ćelije mijeloma uz postojanje sinergističkog anti-mijelomskog dejstva kada se kombinuje sa lanalidomidom ili bortezomibom [9,10]. Međutim, visoka ekspresija muktifunkcionalnog molekula CD38 u ljudskom telu i nedostatak pogodnih životinjskih modela za prekliničko testiranje potencijalne toksičnosti izazvali su zabrinutost. Situaciju je dodatno zakomplikovala nedavna katastrofa koja se dogodila prilikom kliničkog ispitivanja antitela CD38 koja je vlastima skrenula pažnju na potencijalnu opasnost koju može da izazove korišćenje monoklonskih antitela u vidu terapije [11]. Bilo je jasno da početna testiranja daratumumaba u okviru kliničkog istraživanja moraju biti pažljivo isplanirana. Kada se počelo sa testiranjem 2008. godine primenjena je strategija koja je podrazumevala davanje veoma male početne doze jednom po jednom pacijentu, uz dovoljno dugačak period posmatranja kako bi se otkrili eventualni neželjeni efekti, i malo povećanje doze antitela svakoj narednoj grupi pacijenata. Pošto je polje istraživanja bilo potpuno novo, prvobitni protokol GEN501 je dosta prilagođavan, u hodu, a do kraja je uneto čak 14 izmena. Spor napredak je bio neizbežan, a Genmab se istovremeno, poput mnogih drugih malih biotehnoloških kompanija, borio da preživi usled finansijskih problema. Tokom prve četiri godine, u istraživanje je uključeno svega 23 pacijenta.

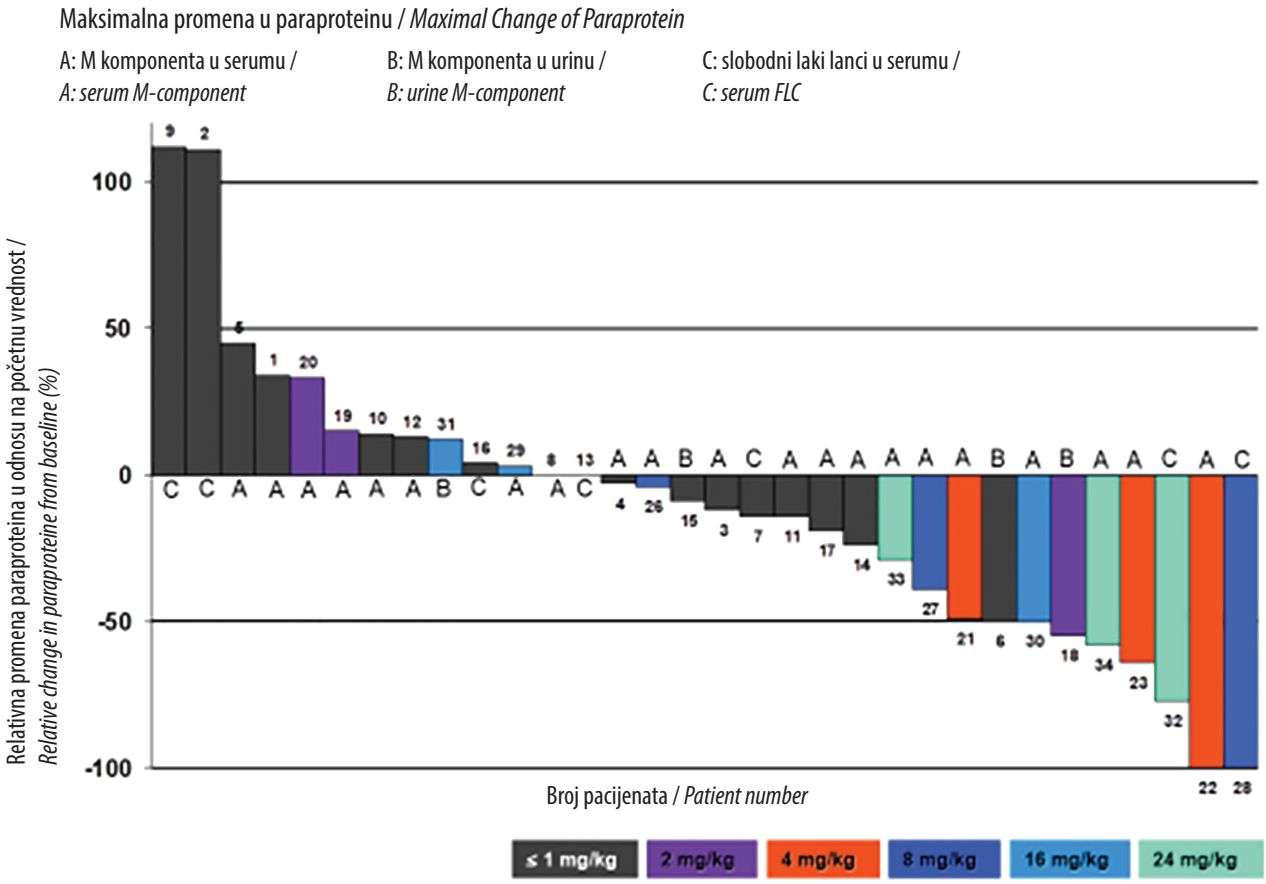
Uprkos postovanju zajedničkog sna o tome da će jednoga dana biti pronađen „rituksimab za mijelom", prevladao je skepticizam i kada su predstavljeni prvi rezultati iz GEN501na ASH 2011 za njih je pokazano veoma malo interesovanje, a citiranost je bila na nuli. Naredne godine, doza daratumumaba je porasla na 2 i 4 mg/kg telesne težine i odgovor je počeo da se nazire. To je promenilo celokupnu sliku i na ASH 2012 rezultati iz GEN501 privukli su znatnu pažnju, a bilo je 23 citata (Grafikon 1) (Genmab: Podaci u dosijeu). Shodno tome, ubrzano je uključivanje pacijenata u istraživanje, a u Severnoj Americi započeto je prateće istraživanje (SIRIUS), kao i kombinovane studije sa lenalidomidom i bortezomibom.

Monoterapija daratumumabom značajno je poboljšala preživljavanje. Ciljana populacija je imala srednje preživljavanje 20 meseci, ali još je zanimljivija činjenica da je daratumumab produžio ukupno preživljavanje 52% pacijenata kod kojih nije bilo formalnog odgovora prema kriterijumima koje je propisala IMWG (International Myeloma Working Group), već samo stabilizacije bolesti ili minimalnog odgovora, na 18.5 meseci [12-14] (Grafikon 2). Ovo je bilo dvotruko veće preživljavanje od očekivanog u to vreme za pacijente

tionale was a strong expression of the CD38 target by myeloma cells and demonstration of the ability of the antibody to kill myeloma cells in vitro along with synergistic anti-myeloma activity when combined with lenalidomide or bortezomib [9,10]. However, wide expression of the multifunctional CD38 molecule in the human body and a lack of suitable animal models for preclinical testing of potential toxicities caused worries. Furthermore, the situation was complicated by a recent disaster in a clinical trial of a CD28 antibody that alerted the authorities to the potential danger of using monoclonal antibodies for therapy [11]. It was clear that the initial testing of daratumumab in a clinical trial had to be planned with great care. A very low starting dose, one patient included at a time with a sufficient observation period to detect potential side effects, and small increments of the dose of antibody from each cohort of patients to the next was the strategy, when starting up in 2008. Since the field was entirely new, many adjustments of the first protocol GEN501 had to be made along the way coming up to a total of 14 amendments to the protocol. Slow progress was inevitable and at the same time, Genmab, like many small biotech companies, was fighting for its life due to financial constraints. In the first 4 years of the trial only 23 patients were enrolled.

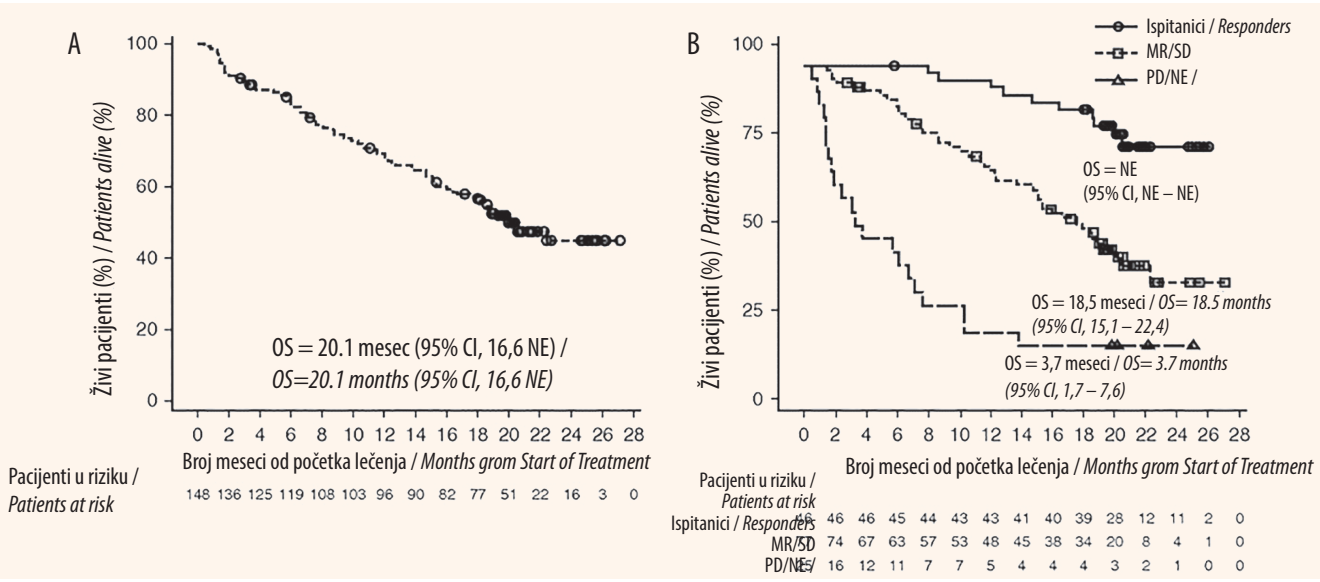
Despite a common dream of having a "rituximab for myeloma" one day, skepticism prevailed, and when the first data from GEN501 were presented at ASH 2011 it received very little interest and zero citations. The following year, dosing of daratumumab passed 2 and 4 mg/kg of body weight and the first signs of a response started to appear. This changed the whole picture, and at ASH 2012 the results of GEN501 received considerable interest and 23 citations (Chart 1) (Genmab: Data on file). Consequently, enrolment of patients into the trial accelerated and a companion study (SIRIUS) in North America and combination studies with lenalidomide and bortezomib were launched.

As monotherapy, daratumumab improved survival considerably. The intention to treat population had a median overall survival of 20 months, but perhaps most interestingly, daratumumab also prolonged the overall survival of the 52% of patients that did not obtain a formal response according to IMWG criteria, but only stable disease or a minor response, to 18.5 months [12-14] (Chart 2). This was a doubling of the survival that could be expected at that time for patients refractory to bortezomib and lenalidomide [8]. The reason for this extension of survival in the absence of significant killing of tumor cells is not well understood, but modulation of the immune system or the bone marrow microenvironment are likely explanations.



Grafikon 1. Prvo kliničko istraživanje upotrebe daratumumaba na ljudima GEN501 započelo je u martu 2008. godine. Regrutacija je u početku išla veoma sporo i samo 23 pacijenta uključeno je u projekat tokom prve četiri godine. Sa prvim znacima kliničke aktivnosti pri dozi od 2 i 4 mg/kg koja je predstavljena na ASH 2012 interesovanje je značajno poraslo, ubrzano je uključivanje novih pacijenata i prateće istraživanje (SIRIUS) pokrenuto je u Severnoj Americi (Genmab: Podaci u dosijeu).

Chart 1. The first human clinical trial with daratumumab GEN501 started in March 2008. The recruitment was initially very slow with only 23 patients enrolled in 4 years. With the first sign of clinical activity at 2 and 4 mg/kg presented at ASH 2012 interest increased considerably, recruitment for the trial accelerated and a companion study (SIRIUS) was initiated in North America (Genmab: Data on file)



Grafikon 2. Monoterapija daratumumabom poboljšala je ukupno preživljavanje i kod ispitanika i kod pacijenata kod kojih je odgovor bio minimalan (MR) ili je došlo do stabilizacije bolesti (SD) (52%)

Chart 2. Daratumumab monotherapy improved overall survival both for responders (31%) and for patients obtaining only MR or SD (52%)

otporne na bortezomib i lenalidomid [8]. Razlog za ovo produženje preživljavanja uprkos činjenici da ćelije tumora nisu ubijene nije potpuno jasan, ali moguća objašnjenja mogu biti modulacija imunog sistema ili koštano mikrookruženje.

Narednih godina bismo mogli biti svedoci veoma aktivnog razvoja programa za upotrebu daratumumaba zahvaljujući saradnji kompanija Genmab i Janssen. Daratumumab je korišćen u svim terapijskim linijama i u kombinaciji sa svim najvažnijim lekovima koji se koriste za lečenje mijeloma. Pokazalo se da je uvođenje daratumumaba u terapiju poboljšalo ishod lečenja u svim slučajevima bez značajnijeg povećanja toksičnosti. Utvrđeno je da je rizik od razvoja pojave neutropenije i infekcija u blagom porastu, ali stvari se mogu dovesti u ravnotežu uz pomoć adekvatne nege. Reakcije izazvane infuzijom bile su prisutne kod otprilike polovine pacijenata prilikom prve primene infuzije, ali nakon togsu se retko javljale, i bile su blage. Dostupnost subkutanog daratumumaba povoljno je uticala na reakcije usled primene infuzije i olakšala je primenu leka.

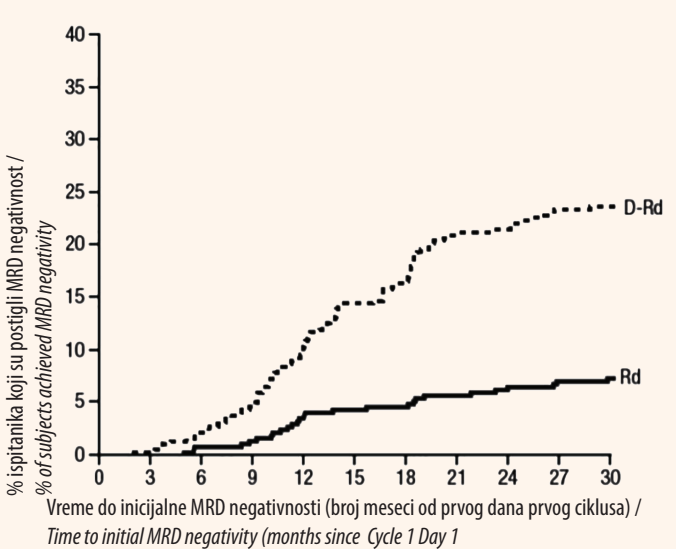
Kako trenutno postoji više opcija za lečenje pacijenata sa relapsnim refraktornim mijelomom sve je teže prikazati poboljšanje ukupnog preživljavanja u kliničkim istraživanjima, iako je nedavno otkriveno da postoji korist za preživljavanje kod pacijenata koji primaju daratumumab u istraživanjima ALCYONE, POLLUX, CASTOR i MAIA [15-18].

Zabrinutost da bi sveukupna korist za preživljavanje ostvarena u jednoj liniji terapije mogla loše da se odrazi na ishod naredne linije terapije nije potvrđena u praksi. Naprotiv, korist za preživljavanje dobijena upotrebom daratumumaba preneta je u sledeću liniju terapije kao što je pokazano u PFS-2 u okviru istraživanja MAIA (Slika 3) [18]. Takođe se pokazalo da produženo lečenje daratumumabom dovodi do progresivnog produbljivanja remisije što se odražava negativnošću minimalne rezidualne bolesti (MRD) (Grafikon 4) [19].

U okviru studije CASSIOPEIA pokazano je da se dodavanjem daratumumaba indukcionom tretmanu pre autologne transplantacije matičnih ćelija, kao i kasnije terapiji održavanja povećava preživljavanje bez progresije (PFS) i stopa negativnosti minimalne rezidualne bolesti (MRD) [20].

Pored potrebe za dugoročnim lečenjem, važno je primetiti da se tokom lečenja daratumumabom kvalitet života postepeno popravlja [21]. Pošto se daratumumab veoma dobro podnosi, i kao jedini lek i u kombinaciji sa drugim lekovima, i oslabljeni stariji pacijenti mogu imati koristi od lečenja.

Daratumumab deluje na više različitih načina, ali nije poznato koji načini su najvažniji, dok su razlozi za izostanak odgovora na lečenje daratumumabom ili



Grafikon 3. Stopa MRD negativnosti u rendomiziranom istraživanju MAIA

Chart 3. Rate of MRD negativity (10-5) in the intention to treat population of the MAIA trial.

In the following years, we could witness a very active development program for daratumumab owing to collaboration between Genmab and Janssen. Daratumumab was used in all lines of therapy and in combination with all most important drugs used for the treatment of myeloma. The emerging picture showed that the addition of daratumumab improved the outcome in all cases without adding significant toxicity. A slight increase in the risk of neutropenia and infections has been found, but this can be counterbalanced by appropriate supportive care. Infusion-related reactions were seen in about half of the patients during the first infusion but rarely thereafter and were mild in nature. The infusion -related reactions and the ease of administration have been improved by the availability of a subcutaneous formulation of daratumumab.

In the present scenario of multiple treatment options for patients with relapsed refractory myeloma it is increasingly difficult to demonstrate improved overall survival in clinical trials, but recently an overall survival benefit was found for patients receiving daratumumab both in the ALCYONE, the POLLUX, the CASTOR, and the MAIA trial [15-18].

Worries that an overall survival benefit in one line of therapy might translate into a poorer outcome of the subsequent line of therapy were not supported. On the contrary, the survival benefit from daratumumab was carried forward into the subsequent line of therapy as shown by the PFS-2 of the MAIA trial (Figure 2) [18]. It has also been shown that prolonged treatment with daratumumab will result in progressive deepening of remission as reflected by MRD negativity (Figure 3) [19].

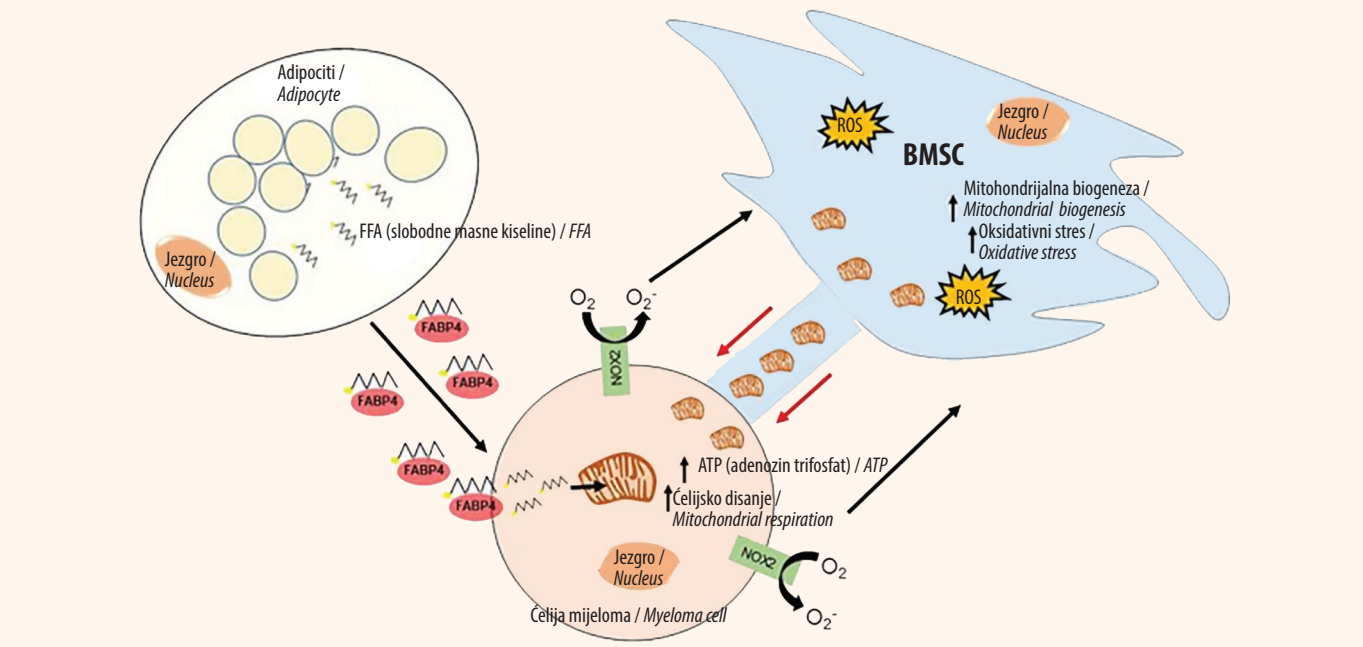
nestanak početnog odgovora nejasni. Neki od načina delovanja daratumumaba (citotoksičnost zavisna od komplementa (CDC), ćelijska citotoksičnost zavisna od antitela (ADCC) i ćelijska fagocitoza zavisna od antitela (ADCP)) zavise od jačine ekspresije CD38. Slaba ekspresija CD38 može negativno da utiče na ove načine delovanja, a do nje može doći vremenom s obzirom na to da primena leka daratumumab smanjuje ekspresiju CD38 u ćelijama mijeloma [22,23]. S druge strane, smanjen nivo CD38 može imati i pozitivan efekat. Stvaranje imunosupresivnog adenozina je ometeno u mikrookruženju koštane srži [24]. Oslabljeno je potencijalno zaštitno pričvršćivanje ćelije mijeloma za stromu [25]. Osim toga, blokirno je stvaranje nanotuba koje povezuju stromalne ćelije sa ćelijama mijeloma i prenose mitohondrije koje daju energiju ćelijama mijeloma (Slika 2) [26].

U kliničkoj praksi, brz početni odgovor na daratumumab je često praćen dugim periodom sporog ali postojanog opadanja M-proteina. U teoriji, za brz početni odgovor na daratumumab mogu biti zaslužni CDC, ADCC i ADCP koje najbolje funkcionišu kada je ekspresija CD38 visoka. Nakon toga može uslediti dug period u kojem značajniju ulogu imaju reprogramiranje imunog sistema i modulacija mikrookruženja do kojih dolazi zahvaljujući smanjenom stvaranju adenozina, slabijem pričvršćivanju ćelija mijeloma za stromu, ometanju stvaranja nanotuba i eleminaciji regulatornih T, B i M ćelija [27].

The CASSIOPEIA study has revealed that adding DARA to the induction treatment before autologous stem-cell treatment and to the consolidation treatment afterwards increases the PFS and the rate of MRD negativity [20].

Along with a need for a long-term treatment it is important to notice that the quality of life is improving over time during treatment with Daratumumab [21]. Since daratumumab is so well tolerated both as a single agent and combined, frail elderly patients obtain benefits from the treatment as well.

Daratumumab has multiple modes of action but it is unknown which are the most important and the reason for failure to respond to treatment with daratumumab or loss of response are obscure. Some of daratumumab´s modes of action (complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP)) depend on the level of CD38 expression. These modes of action may be impaired by a low level of expression of CD38, which may occur with time as treatment with daratumumab reduces the expression of CD38 by myeloma cells [22,23]. On the other hand, the reduced level of CD38 may also be beneficial. The formation of immunosuppressive adenosine is inhibited in the bone marrow microenvironment [24]. Potentially protective adhesion of myeloma cells to stroma is impaired [25]. Apart from this, the formation of nanotubes connecting stromal cells with myeloma



Slika 2. Mitohondrije se prenose od stromalnih ćelija do ćelija mijeloma putem međusobno povezanih nanotuba koje obezbeđuju energiju i jačaju maligni fenotip ćelija mijeloma. Stvaranje nanotuba zavisi od CD38 i može biti blokirano od strane CD38 antitela (prilagođeno i preuzeto iz Oncoscience 4, 173, 2017).

Figure 2. Mitochondria are transferred from stromal cells to myeloma cells trough interconnecting nanotubes providing energy and boosting the malignant phenotype of the myeloma cell. The formation of nanotubes is dependent on CD38 and may be blocked by CD38 antibody (modified and reprinted from Oncoscience 4, 173, 2017)

Uvođenje daratumumaba u protokol lečenja pacijenata sa mijelomom predstavlja retku kombinaciju efikasnog načina lečenja i lečenja koje se dobro podnosi. Zajedno sa imunomodulatornim lekovima i proteazomnim inhibitorima, daratumumab predstavlja prvi veliki korak dalje od staromodne terapije zasnovane na alkilatorima ka novom dobu u kome je imuni sistem podešen tako da može da se bori protiv mijeloma. Kao rezultat toga, pacijenti oboleli od mijeloma živeće duže i bolje kako se budemo sistematski kretali ka svom cilju izlečenja mijeloma.

Sukob interesa: Nije prijavljen.

cells and transferring energizing mitochondria to the myeloma cells is blocked (Figure 2) [26].

In clinical practice, a rapid initial response to daratumumab is often followed by a long period with a slow but steady decline of the M-protein over time. In theory, the rapid initial response to daratumumab could be due to CDC, ADCC and ADCP that work best when CD38 expression is high. This may be followed by a long period where reprogramming of the immune system and modulation of the microenvironment by reduced formation of adenosine, impaired adhesion of myeloma cells to stroma, inhibition of formation of nanotubes and elimination of regulatory cells of the T, B and M cell systems become more important [27].

The introduction of daratumumab in the treatment of patients with myeloma offers a rare combination of a very efficient and well-tolerated new treatment modality. Together with the immunomodulatory drugs and proteasome inhibitors, it represents the first major step away from old-fashioned alkylator based therapy towards a new era where the immune system is tuned to cope with myeloma. As a result, myeloma patients will survive longer and live better lives as we systematically move forward towards the goal of curing myeloma.

Conflict of interest: None declared.

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EKSPRESIJA *NCAM* I *FGFR1* MOLEKULA I NJIHOV UTICAJ NA BIOLOŠKO PONAŠANJE KARCINOMA BUBREŽNIH ĆELIJA

ORIGINALNI RAD

ORIGINAL ARTICLE

POSSIBLE IMPACT OF NCAM AND FGFR1 MOLECULE EXPRESSION PATTERNS ON THE BIOLOGICAL BEHAVIOR OF RENAL CELL CARCINOMA

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SAŽETAK

Uvod: Poslednjih decenija raste stopa javljanja tumora bubrežnih ćelija (engl. *renal cell tumors - RCT*) i njima uzrokovanih smrtnih ishoda. Iako karcinomi bubrežnih ćelija (*engl. renal cell carcinoma – RCC*) predstavljaju samo 2% svih karcinoma, ovi tumori spadaju u prvih deset uzročnika smrti među karcinomima u Evropi.
Cilj: Kako je poznato da neuralni ćelijski adhezioni molekul (engl. *neural cell adhesion molecule, NCAM*) i receptor 1 za fibroblastni faktor rasta (engl. *fibroblast growth factor receptor 1, FGFR1*) stupaju u interakcije na površini ćelijske membrane, kao i da se mogu eksprimirati i na drugim ćelijskim lokalizacijama, odlučili smo da ispitamo potencijalni uticaj različitih obrazaca njihove koekspresije na kliničko-patološke karakteristike tumora bubrega.
Materijal i metode: Analizirano je 100 tumora bubrega, dijagnostikovanih na Institutu za Patologiju Medicinskog fakulteta Univerziteta u Beogradu. Imunohistohemijska analiza urađena je na pločicama tkivnog mikroniza, korišćenjem *NCAM* (1:50, klon123C3.D5) i *FGFR1* (1:100, klon M19B2) antitela. Kliničke i patohistološke karakteristike tumora bubrega ispitane su u odnosu na prisustvo i lokalizaciju koekspresije *NCAM i FGFR1* molekula.
Rezultati: Koekspresija *NCAM i FGFR1* molekula u tumorima bubrega uočena je u citoplazmi i na membrani, ali ovi obrasci ne zavise od patohistološkog tipa tumora. Svaki tumor u čijem jedru je uočena *FGFR1* imunopozitivnost pokazivao je i membransku pozitivnost na oba ispitivana molekula. Primećeno je da sa povećanjem T stadijuma raste učestalost koekspresije *NCAM i FGFR1* molekula, ali nalaz nije bio statistički značajan.
Zaključak: Membranska koekspresija nije uočena ni kod jednog benignog tumora, uprkos prisustvu citoplazmatske koekspresije. Postoji mogućnost i da pojava *FGFR* molekula u jedru indukuje pojavu membranske koekspresije.

Ključne reči: *RCT, RCC, NCAM, FGFR1*, tumori bubrega

ABSTRACT

Introduction: The incidence of renal cell tumors (RCT) and the deaths caused by them has been increasing in recent decades. Although renal cell carcinomas (RCCs) represent only 2% of all cancers, these tumors are among the top ten causes of death in Europe, when cancers are concerned.
Aim: As it is known that the neural cell adhesion molecule (NCAM) and fibroblast growth factor receptor 1 (FGFR1) interact on the surface of the cell membrane and can also be expressed in other cellular localizations, we decided to examine the potential influence of different patterns of their co-expression on the clinical and pathological characteristics of renal tumors.
Material and methods: A total of 100 renal tumors, diagnosed at the Institute of Pathology, Faculty of Medicine, University of Belgrade, were analyzed. Immunohistochemical analysis was performed on tissue microarray slides, using NCAM (1:50, clone123C3.D5) and FGFR1 (1:100, clone M19B2) antibodies. Clinical and pathohistological characteristics of renal tumors were examined in relation to the presence and localization of the co-expression of NCAM and FGFR1 molecules.
Results: Co-expression of NCAM and FGFR1 molecules in renal tumors was observed in the cytoplasm and on the membrane, however, these patterns did not depend on the pathohistological type of tumor. Each tumor in which FGFR1 immunopositivity was observed in the nucleus also showed membranous positivity for both tested molecules. It was observed that the frequency of co-expression of NCAM and FGFR1 molecules increased with increasing T stage, but the finding was not statistically significant.
Conclusion: Membranous co-expression was not observed in any benign tumor, despite the presence of cytoplasmic co-expression. There is also a possibility that the presence of FGFR in the nucleus induces the occurrence of membranous co-expression.

Keywords: RCT, RCC, NCAM, FGFR1, renal tumors

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Primljeno • *Received*: September 8, 2023; **Revidirano • *Revised*:** September 23, 2023; **Prihvaćeno • *Accepted*:** September 28, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-46414

UVOD

Tokom poslednje tri decenije, incidencija tumora bubrega je u stalnom porastu u Evropi, SAD-u i Australiji [1,2]. U adultnoj populaciji, karcinomi bubrega čine 2% svih karcinoma [3], a najčešći je karcinom bubrežnih ćelija (engl. *renal cell carcinoma, RCC*), koji ima najveći mortalitet među karcinomima urogenitalnog sistema [4]. Izdvaja se nekoliko patohistoloskih podtipova, među kojima postoje razlike u morfologiji, genetici, poreklu i biološkom ponašanju. Ubedljivo je najčešći svetloćelijski (80 – 90%) karcinom, za kojim slede papilarni, hromofobni i karcinom sabirnih kanalića [5]. Iako su među tumorima bubrežnih ćelija najčešći karcinomi, postoje i benigni tumori poznati kao onkocitomi [6]. Godišnje se širom sveta dijagnostikuje oko 270.000 novih slučajeva *RCC*-a godišnje, a oko 116.000 pacijenata umire [1,2]. S obzirom na činjenicu da ovi tumori retko pokazuju rane znake bolesti (što rezultira visokom proporcijom pacijenata sa metastazama), kao i da se karakterišu raznolikim kliničkim manifestacijama, visokom rezistencijom na radioterapiju i hemioterapiju [7], sprovedena su mnoga kliničko-patološka ispitivanja u cilju otkrivanja potencijalnih biomarkera, kako bi se omogućila rana dijagnostika i imunomodulacija u cilju inhibicije tumorskog rasta.

Neuralni ćelijski adhezioni molekul (engl. *neural cell adhesion molecule, NCAM*) je transmembranski protein, eksprimiran u mnogim tkivima tokom organogeneze. Značajnu ulogu tokom embrionalnog razvoja ostvaruje ne samo u nervnom, mišićnom, neuroektodermalnom i neuroendokrinom tkivu, već i u organima drugačijeg porekla, uključujući i bubrege, igrajući važnu ulogu u procesu mezenhimno-epitelne transformacije (MET), migracije i proliferacije [8]. U adultnom bubregu, *NCAM* je prisutan samo u retkim intersticijumskim ćelijama [9], kao i u bubrežnim neoplazmama [10].

Receptor za fibroblastni faktor rasta (engl. *fibroblast growth factor receptor, FGFR*) pripada familiji tirozin-kinaznih receptora, značajnih za ćelijsku proliferaciju i migraciju, diferencijaciju, apoptozu, epitelno-mezenhimnu transformaciju (EMT) i kancerogenezu [11–14]. *FGFR* receptori mogu biti aktivirani i nekim transmembranskim molekulima, uključujući *NCAM* [15]. Interakcije ova dva molekula opisane su u nervnom [16] i ne-nervnom tkivu [17], ali i u tumorima [18].

Osim podataka da svaki od ova dva molekula učestvuje u procesima migracije, proliferacije i procesima epitelno-mezenhimne transformacije (EMT), koji dovode do transformacije normalne epitelne ćelije u neoplastičnu ćeliju mezenhimalnih karakteristika, postoje podaci i o njihovoj interakciji, kao faktoru koji pospešuje invazivni potencijal pojedinih karcinoma [19]. Interakcija *NCAM* i *FGFR* molekula, njihova ekspresija u

INTRODUCTION

Over the past three decades, the incidence of renal tumors has been steadily increasing in Europe, USA, and Australia [1,2]. In the adult population, kidney cancers account for 2% of all cancers [3], with the most common one being renal cell carcinoma (RCC), which has the highest mortality among urogenital system cancers [4]. There are several pathohistological subtypes, among which there are differences in morphology, genetics, origin, and biological behavior. Clear cell carcinoma is by far the most common (80% – 90%) type, followed by papillary, chromophobe, and collecting duct carcinoma [5]. Although the most common renal cell tumors are carcinomas, there are also benign tumors known as oncocytomas [6]. About 270,000 new cases of RCC are diagnosed annually worldwide, and about 116,000 patients die [1,2]. Given the fact that these tumors rarely show early signs of disease (resulting in a high proportion of patients with metastases), as well as the fact that they are characterized by diverse clinical manifestations and increased resistance to radiotherapy and chemotherapy [7], many clinical and pathological examinations have been conducted for the purpose of discovering potential biomarkers and enabling early diagnosis and immunomodulation with the aim of inhibiting tumor growth.

Neural cell adhesion molecule (NCAM) is a transmembrane protein expressed in many tissues during organogenesis. It plays a significant role during embryonic development, not only in nerve, muscle, neuroectodermal and neuroendocrine tissue, but also in organs of different origin, including kidneys, with an important role in the process of mesenchymal-epithelial transformation (MET), migration and proliferation [8]. In the adult kidney, NCAM is present only in rare interstitial cells [9], as well as in renal neoplasms [10].

The fibroblast growth factor receptor (FGFR) belongs to the family of tyrosine-kinase receptors, important for cell proliferation and migration, differentiation, apoptosis, epithelial-mesenchymal transition (EMT) and carcinogenesis [11–14]. FGFR receptors can also be activated by some transmembrane molecules, including NCAM [15]. The interactions between these two molecules have been described in nervous [16] and non-nervous tissue [17], but also in tumors [18].

Apart from data supporting the fact that each of these two molecules participates in the processes of migration, proliferation, as well as processes of epithelial-mesenchymal transition (EMT), leading to the transformation of a normal epithelial cell into a neoplastic cell with mesenchymal characteristics, there are also data on their interaction as a factor enhancing the invasive potential of certain carcinoma [19]. The

proliferišućim tumorskim ćelijama i metastazama različitih tumora, ali i opisana ekspresija u bubrežnim neoplazmama, čini ove molekule, kao površinske markere, pogodnim za uspostavljanje dijagnoze, ali i potencijalnom metom za primenu novih terapijskih modaliteta [20 – 28].

Kako je poznato da *NCAM* i *FGFR* stupaju u interakcije na površini ćelijske membrane, odlučili smo da ispitamo potencijalni uticaj različitih obrazaca njihove koekspresije na kliničko-patološke karakteristike tumora bubrežnih ćelija.

MATERIJALI I METODE

Uzorci tkiva za analizu i tkivni mikroniz

Iz parafinskih kalupa tkiva tumora bubrega, dijagnostikovanih u periodu 2010 – 2013. godine na Institutu za patologiju Medicinskog fakulteta Univerziteta u Beogradu, uzeti su cilindri tkiva za pravljenje tkivnog mikroniza. Uzorkovanje je rađeno korišćenjem šuplje medicinske igle prečnika 0,6 mm, iz parafinskih kalupa tumora bubrežnih ćelija. Iz svakog kalupa su uzeta tri tkivna cilindra koja su zatim ubačena u parafinski blok i precizno raspoređena u obliku niza. Pomoću mikrotoma, parafanski kalupi tkivnog mikroniza su sečeni na isečke debljine 5 µm i postavljani na mikroskopske pločice, koje su dalje korišćene za imunohistohemijsku analizu.

Uzorci tumorskog tkiva su dobijeni iz 100 tumora bubrega, među kojima je bilo 69 svetloćelijskih *RCC*-a, 12 papilarnih *RCC*-a, 7 hromofobnih *RCC*-a, 5 multilokularnih cističnih *RCC*-a, dva karcinoma Belinijevih sabirnih kanalića, kao i 5 onkocitoma.

Imunohistohemija

Imunohistohemija je urađena na pločicama tkivnih mikronizova. Nakon deparafinizacije u ksilolu i hidratacije, pločice su ubačene u citratni pufer (pH 6,0) i izložene mikrotalasima u trajanju od 20 min na 400 W. Blokada peroksidazne aktivnosti je izvršena sa 1% govođim serumskim albuminom (engl. *bovine serum albumin – BSA*). Nakon ekstrakcije antigena, urađena je inkubacija sa primarnim antitelima *NCAM* (1:50, klon 123C3. D5, *LabVision, USA*) i *FGFR1* (1:100, klon M19B2, *Abcam, USA*) u trajanju od jednog sata. *EnVision™* (*DAKO*, Danska) je korišćen za vizuelizaciju antigen-antitelo reakcije sa 3,3'-diaminobenzidinom (DAB) i sledstvenim kontrastiranjem sa hemalaunom (*Merc, USA*). Negativne kontrole su dobijene izostavljanjem primarnog antitela. Pločice su pregledane upotrebom *BX53* svetlosnog mikroskopa sa *DP12CCD* kamerom (*Olympus*, Nemačka).

interaction between NCAM and FGFR molecules, their expression in proliferating tumor cells and metastases of various tumors, but also the described expression in renal neoplasms, makes these molecules, as surface markers, suitable for establishing a diagnosis, but also makes them a potential target for the application of new therapeutic modalities [20 – 28].

As NCAM and FGFR are known to interact on the surface of the cell membrane, we decided to investigate the potential impact of different patterns of their co-expression on the clinicopathological characteristics of renal cell tumors.

MATERIALS AND METHODS

Tissue samples for analysis and tissue microarray

Sample cylinders of tissue were taken from paraffin molds of renal tumor tissue, diagnosed in the period 2010 – 2013 at the Institute of Pathology of the Faculty of Medicine, University of Belgrade, for making a tissue microarray. Sampling was performed from paraffin molds of renal cell tumors with a hollow needle (0.6 mm in diameter). Three tissue cylinders were taken from each mold, which were then embedded in a paraffin block and precisely arranged in an array. Using a microtome, tissue microarray paraffin molds were cut into 5 µm thick sections and mounted on microscope slides, which were further used for immunohistochemical analysis.

Tumor tissue samples were obtained from 100 renal tumors, among which there were 69 clear cell RCCs, 12 papillary RCCs, 7 chromophobe RCCs, 5 multilocular cystic RCCs, two Bellini duct carcinomas, and 5 oncocytomas.

Immunohistochemistry

Immunohistochemistry was performed on tissue microarray slides. After deparaffinization in xylene and hydration, the slides were placed in a citrate buffer (pH 6.0) and exposed to microwaves for 20 min, at 400 W. Peroxidase activity was blocked with 1% bovine serum albumin (BSA). After antigen extraction, incubation with primary NCAM antibodies (1:50, clone 123C3.D5, LabVision, USA) and FGFR1 (1:100, clone M19B2, Abcam, USA) was performed for one hour. EnVisionTM (DAKO, Denmark) was used to visualize the antigen-antibody reaction with 3,3'-diaminobenzidine (DAB) and subsequent contrast with hemalaun (Mertz, USA). Negative controls were obtained by excluding the primary antibody. Plates were examined using a BX53 light microscope with a DP12CCD camera (Olympus, Germany).

Statistička analiza

Statistička analiza je izvršena upotrebom *IBM SPSS* softvera, verzije 20.0. Korišćeni su χ2 test, Fišerov test, Studentov *t* test, Men-Vitnijev U test, Kruskal-Valisov test i *ANOVA* test, a vrednost $p < 0,05$ je smatrana statistički značajnom. Demografske, kliničke i patohistološke karakteristike tumora bubrega (pol pacijenta, veličina tumora, tip tumora, nuklearni gradus i TNM stadijum bolesti) ispitane su u odnosu na prisustvo i lokalizaciju koekspresije *NCAM* i *FGFR1* molekula.

REZULTATI

Analizirajući 100 tumora, od čega je 68 pripadalo pacijentima muškog, a 32 ženskog pola, istovremenu ekspresiju *NCAM* i *FGFR1* molekula smo zabeležili u 77 tumora (87,8%).

NCAM molekul je uočen na membrani i u citosolu, dok je *FGFR1* uz ove lokalizacije obuhvatio i jedarnu distribuciju.

Kod većine patohistoloških tipova, učestalost koekspresije je bila u rasponu 80% – 100%, dok je od dva karcinoma Belinijevih sabirnih kanalića, samo jedan pokazivao istovremenu ekspresiju *NCAM* i *FGFR1* molekula (Tabela 1).

Primetili smo da je porast javljanja koekspresije pratila porast nuklearnog gradusa, iako nije bilo statističke značajnosti, kao i da su svi tumori sa najvišim nuklearnim gradusom istovremeno eksprimirali ove molekule (Tabela 1).

Statistical analysis

Statistical analysis was performed using IBM SPSS software, version 20.0. The χ2 test, Fisher's test, Student's t test, Mann-Whitney U test, Kruskal-Wallis test, and the ANOVA test were used, and a value of $p < 0.05$ was considered statistically significant. Demographic, clinical and pathohistological characteristics of renal tumors (patient gender, tumor size, tumor type, nuclear grade, and TNM stage of the disease) were examined in relation to the presence and localization of the co-expression of NCAM and FGFR1.

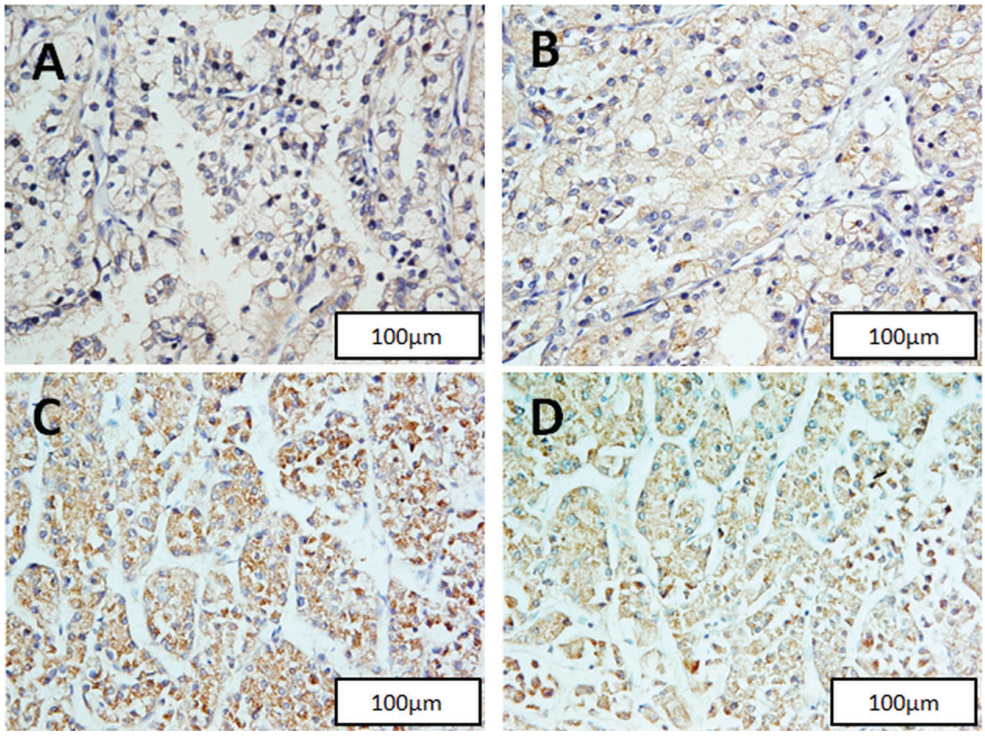
RESULTS

The analysis of 100 tumors, of which 68 were found in male patients and 32 in female patients, we recorded the simultaneous expression of NCAM and FGFR1 in 77 tumors (87.8%).

The NCAM molecule was observed on the membrane and in the cytosol, while FGFR1 included nuclear distribution in addition to these localizations.

In most pathohistological types, the frequency of co-expression was in the 80% – 100% range, while of the two Bellini duct carcinomas, only one showed simultaneous expression of NCAM and FGFR1 (Table 1).

We observed that the increase in the occurrence of co-expression followed the increase in nuclear grade, although without statistical significance, and that all tumors with the highest nuclear grade simultaneously expressed these molecules (Table 1).



Slika 1. Prikaz membranske koekspresije *NCAM* (A) i *FGFR1* (B) molekula u svetloćelijskom RCC-u i citoplazmatske imunoreaktivnosti oba molekula u onkocitomu (*C – NCAM, D – FGFR1*)

Figure 1. Representation of membrane co-expression of NCAM (A) and FGFR1 (B) molecules in clear cell RCC and of cytoplasmic immunoreactivity of both molecules in oncocytoma (C – NCAM, D – FGFR1)

Tabela 1. Patohistološke karakteristike tumora bubrega u odnosu na prisustvo FGFR1-NCAM koekspresije

Table 1. Pathohistological characteristics of renal tumors in relation to the presence of FGFR1-NCAM co-expression

Patohistološke karakteristike / *Pathohistological characteristics*		Koekspresija FGFR1-NCAM / *FGFR1-NCAM co-expression* n (%)		p-vrednost/ *p-value*
		Odsutna / *Absent*	Prisutna / *Present*	
Tip tumora / *Type of tumor*	Svetloćelijski RCC / *Clear cell RCC*	9 (15%)	51 (85%)	0.383
	Papilarni RCC, niski gradus / *Papillary RCC, low grade*	0 (0.0%)	2 (100.0%)	
	Papilarni RCC, visoki gradus / *Papillary RCC, high grade*	0 (0%)	9 (100%)	
	Multilokularni cistični RCC / *Multilocular cystic RCC*	1 (20%)	4 (80%)	
	Hromofobni RCC / *Chromophobe RCC*	0 (0.0%)	6 (100.0%)	
	Karcinom Belinijevih sabirnih kanalića / *Bellini duct carcinoma*	1 (50%)	1 (50%)	
	Onkocitom / *Oncocytoma*	0 (0.0%)	5 (100.0%)	
Nuklearni gradus / *Nuclear grade* (NG)	NG I	1 (14.3%)	6 (85.7%)	0.821
	NG II	6 (15.4%)	33 (84.6%)	
	NG III	4 (12.9%)	27 (87.1%)	
	NG IV	0 (0%)	5 (100%)	
T stadijum / *T stage*	T1	7 (22.6%)	24 (77.4%)	0.121
	T2	2 (22.2%)	7 (77.8%)	
	T3	1 (3.1%)	31 (96.9%)	
	T4	0 (0.0%)	1 (100%)	
N stadijum / *N stage*	N0	0 (0.0%)	8 (100%)	1.000
	N1	0 (0.0%)	2 (100.0%)	
M stadijum / *M stage*	M0	0 (0.0%)	1 (100.0%)	1.000
	M1	0 (0.0%)	2 (100.0%)	

n – broj slučajeva; N0 – bez regionalnih metastaza; N1 – sa regionalnim metastazama; M0 – bez sistemskih metastaza; M1 – sa sistemskim metastazama

n – number of cases; N0 – without regional metastases; N1 – with regional metastases; M0 – without systemic metastases; M1 – with systemic metastases

Sa povećanjem T stadijuma uočen je porast učestalosti istovremene ekspresije *NCAM* i *FGFR1* molekula u tumorima bubrega. Među tumorima viših stadijuma (T3 i T4), samo jedan tumor nije pokazao koekspresiju, dok koekspresije nije bilo u 22,9% tumora u stadijumima T1 i T2. Međutim, nije bilo statistički značajne razlike (Tabela 1).

Budući da nam podaci o nodalnim i sistemskim metastazama za veći broj uzoraka nisu bili dostupni, nismo bili u prilici da ispitamo odnos njihovog postojanja i prisustva koekspresije. Ipak, uočili smo da su među tumorima o kojima smo dobili ove podatke, svi tumori sa metastazama, kao i svi tumori bez metastaza, pokazali koekspresiju (Tabela 1).

Prisustvo membranske ekspresije i *NCAM* i *FGFR1* molekula zapazili smo kod svega 59% tumora, pri čemu je ona bila vrlo varijabilna u odnosu na patohistološki tip tumora. Ni kod jednog tumora među karcinomi-

With an increasing T stage, an increase in the frequency of simultaneous expression of NCAM and FGFR1 in renal tumors was observed. Among high stage tumors (T3 and T4), only one tumor showed no co-expression, while co-expression was absent in 22.9% of T1 and T2 stage tumors. However, there was no statistically significant difference (Table 1).

Since data on nodal and systemic metastases for a larger number of samples were not available to us, we were unable to examine the relationship between their occurrence and the presence of co-expression. However, we observed that among the tumors for which we had obtained this data, all tumors with metastases, as well as all tumors without metastases, showed co-expression (Table 1).

We observed the presence of membranous expression of both NCAM and FGFR1 in only 59% of tumors, with great variations depending on the pathohistolog-

Tabela 2. Patohistološke karakteristike tumora bubrega u odnosu na lokalizaciju FGFR1-NCAM koekspresije

Table 2. Pathohistological characteristics of renal tumors in relation to the presence of FGFR1-NCAM co-expression

Patohistološke karakteristike / *Pathohistological characteristics*		Membranska lokalizacija koekspresije FGFR1-NCAM / *Membranous localization of FGFR1-NCAM co-expression* n (%)		p-vrednost/ *p-value*
		Odsutna / *Absent*	Prisutna / *Present*	
Tip tumora / *Type of tumor*	Svetloćelijski RCC / *Clear cell RCC*	24 (40%)	36 (60%)	0.372
	Papilarni RCC, niski gradus / *Papillary RCC, low grade*	1 (50.0%)	1 (50.0%)	
	Papilarni RCC, visoki gradus / *Papillary RCC, high grade*	3 (33.3%)	6 (66.7%)	
	Multilokularni cistični RCC / *Multilocular cystic RCC*	1 (20%)	4 (100%)	
	Hromofobni RCC / *Chromophobe RCC*	2 (28.6%)	5 (71.4%)	
	Karcinom Belinijevih sabirnih kanalića / *Bellini duct carcinoma*	2 (100%)	0 (0%)	
	Onkocitom / *Oncocytoma*	3(75%)	1 (25%)	
Nuklearni gradus / *Nuclear grade* (NG)	NG I	2 (28.6%)	5 (71.4%)	0.854
	NG II	14 (35.9%)	25 (64.1%)	
	NG III	14 (43.8%)	18 (56.3%)	
	NG IV	2 (40%)	3 (60%)	
T stadijum / *T stage*	T1	15 (48.4%)	16 (51.6%)	0.638
	T2	4 (44.4%)	5 (56.6%)	
	T3	12 (36.4%)	21 (63.6%)	
	T4	0 (0%)	1 (100%)	
N stadijum / *N stage*	N0	2 (22.2%)	7 (77.8%)	1.000
	N1	0 (0%)	2 (100%)	
M stadijum / *M stage*	M0	0 (0%)	1 (100%)	1.000
	M1	0 (0%)	2 (100%)	

n – broj slučajeva; N0 – bez regionalnih metastaza; N1 – sa regionalnim metastazama; M0 – bez sistemskih metastaza; M1 – sa sistemskim metastazama

n – number of cases; N0 – without regional metastases; N1 – with regional metastases; M0 – without systemic metastases; M1 – with systemic metastases

ma sabirnih kanalića nismo uočili membransku koekspresiju, dok je među onkocitomima ona bila prisutna samo kod jednog pacijenta, a kod svih ostalih tipova je koekspresija bila prisutna sa učestalošću većom od 50%, kao što je prikazano u Tabeli 2. Na Slici 1 prikazani su različiti obrasci *NCAM* i *FGFR1* ekspresije.

Nije uočena povezanost nuklearnog gradusa i membranske koekspresije, ali je primećeno da je porast T stadijuma pratilo i povećanje procenta tumora koji su na membranama imali oba molekula, iako nije bilo statistički značajne razlike (Tabela 2).

Ispitivanjem povezanosti veličine tumora i lokalizacije *NCAM* i *FGFR1* koekspresije, ustanovljeno je da su tumori bubrega bez membranske koekspresije bili prosečno nešto manje veličine (6,3 ± 2,7) od onih koji su imali membransku pozitivnost (6,9 ± 4,3), $p = 0,390$.

ical type of the tumor. We did not observe membranous co-expression in any tumor among the collecting duct carcinomas, while among oncocytomas it was present in only one patient, whereas in all other types of tumors, co-expression was present with a frequency greater than 50%, as shown in Table 2. Figure 1 shows different patterns of NCAM and FGFR1 expression.

No association between nuclear grade and membranous co-expression was observed, but it was noted that the increase in T stage was followed by an increase in the percentage of tumors that had both molecules on the membranes, although there was no statistically significant difference (Table 2).

The examination of the relationship between tumor size and localization of NCAM and FGFR1 co-expression showed that renal tumors without membra-

Analizom lokalizacije ekspresije svakog od ova dva molekula, uvideli smo da imaju veoma sličnu distribuciju. Tumori sa membranskom ekspresijom *NCAM* molekula su u 83% slučajeva na membranama eksprimirali i *FGFR1*, dok je ekspresiju *FGFR1* molekula na membrani pratila i membranska ekspresija *NCAM* molekula u 86% slučajeva. Zanimljivo je da su svi tumori u čijem smo jedru našli *FGFR1* molekule imali i *FGFR1* i *NCAM* molekule na površini membrane.

DISKUSIJA

Karcinogeneza je višestepeni proces koji često kulminira invazijom tumorskih ćelija u okolno tkivo i u krvne sudove, na taj način doprinoseći njihovoj diseminaciji i u udaljena tkiva. Otkrivanje molekularnih interakcija koje omogućavaju inicijaciju i progresiju ovog procesa u mnogome bi olakšalo definisanje ključnih karika, koje bi mogle biti meta ciljnog terapijskog delovanja.

Džimbo i saradnici su otkrili da *NCAM* u različitim tumorskim ćelijama indukuje stvaranje proteina koji onemogućava pripajanje tumorskih ćelija za matriks i bazalnu membranu [29]. Ovi autori su jednom delu eksperimentalnih životinja preneli tumorske ćelije koje su eksprimirale taj protein, dok su drugom delu preneli ćelije koje nisu posedovale ovaj protein. Broj životinja kod kojih se tumor razvio nakon prenošenja je kod prve grupe bio značajno manji od broja životinja u drugoj grupi. Ovi rezultati ukazuju na to da *NCAM*, posredstvom drugog proteina za čiju je ekspresiju odgovoran, negativno utiče na procese ključne za širenje malignog procesa.

S druge strane, postoje podaci koji ukazuju na to da agresivnost neuroblastoma i neuroendokrinih tumora raste s javljanjem *NCAM* proteina [30,31]. Ovakvi, naizgled suprotstavljeni rezultati, navode na ideju da za procenu biološkog ponašanja tumora možda nije korisno ispitivanje nezavisne ekspresije ovog molekula, već da su značajni i drugi molekuli sa kojima on stupa u različite interakcije koje dovode do stimulacije ili inhibicije različitih procesa. Tako je uočeno da se kolokalizacija *NCAM* molekula i aldehid dehidrogenaze 1 (ALDH1) u blastemskoj komponenti Vilmsovog tumora javlja u 33% slučajeva, a utvrđeno je da ovakav imunomorfološki profil značajno utiče na pojavu metastaza, recidiva bolesti i smrti pacijenata, kao i da determiniše odgovor na *ifosfamide-carboplatin-etoposide* (*ICE*) protokol hemoterapije [22]. U svojoj studiji, Jang i Lu su pokazali da koekspresija *CCND1* i *FGFR1* molekula postoji kod karcinoma pluća, kao i da *FGFR1* promoviše EMT [21]. Ispitivanjem ćelija pleuropulmonalnog blastoma, Šukrun i Golan su primetili da tretiranjem anti-*NCAM* imunokonjugatom dolazi do supresije rasta tumorskih ćelija u ovom tumoru [23]. Egbivi i Kokl su u

nous co-expression were, on average, slightly smaller in size (6.3 ± 2.7) than those with membranous positivity (6.9 ± 4.3), $p = 0.390$.

By analyzing the localization of the expression of each of these two molecules, we saw that they had very similar distribution. Tumors with membranous expression of NCAM also expressed FGFR1 on the membranes in 83% of cases, while the expression of FGFR1 on the membrane was accompanied by membranous expression of NCAM in 86% of the cases. It is interesting that all tumors in whose nucleus we found FGFR1 molecules, had both FGFR1 and NCAM molecules on the membrane surface.

DISCUSSION

Carcinogenesis is a multistage process that often culminates in the invasion of tumor cells into the surrounding tissue and blood vessels, thus contributing to their dissemination to distant tissues. The discovery of molecular interactions that enable the initiation and progression of this process would greatly facilitate the defining of key links, which could be the focus of targeted treatment.

Jimbo et al. found that NCAM in various tumor cells induces the production of a protein that prevents the attachment of tumor cells to the matrix and the basement membrane [29]. These authors transferred tumor cells expressing this protein to one group of experimental animals, while they transferred cells that did not possess this protein to the other group of experimental animals. The number of animals developing tumors after transfer was significantly lower in the first group than in the second group. These results indicate that NCAM, via another protein whose expression it is responsible for, has a negative effect on the processes crucial for the dissemination of the malignant process.

On the other hand, there are data indicating that the aggressiveness of neuroblastoma and neuroendocrine tumors increases with the presence of the NCAM protein [30,31]. These seemingly contradictory results indicate that for the assessment of the biological behavior of tumors it may not be useful to examine the independent expression of this molecule, but that other molecules, with which NCAM enters into various interactions that lead to the stimulation or inhibition of various processes, are also important. Thus, it was observed that the colocalization of the NCAM molecule and aldehyde dehydrogenase 1 (ALDH1) in the blastema component of Wilms' tumor occurs in 33% of cases, and it was found that this immunomorphological profile significantly affects the occurrence of metastases, disease recurrence, and patient death, as well as that it determines the response to the ifosfamide-carbo-

svojoj studiji primetili da je povećana ekspresija *FGFR1* molekula među astrocitomima u pedijatrijskoj populaciji bila povezana sa uzrastom, lokacijom i gradusom tumora, dok je membranska ekspresija *pFGFR1* molekula bila povezana sa stepenom maligniteta i gradusom tumora [27].

Poznato je da *FGFR1* u neinvazivnim tumorima stimuliše rast i proliferaciju, dok u invazivnim tumorima stimuliše i proces migracije [32]. Interakcije između *FGFR1* i *NCAM* molekula opisane su prvi put u neuronima [16], a kasnije su opisane i u drugim tkivima [17,18]. Pokazano je da interakcija između ova dva molekula na membrani fibroblasta stimuliše migraciju ovih ćelija [28], dok je studija izvedena na eksperimentalnim ćelijskim kulturama epitelijalnog karcinoma jajnika ukazala na to da aktivacija *FGFR1* molekula *NCAM* molekulom povećava invazivnost tumorskih ćelija [19].

Ispitujući uticaj interakcija ova dva molekula na invazivnost karcinoma jajnika, Kolombo i Kalavaro su indukovali ekspresiju *NCAM* proteina u ćelijskim linijama koje su eksprimirale *FGFR1*, što je dovelo do transformisanja indolentnog karcinoma u invazivni. Međutim, indukcija ekspresije *NCAM* proteina modifikovanog tako da ne poseduje *FGFR1* vezujući domen, nije uticala na ponašanje karcinoma [33], čime je pokazano da su interakcije ova dva molekula, koje su do sada opisivane samo na površini ćelijske membrane, važne za agresivnost tumora. Pored mnogobrojnih karcinoma, u našoj studiji je koekspresija *NCAM* i *FGFR1* molekula detektovana i u svim onkocitomima. Međutim, obrazac ove koekspresije u benignim tumorima je bio isključivo sa citoplazmatskom lokalizacijom. Stoga bismo mogli reći da je, uprkos prisustvu oba molekula, u onkocitomima njihova interakcija izostala, jer je membranska imunopozitivnost bila isključivo karakteristika malignih tumora porekla bubrežnih ćelija.

Kolombo i Kalavaro su takođe otkrili da je koekspresija *NCAM* i *FGFR1* molekula bila najizraženija na ćelijama lokalizovanim na samoj periferiji tumora. Shvatili su to kao podatak koji govori u prilog hipotezi da koekspresija ovih molekula stimuliše migraciju i adheziju, procese ključne za metastaziranje tumora. Iako su kod najvećeg broja pacijenata u našoj studiji nedostajale informacije o prisustvu regionalnih i sistemskih metastaza tumora bubrega, ipak, analizirajući dostupne podatke nismo uočili povezanost između postojanja metastaza i membranske koekspresije *NCAM* i *FGFR1* molekula. Imajući u vidu značaj dimenzija tumora u određivanju stadijuma bolesti [34], mogli bismo pretpostaviti da je membranska koekspresija *NCAM* i *FGFR1* molekula imunomorfološki supstrat lokalnog tumorskog rasta. Tako je porast učestalosti membranske koekspresije ispitivanih proteina pratio porast T stadiju-

platin-etoposide (ICE) chemotherapy protocol [22]. In their study, Yang and Lu showed that co-expression of CCND1 and FGFR1 molecules exists in lung cancer, and that FGFR1 promotes EMT [21]. Examining pleuropulmonary blastoma cells, Shukrun and Golan observed that treatment with anti-NCAM immunoconjugate suppresses the growth of tumor cells in this tumor [23]. In their study, Egbivwie and Cockle observed that increased expression of FGFR1 among astrocytomas in the pediatric population was associated with age, location, and tumor grade, while membrane expression of pFGFR1 was associated with malignancy and tumor grade [27].

It is known that in non-invasive tumors FGFR1 stimulates growth and proliferation, while in invasive tumors it also stimulates the process of migration [32]. Interactions between FGFR1 and NCAM molecules were described for the first time in neurons [16], and were later described in other tissues [17,18]. It has been shown that the interaction between these two molecules on the membrane of fibroblasts stimulates the migration of these cells [28], while a study performed on experimental cell cultures of epithelial ovarian cancer indicated that the activation of the FGFR1 molecule by the NCAM molecule increases the invasiveness of tumor cells [19].

Examining the influence of the interaction between these two molecules on the invasiveness of ovarian cancer, Colombo and Callavaro induced the expression of the NCAM protein in cell lines expressing FGFR1, which led to the transformation of indolent cancer to invasive carcinoma. However, the induction of the expression of the NCAM protein, modified so that it does not possess the FGFR1 binding domain, did not affect the behavior of the cancer [33], thus showing that the interactions between these two molecules, which have been described thus far only on the surface of the cell membrane, are significant for tumor aggressiveness. In our study, in addition to numerous cancers, co-expression of NCAM and FGFR1 was also detected in all oncocytomas. However, the pattern of this co-expression in benign tumors was exclusively linked to cytoplasmic localization. Therefore, we could say that, despite the presence of both molecules, their interaction was absent in oncocytomas, because membrane immunopositivity was exclusively a characteristic of malignant tumors of renal cell origin.

Colombo and Callavaro also found that the co-expression of NCAM and FGFR1 was most pronounced in cells located at the very periphery of the tumor. They understood this to speak in favor of the hypothesis that the co-expression of these molecules stimulates migration and adhesion, processes crucial for tumor

ma tumora bubrega, što bi moglo indirektno da ukaže na veću sklonost *NCAM-FGFR1* pozitivnih tumora ka metastaziranju, budući da je TNM klasifikacija tumora važna, ne samo prilikom donošenja odluke o terapijskom pristupu, već ima uticaj i na prognozu bolesti i ukazuje na mogućnost metastaziranja [35].

Studija koju su sproveli Ronkainen i saradnici na različitim patohistološkim tipovima *RCC*-a, uključujući svetloćelijski, papilarni i hromofobni karcinom, ispitivala je ekspresiju *NCAM* molekula, pri čemu nije uočena korelacija između *NCAM* ekspresije i tipa, gradusa ili stadijuma tumora [10]. Činjenica da u ovoj studiji nije izučavana istovremena ekspresija drugih molekula, koji bi mogli da stupaju u interakcije sa *NCAM*-om u procesima bitnim za napredovanje tumora, mogla bi da objasni prividno neslaganje zaključaka ovog istraživanja i naših rezultata.

Danijel i saradnici su izneli tvrdnju da su *NCAM* pozitivni tumori agresivniji i da češće metastaziraju u nervna i neuroendokrina – *NCAM* pozitivna tkiva, poput nadbubrežne žlezde i centralnog nervnog sistema. Oni su opisali membransku ekspresiju u svetloćelijskom, ali ne i u papirilarnom i hromofobnom *RCC*-u [36]. Mi smo, s druge strane, u većini tumora istih patohistoloških tipova, uočili ne samo samostalnu *NCAM* ekspresiju, već i koekspresiju sa *FGFR1* molekulom.

Keresteš i Bunstra su odavno ukazali na potencijalni značaj nuklearne lokalizacije različitih receptora za faktore rasta. Ukazali su na činjenicu da prisustvo receptora i njihovih liganada u jedru dovodi do porasta proliferacije [37]. Čioni i Grous su, radeći na karcinomima dojke, otkrili da je granzim B odgovoran za dospevanje *FGFR*1 u jedro ćelije i da njegovim blokiranjem izostaje efekat aktivacije *FGFR1* molekula na proliferaciju, kao i to da *FGFR1* može da deluje kao transkripcioni faktor za neke gene odgovorne za proliferaciju [38]. Svi tumori bubrega u čijim smo jedrima detektovali *FGFR1* molekul pokazali su koekspresiju *FGFR1* i *NCAM* molekula na membrani. S obzirom na podatke o tome da *FGFR1* deluje kao transkripcioni faktor za neke gene, ne možemo isključiti mogućnost da je membranska ekspresija *NCAM* proteina rezultat ovakvog vida aktivnosti *FGFR1* molekula, ali to zahteva dodatna ispitivanja. Takođe, nije isključeno da je ekspresija *FGFR1* molekula u jedru odgovorna za napredovanje karcinoma bubrega, kao što je pokazano u tumorima dojke, mehanizmom koji ne podrazumeva interakcije sa *NCAM* proteinom [39].

Ispitivanja različitih molekularnih interakcija u patologiji tumora imaju za cilj definisanje ključnih procesa važnih u inicijaciji i progresiji rasta tumora, sposobnosti invazije u okolna tkiva i metastaziranju tumora. Nedavno je otkriveno da sintetska supstanca *PD173074*, koja predstavlja potentni *FGFR1* inhibitor,

metastases. For the majority of patients in our study information on the presence of regional and systemic metastases of renal tumors was lacking. However, analyzing the available data, we did not observe an association between the presence of metastases and membranous co-expression of NCAM and FGFR1. Bearing in mind the importance of tumor size in determining the stage of disease [34], we could assume that membranous co-expression of NCAM and FGFR1 is an immunomorphological substrate of local tumor growth. Thus, the increase in the frequency of membranous co-expression of the analyzed proteins was accompanied by an increase in the T stage of renal tumors, which could indirectly indicate a greater propensity of NCAM-FGFR1 positive tumors to metastasize, since the TNM classification of tumors is important, not only when deciding on a therapeutic approach, but it also has an impact on the prognosis of the disease and indicates the possibility of metastasis [35].

A study by Ronkainen et al. performed on different pathohistological types of RCC, including clear cell, papillary and chromophobe carcinoma, examined the expression of NCAM molecules. In this study, no correlation was observed between NCAM expression and tumor type, grade or stage [10]. The fact that the simultaneous expression of other molecules, which could interact with NCAM in processes essential for tumor progression, was not examined in this study could explain the apparent discrepancy between the conclusions of this study and our results.

Daniel et al. claimed that NCAM-positive tumors are more aggressive and that they more often metastasize to nervous and neuroendocrine – NCAM-positive tissues, such as the adrenal gland and the central nervous system. They described membranous expression in clear cell but not in papillary and chromophobe RCCs [36]. On the other hand, in most tumors of the same pathohistological types, we observed not only independent NCAM expression, but also co-expression with FGFR1.

Keresztes and Boonstra pointed out long ago the potential importance of the nuclear localization of different growth factor receptors. They highlighted the fact that the nuclear presence of receptors and their ligands leads to an increase in proliferation [37]. Chioni and Grose, working on breast cancers, discovered that granzyme B is responsible for the delivery of FGFR1 to the cell nucleus and that blocking it eliminates the effect of FGFR1 activation on proliferation, as well as that FGFR1 can act as a transcription factor for some genes responsible for proliferation [38]. All renal tumors in whose nuclei we detected FGFR1 showed co-expression of FGFR1 and NCAM molecules on the membrane.

sprečava proliferaciju tumorskih ćelija i indukuje promenu njihove morfologije putem indukcije mezenhimno-epitelne transformacije, redukujući invazivnost i rast tumora [40,41]. S obzirom na iznete zaključke o uticaju interakcije *NCAM* i *FGFR1* molekula, u daljim istraživanjima moglo bi se otvoriti pitanje mogućnosti primene *FGFR1* inhibitora (*PD173074*) u cilju usporavanja lokalnog rasta tumora bubrega i redukcije njegovog invazivnog potencijala.

ZAKLJUČAK

Moguće je da samo membranska koekspresija *NCAM* i *FGFR1* molekula imaju uticaja na agresivnije biološko ponašanje tumora, utičući tako i na stadijum bolesti, te je samo ovakav obrazac koekspresije značajan za procenu njihove biološke aktivnosti, koja nije uočena ni kod jednog benignog tumora, uprkos prisustvu citoplazmatske koekspresije. Postoji mogućnost da je kod manjeg broja pacijenata fenomen membranske *NCAM-FGFR1* koekspresije rezultat prisustva *FGFR1* molekula u jedru tumorskih ćelija. Potrebno je sprovesti dalja ispitivanja, na većem broju pacijenata, kako bi se detaljno ispitao značaj koekspresije *NCAM* i *FGFR1* molekula kod pacijenata sa tumorima bubrega.

Sukob interesa: Nije prijavljen.

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Given the data that FGFR1 acts as a transcription factor for some genes, we cannot rule out the possibility that membranous expression of the NCAM protein is the result of this kind of FGFR1 activity, but this requires additional research. Also, it is possible that the expression of FGFR1 in the nucleus is responsible for the progression of renal cancer, as shown in breast tumors, by a mechanism that does not involve interactions with the NCAM protein [39].

Investigations of various molecular interactions in tumor pathology aim to define the key processes important in the initiation and progression of tumor growth, the ability to invade surrounding tissues, and tumor metastasis. It was recently discovered that the synthetic substance PD173074, which is a potent FGFR1 inhibitor, prevents the proliferation of tumor cells and induces a change in their morphology through the induction of mesenchymal-epithelial transformation, reducing invasiveness and tumor growth [40,41]. Considering the above conclusions about the effect of the NCAM-FGFR1 interaction, further research could open the question of the possibility of applying the FGFR1 inhibitor (PD173074) in order to slow down the local growth of renal tumors and reduce their invasive potential.

CONCLUSION

It is possible that only membranous co-expression of NCAM and FGFR1 affects more aggressive biological behavior of a tumor, thus affecting the stage of the disease, and that only this pattern of co-expression is significant for the assessment of their biological activity, which was not observed in any benign tumor, despite the presence of cytoplasmic co-expression. It is possible that in a smaller number of patients the phenomenon of membranous NCAM-FGFR1 co-expression is the result of the presence of FGFR1 molecules in the nucleus of the tumor cells. It is necessary to perform further studies, on a larger number of patients, in order to make a detailed analysis of the significance of the co-expression of NCAM and FGFR1 in patients with renal tumors.

Conflict of interest: None declared.

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EKSPRESIJA NEURALNOG ĆELIJSKOG ADHEZIONOG MOLEKULA U INTERSTICIJUMU BUBREGA SA RAZLIČITIM STEPENOM FIBROZE

ORIGINALNI RAD

ORIGINAL ARTICLE

EXPRESSION OF THE NEURAL CELL ADHESION MOLECULE IN THE RENAL INTERSTITIUM IN DIFFERENT STAGES OF FIBROSIS

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SAŽETAK

Uvod: U zdravim adultnim bubrezima diferentovane tubulske epitelne ćelije ne eksprimiraju neuralni ćelijski adhezioni molekul (engl. *neural cell adhesion molecule – NCAM*), dok se malobrojne *NCAM* eksprimirajuće ćelije mogu detektovati u bubrežnom intersticijumu. Uloga i značaj ovih ćelija još nisu razjašnjeni, ali je primećeno da se broj *NCAM* eksprimirajućih ćelija povećava u stadijumu početne intersticijske fibroze.

Cilj rada: Cilj rada je da se ispita značaj ekspresije *NCAM* molekula u intersticijumu bubrega kod etiološki različitih oboljenja sa različitim stepenom intersticijske fibroze i da se definišu patohistološki i klinički pokazatelji (prediktori) oštećenja funkcije bubrega.

Materijal i metode: Ispitivanje je obuhvatilo 69 pacijenata kojima su iglene biopsije bubrega urađene tokom 2011. i 2012. godine. Prikupljeni su klinički i laboratorijski podaci u vreme biopsije i u vreme poslednjeg kontrolnog pregleda. Patohistološke karakteristike definisane su optičko-mikroskopski, dok su imunohistohemijskim bojenjem, korišćenjem primarnog *NCAM* antitela (1:50, klon *123C3.D5*), detektovane *NCAM* eksprimirajuće intersticijske ćelije.

Rezultati: *NCAM* eksprimirajuće intersticijske ćelije detektovane su u 59,4% biopsija bubrega, a prisustvo ovih ćelija bilo je značajno češće u početnim fazama intersticijske fibroze nego u drugim stadijumima ($p < 0,001$) i nije zavisilo od patohistološke dijagnoze ($p = 0,995$). Pacijenti kod kojih su detektovane *NCAM* ćelije imali su znatno niže vrednosti proteinurije u vreme biopsije u odnosu na pacijente bez *NCAM* intersticijskih ćelija ($p = 0,024$). Vrednosti serumskog kreatinina ($p < 0,001$) i uree ($p = 0,007$) značajno su uticale na verovatnoću pogoršanja bubrežne funkcije.

Zaključak: Prisustvo *NCAM* ćelija u u intersticijumu bubrega je karakteristika ranih faza hroničnih bolesti bubrega sa početnom intersticijskom fibrozom i blažim stepenom proteinurije.

Ključne reči: *NCAM* eksprimirajuće ćelije, intersticijska fibroza, bubrežno oštećenje, prediktori

ABSTRACT

Introduction: In healthy adult kidneys, differentiated tubular epithelial cells do not express the neural cell adhesion molecule (NCAM), while a small number of NCAM-expressing cells can be detected in the renal interstitium. The role and the significance of these cells have not yet been clarified, but it has been observed that the number of NCAM-expressing cells increases in the initial stage of interstitial fibrosis.

Aim: The aim of the study is to examine the significance of the expression of NCAM molecules in the renal interstitium, in etiologically different diseases, with varying degrees of interstitial fibrosis, as well as to define the pathohistological and clinical indicators (predictors) of impaired kidney function.

Materials and methods: The study included 69 patients who underwent needle biopsies of the kidneys in 2011 and 2012. Clinical and laboratory data were collected at the time of the biopsy and at the time of the latest follow-up examination. Pathohistological characteristics were defined optically-microscopically, while NCAM-expressing interstitial cells were detected with immunohistochemical staining, using the primary NCAM antibody (1:50, clone 123C3.D5).

Results: NCAM-expressing interstitial cells were detected in 59.4% of kidney biopsies, the presence of these cells was significantly more frequent in the initial stages of interstitial fibrosis than in the remaining stages ($p < 0.001$), and it did not depend on the pathohistological diagnosis ($p = 0.995$). Patients in whom NCAM cells were detected had significantly lower proteinuria levels at the time of biopsy, as compared to patients without NCAM interstitial cells ($p = 0.024$). The levels of serum creatinine ($p < 0.001$) and urea ($p = 0.007$) significantly influenced the probability of the deterioration of renal function.

Conclusion: The presence of NCAM cells in the kidney interstitium is a characteristic of the early stages of chronic kidney disease with incipient interstitial fibrosis and a lesser degree of proteinuria.

Keywords: NCAM-expressing renal interstitial cells, interstitial fibrosis, renal impairment, predictors

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Primljeno • *Received*: August 13, 2023; **Revidirano • *Revised*:** October 6, 2023; **Prihvaćeno • *Accepted*:** October 13, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-46516

UVOD

Neuralni ćelijski adhezioni molekul (engl. *neural cell adhesion molecule – NCAM*) je sijaloglikoprotein uključen u ćelijsko-ćelijske interakcije i u interakcije ćelije sa ekstracelularnim matriksom [1,2].

Ovaj molekul ima veoma značajnu ulogu u toku embrionalnog razvoja mozga, perifernih nerava, mišića i bubrega [3]. Ćelije metanefričnog mezenhima obilno eksprimiraju *NCAM*, ali se ekspresija ovog molekula postepeno gubi sa napredovanjem diferencijacije ćelija koje će u najvećoj meri graditi epitel tubula bubrega [4]. U zdravim adultnim bubrezima, diferentovane epitelne ćelije ne eksprimiraju *NCAM* [5]. Međutim, malobrojne *NCAM* eksprimirajuće ćelije se mogu detektovati u intersticijumu zdravih bubrega, i za njih se smatra da predstavljaju ćelije metanefričnog mezenhima koje su zaostale nakon embrionalnog razvoja bubrega [3,4]. Uloga i značaj ovih ćelija nisu razjašnjeni ali je primećeno da se broj *NCAM* eksprimirajućih ćelija povećava u stadijumu početne intersticijske fibroze, te se sve više spekuliše o značaju ovih ćelija u ranoj fazi reparacije bubrežnog parenhima [4]. Ovoj hipotezi doprinose i rezultati drugih istraživača koji su ukazali na značaj *NCAM* molekula u procesu fibroze skeletnih mišića i pankreasa [6].

NCAM je takođe i specifični marker neuroektodermalne i neuroendokrine diferencijacije ćelija [1,2]. S obzirom na to da se pretpostavlja da eritropoetin produkujuće ćelije u bubrezima vode poreklo od neuralnog grebena, tj. da imaju neuroektodermalno poreklo [7,8,9], nije isključena mogućnost da *NCAM* ekprimirajuće intersticijske ćelije zapravo predstavljaju eritropoetin produkujuće ćelije. Zapažena je indukcija transkripcije nekoliko *NCAM* izoformi zajedno sa *FGFR1* receptorom, što ukazuje na mehaničku vezu između *NCAM/FGFR1* signalizacije i indukcije fibrogeneze u bubrezima [10].

Imajući u vidu da je intersticijska fibroza patomorfološki supstrat narušavanja funkcije bubrega i da se javlja kod mnogih, etiološki raznovrsnih oboljenja bubrega, ulažu se veliki napori u ispitivanje molekurne osnove i signalnih puteva koji doprinise ovom procesu. Stoga je cilj ove studije bio da se ispita značaj ekspresije *NCAM* molekula u intersticijumu bubrega kod etiološki raznovrsnih oboljenja bubrega sa različitim stepenom intersticijske fibroze i da se definišu kliničke karakterstike bolesnika kod kojih su detektovane ove ćelije. Takođe, ova studija je sprovedena i sa ciljem da se definišu pokazatelji (prediktori) narušavanja funkcije bubrega.

MATERIJAL I METODE

Optičko-mikroskopski su retrospektivno analizirane iglene biopsije bubrega pacijenata dijagnostikovanih tokom 2011. i 2012. godine, na Institutu za patologiju Medicinskog fakulteta, Univerziteta u Beogradu. Odabrano je 69

INTRODUCTION

Neural cell adhesion molecule (NCAM) is a sialoglycoprotein involved in cell-cell interactions and cell interactions with the extracellular matrix [1,2].

This molecule plays a very important role in the embryonic development of the brain, the peripheral nerves, the muscles and the kidneys [3]. The cells of the metanephric mesenchyme abundantly express NCAM, but the expression of this molecule gradually disappears with the progression of the differentiation of the cells that will predominantly build the renal tubular epithelium [4]. In healthy adult kidneys, differentiated epithelial cells do not express NCAM [5]. However, a small number of NCAM-expressing cells can be detected in the interstitium of healthy kidneys, and they are thought to represent metanephric mesenchymal cells left behind after embryonic kidney development [3,4]. The role and the importance of these cells have not as yet been clarified, but it has been observed that the number of NCAM-expressing cells increases in the initial stage of interstitial fibrosis, and there is increasing speculation about the importance of these cells in the early stage of renal parenchymal repair [4]. This hypothesis is supported by the results of other researchers who have indicated the importance of the NCAM molecule in the process of skeletal muscle and pancreatic fibrosis [6].

NCAM is also a specific marker of neuroectodermal and neuroendocrine cell differentiation [1,2]. Given that it is assumed that the erythropoietin-producing cells in the kidneys originate from the neural crest, i.e., they are believed to have neuroectodermal origin [7,8,9], the possibility that NCAM-expressing interstitial cells actually represent erythropoietin-producing cells should not be excluded. Transcriptional induction of several NCAM isoforms was observed along with FGFR1, suggesting a mechanical link between NCAM/FGFR1 signaling and fibrogenesis induction in the kidney [10].

Bearing in mind that interstitial fibrosis is a pathomorphological substrate of impaired kidney function and that it occurs in many, etiologically diverse kidney diseases, significant effort is being made to investigate the molecular basis and the signaling pathways contributing to this process. Therefore, the aim of this study was to examine the significance of the expression of NCAM molecules in the kidney interstitium in etiologically diverse kidney diseases with different degrees of interstitial fibrosis, as well as to define the clinical characteristics of patients in whom these cells were detected. Also, this study was conducted with the aim of defining indicators (predictors) of impaired kidney function.

pacijenata kod kojih je bilo dovoljno tkiva u parafinskim kalupima biopsija iz kojih bi se izradile pločice za imunohistohemijsko bojenje. Takođe, pregledom istorija bolesti ovih 69 pacijenata, prikupljeni su relevantni klinički i laboratorijski podaci zabeleženi u vreme biopsije, kao i podaci sa poslednje redovne kontrole pacijenata.

Iz parafinskih blokova su izrađene pločice sa tkivom sečenim na debljinu od 5 μm. Nakon deparafinizacije u ksilolu i hidratacije, pločice su ubačene u citratni pufer (pH = 6,0) i izložene mikrotalasima u trajanju od 20 minuta na 400 W. Blokada peroksidazne aktivnosti je izvršena sa 1% *BSA* (engl. *bovine serum albumin – BSA*). Nakon demaskiranja antigena urađena je inkubacija sa primarnim *NCAM* antitelom (1:50, klon 123C3.D5, *LabVision, USA*) u trajanju od 60 minuta. *EnVisionTM* (*DAKO*, Danska) je korišćen za vizualizaciju antigen-antitelo reakcije sa 3,3'-diaminobenzidinom (DAB), nakon čega je usledilo kontrastiranje hematoksilinom. Negativne kontrole dobijene su izostavljanjem primarnog antitela, a kao pozitivna kontrola korišćeno je tkivo fetalnog bubrega. Pločice su pregledane upotrebom *BX53* svetlosnog mikroskopa sa *DP12CCD* kamerom (*Olympus*, Nemačka). Broj *NCAM* eksprimirajućih ćelija je izražen kao broj ćelija po vidnom polju pri uveličanju ×400.

Stepen intersticijske fibroze (engl. *interstitial renal fibrosis – IRF*) je određivan semikvantitativno, primenom skora od 0 do 3, pri čemu: 0 – nema intersticijske fibroze; 1 – manje od 25% tkiva zahvaćeno intersticijskom fibrozom; 2 – između 25% i 50% tkiva zahvaćeno intersticijskom fibrozom; 3 – više od 50% tkiva zahvaćeno intersticijskom fibrozom. Za klasifikovanje pacijenata u stadijume hronične bolesti bubrega (engl. *chronic kidney disease – CKD*), korišćen je najpoznatiji svetski vodič [11].

Statistička analiza je urađena upotrebom *IBM SPSS* softvera, verzije 20.0. U zavisnosti od prirode posmatrane varijable i broja ispitivanih grupa, za ispitivanje razlike među grupama, korišćeni su $\chi 2$ test, Studentov t test i Men-Vitnijev U test. Za određivanje prediktora pogoršanja funkcije bubrega, korišćena je Kaplan-Majerova univarijantna analiza preživljavanja. Statistički značajnim smatrano je $p < 0,05$.

REZULTATI

NCAM eksprimirajuće intersticijske ćelije detektovane su u 59,4% biopsija bubrega, a prisustvo ovih ćelija nije zavisilo od patohistološke dijagnoze ($p = 0,995$). Međutim, utvrđeno je da je učestalost pozitivnih biopsijskih slučajeva bila statistički značajno veća kod pacijenata koji su imali početnu intersticijsku fibrozu (*IRF-1*) u odnosu na pacijente u drugim kategorijama *IRF* ($p < 0,001$; Tabela 1). Na Slici 1 prikazane su *NCAM* eksprimirajuće intersticijske ćelije u biopsijskim uzorcima sa intersticijskom fibrozom.

MATERIALS AND METHODS

Needle biopsies of kidneys of patients diagnosed during 2011 and 2012 at the Institute of Pathology of the Faculty of Medicine, University of Belgrade, were retrospectively analyzed optically and microscopically. Sixty-nine patients, who had enough tissue in paraffin-embedded biopsies to make slides for immunohistochemical staining, were selected. Also, by reviewing the medical histories of these 69 patients, relevant clinical and laboratory data recorded at the time of the biopsy, as well as data from the latest regular follow-up of the patients, were collected.

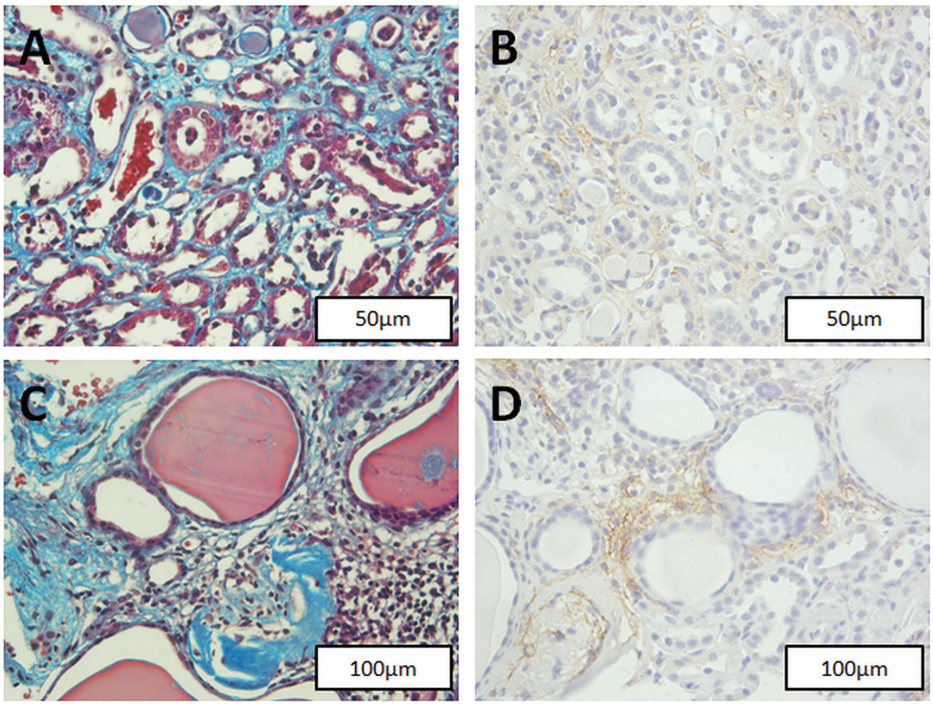
Plates with tissue cut to a thickness of 5 μm were made from paraffin blocks. After deparaffinization in xylene and hydration, the slides were placed in a citrate buffer (pH = 6.0) and exposed to microwaves for 20 minutes at 400 W. Peroxidase activity was blocked with 1% bovine serum albumin (BSA). After antigen unmasking, incubation with the primary NCAM antibody (1:50, clone 123C3.D5, LabVision, USA) was performed for 60 minutes. EnVisionTM (DAKO, Denmark) was used to visualize the antigen-antibody reaction with 3,3'-diaminobenzidine (DAB), upon which counterstaining with hematoxylin was performed. Negative controls were obtained by omitting the primary antibody, and fetal kidney tissue was used as a positive control. Plates were examined using a BX53 light microscope with a DP12CCD camera (Olympus, Germany). The number of NCAM-expressing cells was presented as the number of cells per field of view at ×400 magnification.

The degree of interstitial renal fibrosis (IRF) was determined semiquantitatively, using a score from 0 to 3, whereby the following applied: 0 – no interstitial fibrosis; 1 – less than 25% of tissue affected by interstitial fibrosis; 2 – between 25% and 50% of tissue affected by interstitial fibrosis; 3 – more than 50% of tissue affected by interstitial fibrosis. The best-known international guide was used to classify patients according to the stages of chronic kidney disease (CKD) [11].

Statistical analysis was performed using the IBM SPSS software, version 20.0. Depending on the nature of the observed variable and the number of investigated groups, the $\chi 2$ test, Student's t test and Mann-Whitney U test were used to examine the difference between the groups. Kaplan-Meier univariate survival analysis was used to determine predictors of the deterioration of renal function, whereby $p < 0.05$ was considered statistically significant.

RESULTS

NCAM-expressing interstitial cells were detected in 59.4% of kidney biopsies, and the presence of these cells did not depend on pathohistological diagnosis



Slika 1. Prisustvo NCAM eksprimirajućih intersticijskih ćelija u biopsijskim uzorcima sa fibrozom intersticijuma: (A) *Masone-trichrome* bojenje, ×200; (B) imunohistohemijsko bojenje *NCAM* antitelom (1:50, klon 123C3.D5), ×200; (C) *Masone-trichrome* bojenje, ×400; (D) imunohistohemijsko bojenje *NCAM* antitelom (1:50, klon 123C3.D5), ×400

Figure 1. Presence of NCAM-expressing interstitial cells in biopsy specimens with interstitial fibrosis: (A) Masson's trichrome staining, ×200; (B) immunohistochemical staining with the NCAM antibody (1:50, clone 123C3.D5), ×200; (C) Masson's trichrome staining, ×400; (D) immunohistochemical staining with the NCAM antibody (1:50, clone 123C3.D5), ×400

Tabela 1. Distribucija pacijenata sa NCAM eksprimirajućim intersticijskim ćelijama u odnosu na patohistološke parametre

Table 1. Distribution of patients with NCAM-expressing interstitial cells in relation to pathohistological parameters

Patohistološke parametri / *Pathohistological parameters*		**NCAM eksprimirajuće intersticijske ćelije / *NCAM-expressing interstitial cells* n (%)**		**p-vrednost/ *p-value***
		Odsutna / *Absent*	**Prisutna / *Present***	
Dijagnoza / *Diagnosis*	Fokalno-segmentna glomeruloskleroza / *Focal segmental glomerulosclerosis*	5 (38.8%)	8 (61.5%)	0.995
	Transplantirani bubreg / *Transplanted kidney*	5 (71.4%)	2 (28.6%)	
	Membranozni GN / *Membranous GN*	4 (33.3%)	8 (66.7%)	
	Lupusni nefritis / *Lupus nephritis*	5 (31.2%)	11 (68.8%)	
	Mezangioproliferativni GN / *Mesangioproliferative GN*	0 (0.0%)	4 (100.0%)	
	Membranoproliferativni GN / *Membranoproliferative GN*	2 (33.3%)	4 (66.7%)	
	Minimalne promene / *Minimal changes*	3 (100.0%)	0 (0.0%)	
	IgA nefropatija / IgA nephropathy	2 (66.7%)	1 (33.3%)	
	Rapidno-progresivni GN / Rapidly progressive GN	2 (40.0%)	3 (60.0%)	
Stadijum intersticijske fibroze / *Stage of interstitial fibrosis*	*IRF – 0*	14 (70.0%)	6 (30.0%)	0.001*
	IRF – 1	4 (13.8%)	25 (86.2%)	
	IRF – 2	4 (44.4%)	5 (55.6%)	
	IRF – 3	6 (54.5%)	5 (45.5%)	

*Grupe za koje je razlika bila statistički značajna; IRF – intersticijska fibroza bubrega (engl. *interstitial renal fibrosis*)

*Groups for which the difference was statistically significant; IRF – interstitial renal fibrosis

Tabela 2. Distribucija pacijenata sa NCAM eksprimirajućim intersticijskim ćelijama u odnosu na kliničke i laboratorijske parametre u vreme biopsije

Table 2. Distribution of patients with NCAM-expressing interstitial cells in relation to clinical and laboratory parameters at the time of biopsy

Klinički i laboratorijski parametri u vreme biopsije / *Clinical and laboratory parameters at the time of biopsy*		NCAM eksprimirajuće intersticijske ćelije / *NCAM-expressing interstitial cells*		p-vrednost/ *p-value*
		Odsutna / *Absent*	Prisutna / *Present*	
CKD stadijum n (%) / *CKD stage n (%)*	*CKD 1*	12 (42.9%)	16 (57.1%)	0.954
	CKD 2	3 (33.3%)	6 (66.7%)	
	CKD 3	3 (50.0%)	3 (50.0%)	
	CKD 4	5 (55.6%)	4 (44.4%)	
	CKD 5	2 (28.6%)	5 (71.4%)	
Serumski kreatinin [µmol/l] / *Serum creatinine level [µmol/l]*		146.64 ± 136.28	200.07 ± 239.45	0.244
Klirens kreatinina [ml/min] / *Creatinine clearance level [ml/min]*		77.56 ± 39.49	104.32 ± 70.19	0.199
eGFR [ml/min/1,73m^2] / *eGFR level [ml/min/1.73m2]*		73.80 ± 47.49	74.56 ± 47.21	0.952
Urea [mmol/l] / *Urea level [mmol/l]*		10.61 ± 8.66	11.037 ± 8.17	0.838
Glukoza [mmol/l] / *Glucose level [mmol/l]*		5.15 ± 1.11	4.76 ± 0.81	0.115
Eritrociturija n (%) / *Erythrocyturia n (%)*	Odsutna / *Absen*	15 (44.1%)	19 (55.9%)	0.585
	Prisutna / *Present*	12 (37.5%)	20 (62.5%)	
Proteinurija [g/24 h] / *Proteinuria [g/24 h]*		8.41 ± 9.45	3.97 ± 2.63	0.024*
Eritrociti [×10^{12}/l] / *Erythrocyte count [×10^{12}/l]*		4.09 ± 0.66	4.09 ± 0.76	0.999
Hemoglobin [g/l] / *Hemoglobin level [g/l]*		122.85 ± 16.77	121.61 ± 25.01	0.852
Hematokrit / *Hematocrit level*		0.35 ± 0.91	0.37 ± 0.07	0.297
MCV [fl] / *MCV [fl]*		88.64 ± 52.45	90.56 ± 4.31	0.231

*Grupe za koje je razlika bila statistički značajna; Proteinurija [g/24 h

*Groups for which the difference was statistically significant; Proteinuria [g/24 h]

Distribucija pacijenata sa *NCAM* eksprimirajućim intersticijskim ćelijama u odnosu na *CKD* stadijum se nije značajno razlikovala, kako u vreme biopsije (p = 0,954; Tabela 2), tako i u vreme poslednje kontrole (p = 0,601; Prilog IV, Tabela 3).

Međutim, uočeno je da su prosečne vrednosti serumskog kreatinina (*sCr*) i klirensa kreatinina (*CCr*), u grupi pacijenata kod kojih su *NCAM* ekprimirajuće ćelije detektovane u intersticijumu (*sCr*: 200,1 ± 239,4; *CCr*: 104,3 ± 70,2) bile veće u odnosu na grupu pacijenata bez *NCAM* eksprimirajućih ćelija u intersticijumu (*sCr*: 146,6 ± 136,3; *CCr*: 77,6 ± 39,5). Sličan trend zabeležen je i na poslednjem kontrolnom pregledu, međutim, razlike nisu bile statistički značajne. Takođe, prosečne vrednosti *eGFR*, uree i glukoze, kao i učestalost javljanja eritrociturije, nisu se statistički značajno razlikovale među poređenim grupama (Tabela 2; Tabela 3).

Pacijenti kod kojih su detektovane *NCAM* eksprimirajuće intersticijske ćelije su imali statistički značajno niže vrednosti proteinurije u vreme biopsije, u odnosu na pacijente u čijim biopsijskim uzorcima nije

(p = 0.995). However, the frequency of positive biopsy cases was found to be statistically significantly higher in patients who had incipient interstitial fibrosis (IRF-1), as compared to patients in other IRF categories (p < 0.001; Table 1). Figure 1 shows NCAM-expressing interstitial cells in biopsy samples with interstitial fibrosis. The distribution of patients with NCAM-expressing interstitial cells in relation to CKD stage did not differ significantly, both at the time of biopsy (p = 0.954; Table 2) and at the time of the latest follow-up (p = 0.601; Table 3).

However, it was observed that the average levels of serum creatinine (sCr) and creatinine clearance (CCr), in the group of patients in whom NCAM-expressing cells were detected in the interstitium (sCr: 200.1 ± 239.4; CCr: 104.3 ± 70.2) were higher, as compared to the group of patients without NCAM-expressing cells in the interstitium (sCr: 146.6 ± 136.3; CCr: 77.6 ± 39.5). A similar trend was observed at the latest follow-up; however, the differences were not statistically significant. Also, the average levels of eGFR, urea and glu-

Tabela 3. Distribucija pacijenata sa NCAM eksprimirajućim intersticijskim ćelijama u odnosu na kliničke i laboratorijske parametre na poslednjem kontrolnom pregledu

Table 3. Distribution of patients with NCAM-expressing interstitial cells in relation to clinical and laboratory parameters at the last follow-up examination

Klinički i laboratorijski parametri na poslednjem kontrolnom pregledu / *Clinical and laboratory parameters at the last follow-up examination*		**NCAM eksprimirajuće intersticijske ćelije / *NCAM-expressing interstitial cells***		**p-vrednost/ *p-value***
		Odsutna / *Absent*	**Prisutna / *Present***	
CKD stadijum n (%) / *CKD stage n (%)*	*CKD 1*	9 (45.0%)	11 (55.0%)	0.601
	CKD 2	1 (14.3%)	6 (85.7%)	
	CKD 3	1 (25.0%)	3 (75.0%)	
	CKD 4	4 (100.0%)	0 (0.0%)	
	CKD 5	2 (22.2%)	7 (77.8%)	
Serumski kreatinin [µmol/l] / *Serum creatinine level [µmol/l]*		183.95 ± 242.20	232.33 ± 317.71	0.560
Klirens kreatinina [ml/min] / *Creatinine clearance level [ml/min]*		86.75 ± 46.34	116.34 ± 74.98	0.334
eGFR [ml/min/1,73m^2] / *eGFR level [ml/min/1.73m2]*		74.59 ± 51.60	69.78 ± 44.31	0.744
Urea [mmol/l] / *Urea level [mmol/l]*		12.24 ± 11.64	12.00 ± 10.50	0.938
Glukoza [mmol/l] / *Glucose level [mmol/l]*		5.27 ± 2.24	4.51 ± 0.57	0.175
Eritrociturija n (%) / *Erythrocyturia n (%)*	**Odsutna / *Absen***	10 (34.5%)	19 (65.5%)	0.547
	Prisutna / *Present*	9 (42.9%)	12 (57.1%)	
Proteinurija [g/24 h] / *Proteinuria [g/24 h]*		2.58 ± 2.36	2.57 ± 2.81	0.993
Eritrociti [×10^{12}/l] / *Erythrocyte count [×10^{12}/l]*		3.43 ± 1.43	4.14 ± 0.78	0.962
Hemoglobin [g/l] / *Hemoglobin level [g/l]*		120.20 ± 17.1	123.71 ± 18.54	0.630
Hematokrit / *Hematocrit level*		0.34 ± 0.05	0.39 ± 0.10	0.211
MCV [fl] / *MCV [fl]*		93.52 ± 4.30	82.97 ± 29.32	0.248

*Grupe za koje je razlika bila statistički značajna; Proteinurija [g/24 h

*Groups for which the difference was statistically significant; Proteinuria [g/24 h]

bilo *NCAM* pozitivnih ćelija u intersticijumu (3,97 g/24 h naspram 8,41 g/24 h; $p = 0,024$), (Tabela 2).

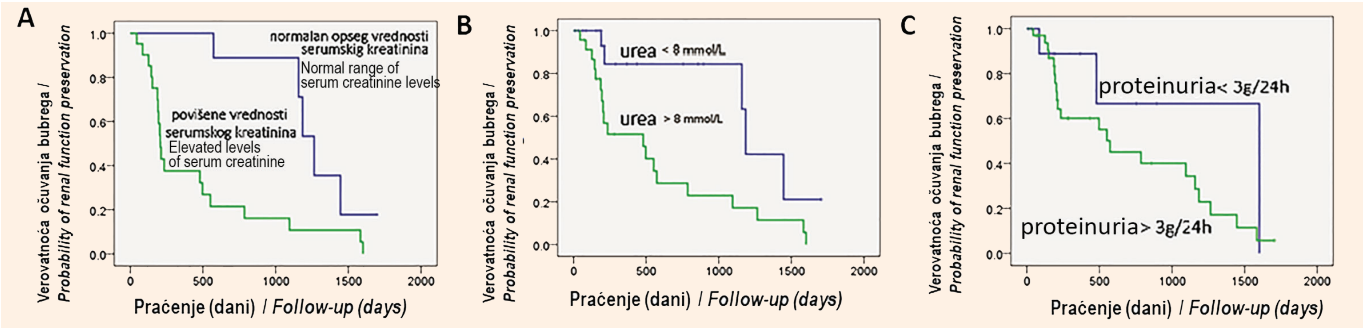
Broj eritrocita, vrednosti hemoglobina, hematokrita i srednje zapremine eritrocita (engl. *mean corpuscular volume – MCV*) se nisu značajno razlikovale među poređenim grupama (Tabela 2; Tabela 3). Pacijenti su prosečno praćeni 16 meseci. Patohistološke i kliničke karakteristike posmatrane su kao potencijalni prediktori progresije *CKD*-a u uznapredovale stadijume. Uočili smo da nijedna osoba sa minimalnim promenama nije progredirala u uznapredovale *CKD* stadijume tokom perioda praćenja, dok je kod svih pacijenata sa rapidno-progresivnim glomerulonefritisom (GN) zabeleženo brzo pogoršanje bubrežne funkcije, međutim, zbog velikog broja patohistoloških dijagnoza i relativno malog broja pacijenata u ovim grupama, statistička analiza nije urađena.

Takođe je primećeno da su pacijenti bez intersticijske fibroze, tokom tri godine praćenja, u 90% slučajeva očuvali bubrežnu funkciju, dok je u drugim stadijumima, vremenom, progresivno opadala funkcija bubrega. Bubrežna funkcija najsporije je opadala kod

cose, as well as the frequency of erythrocyturia, did not differ statistically significantly between the compared groups (Table 2; Table 3).

Patients in whom NCAM-expressing interstitial cells were detected had statistically significantly lower proteinuria levels at the time of biopsy, as compared to patients whose biopsy samples did not have NCAM-positive cells in the interstitium (3.97 g/24 h vs. 8.41 g/24 h; $p = 0.024$), (Table 2).

The erythrocyte count, hemoglobin level, hematocrit level, and the mean corpuscular volume (MCV) did not differ significantly between the compared groups (Table 2; Table 3). Patients were followed up for an average of 16 months. Pathohistological and clinical features were observed as potential predictors of CKD progression to the advanced stages. We observed that none of the patients with minimal changes progressed to advanced stages of CKD during the follow-up period, while all patients with rapidly progressive glomerulonephritis (GN) had a rapid deterioration of renal function. However, due to the large number of different pathohistological diagnoses and the relatively small



Slika 2. Verovatnoća pogoršanja funkcije bubrega u zavisnosti od (A) vrednosti serumskog kreatinina, (B) uree i (C) proteinurije

Figure 2. Probability of renal function deterioration depending on (A) serum creatinine level, (B) urea level, and (C) proteinuriae

pacijenata sa početnom intersticijskom fibrozom, brže u drugom stadijumu, dok je u trećem najbrže dolazilo do stradanja bubrežne funkcije. Međutim, zbog malog broja pacijenata uključenih u studiju preživljavanja, a uz gradiranje stepena fibroze na četiri stadijuma, statistička analiza nije urađena.

Verovatnoća pogoršanja bubrežne funkcije je značajno zavisila od vrednosti serumskog kreatinina ($p < 0,001$) i uree ($p = 0,007$). Bubrežna funkcija je znatno duže bila očuvana kod normalnih vrednosti serumskog kreatinina (< 104 *µmol*/l, referentna vrednost laboratorije Univerzitetskog kliničkog centra Srbije), (Slika 2. A) i uree (< 7,5 mmol/l, referentna vrednost laboratorije Univerzitetskog kliničkog centra Srbije), (Slika 2. B), za razliku od pacijenata koji su imali povišene vrednosti *sCr* i uree, gde je dolazilo do rapidnog pogoršanja bubrežne funkcije. Primetili smo da su pacijenti koji su imali proteinuriju manju od 3 g/24 h značajno duže održavali bubrežnu funkciju, u odnosu na pacijente koji su imali proteinuriju preko 3 g/24 h. Međutim, proteinurija nije bila značajan prediktor lošeg ishoda bolesnika ($p = 0,231$), kao što je prikazano na Slici 3. C.

DISKUSIJA

Intersticijska fibroza se javlja kod etiološki različitih oboljenja bubrega. Napredovanje intersticijske fibroze dovodi do progresivnog gubitka bubrežne funkcije, dovodeći pacijente do potrebe za dijalizom i transplantacijom bubrega [12]. Sve je više studija koje ispituju molekularnu osnovu fibroze, a među najvažnijima su one koje su fokusirane na ispitivanje ranih pokazatelja potencijalne progresije bolesti.

Fibroza predstavlja abnormalnu akumulaciju ekstracelularnog matriksa. Smatra se da različite ćelije mogu doprineti produkciji ekstracelularnog matriksa, ali da su glavne ćelije aktivirani fibroblasti, tj. miofibroblasti [12,13]. Poznato je da su aktivacija i mobilizacija fibroblasta rezultat stimulacije receptora 1 fibroblastnog faktora rasta (engl. *fibroblast growth factor receptor-1 – FGFR-1*). *FGFR-1* može biti stimulisan različitim ligandima uključujući i *NCAM* [14,15,16], što nas je

number of patients in these groups, statistical analysis was not performed.

It was also observed that patients without interstitial fibrosis, during the three years of follow-up, preserved renal function in 90% of cases, while in other stages, renal function progressively declined over time. Renal function declined the slowest in patients with incipient interstitial fibrosis, more rapidly in the second stage, while in the third stage, kidney function declined the fastest. However, due to the small number of patients included in the survival study and the degree of fibrosis (graded into four stages), statistical analysis was not performed.

The probability of renal function deterioration was significantly dependent on the serum creatinine level ($p < 0.001$) and the urea level ($p = 0.007$). Renal function was preserved for a significantly longer period of time with normal levels of serum creatinine (< 104 µmol/l, reference value of the laboratory of the University Clinical Center of Serbia), (Figure 2. A) and normal levels of urea (< 7.5 mmol/l, reference value of the laboratory of the University Clinical Center of Serbia), (Figure 2. B), as opposed to patients who had elevated levels of sCr and urea, in whom there was a rapid deterioration of renal function. We observed that patients who had proteinuria below 3 g/24 h maintained kidney function significantly longer, as compared to patients who had proteinuria above 3 g/24 h. However, proteinuria was not a significant predictor of poor patient outcome ($p = 0.231$), as shown in Figure 2. C.

DISCUSSION

Interstitial fibrosis occurs in etiologically different kidney diseases. Progression of interstitial fibrosis leads to progressive loss of renal function (kidney failure), leading to patients requiring dialysis and kidney transplantation [12]. There is an increasing number of studies examining the molecular basis of fibrosis, and among the most important are those focused on examining early indicators of potential disease progression.

navelo da detaljnije ispitujemo ekspresiju *NCAM* molekula na intersticijskim ćelijama u različitim stadijumima intersticijske fibroze.

U intersticijumu zdravih bubrega, *NCAM* eksprimirajuće ćelije su vrlo retke, međutim tokom određenih patoloških stanja njihov broj može da se poveća [17]. Rezultati našeg istraživanja pokazali su da se veći broj *NCAM* eksprimirajućih ćelija gotovo isključivo pojavljuje u početnim fazama intersticijske fibroze, kod etiološki različitih oboljenja bubrega, dok je u uznapredovalim stadijumima ekspresija znatno niža. Rezultati drugih istraživača sugerisali su da je obim *NCAM* ekspresije u intersticijumu usko povezan sa stepenom oštećenja intersticijuma, kako kod čoveka, tako i kod životinja [4,18]. Tako je primećeno naglo povećanje *NCAM* ćelija u ranoj fazi procesa regeneracije nakon ishemijskog oštećenja tubula kod pacova [19]. Takođe, Luo i saradnici su dokazali značajnu zastupljenost *NCAM*-a u odmaklim stadijumima fibroze jetre, kod pacijenata sa nealkoholnom steatozom jetre [20]. U *in vitro* modelu intersticijske fibroze bubrega, uočena je snažna indukcija ekspresije izoformi *NCAM*-a zajedno sa *FGFR1* receptorom, i to 24 sata nakon stimulacije procesa fibrogeneze pod uticajem transformišućeg faktora rasta beta 1 (engl. *transforming growth factor beta – TGF-β1*), iako u tom trenutku morfološke promene nisu bile vidljive. Nakon 48 sati, primećen je pad nivoa *NCAM* i *FGFR1* mRNA, što ukazuje na ključnu ulogu ovih molekula u inicijaciji procesa fibrogeneze. Takođe, blokiranjem *FGFR1* signalnog puta nakon izlaganja *TGF-β1*, uočena je morfološka reverzija procesa fibrogeneze, čime je potvrđena značajna uloga *NCAM*/*FGFR1* u inicijalnoj fazi fibroze bubrega [10] . Otkrivanje molekularnih mehanizama fibrogeneze, važnih u fazi inicijacije fibroze, značajno je zbog primene novih, ciljanih terapijskih modaliteta, čime bi se smanjila potreba za dijalizom i transplantacijom bubrega kod pacijenata obolelih od različitih, etiološki heterogenih, netumorskih oboljenja bubrega.

Ekspresija *NCAM*-a, kao patološki supstrat, osim u fibrozi bubrega, prepoznata je i u srcu, plućima i hepatobilijarnom sistemu. Studije takođe ukazuju na potencijalni razvoj novih terapijskih modaliteta u cilju usporavanja progresije fibroze, i sugerišu na mogućnost reverzije procesa fibrogeneze [21–25].

Naša studija se jedina bavila ispitivanjem kliničkog značaja detekcije *NCAM* ćelija u intersticijumu bubrega nefroloških bolesnika, pri čemu je ustanovljeno da su pacijenti sa *NCAM* eksprimirajućim ćelijama u intersticijumu imali znatno niže prosečne vrednosti proteinurije. Zbog pretpostavke da postoji mogućnost da *NCAM* eksprimirajuće intersticijske ćelije predstavljaju zapravo eritropoetin

Fibrosis is an abnormal accumulation of extracellular matrix. It is believed that different cells can contribute to the production of extracellular matrix, but that the main cells in this process are activated fibroblasts, i.e., myofibroblasts [12,13]. It is known that the activation and mobilization of fibroblasts is the result of the stimulation of fibroblast growth factor receptor 1 (FGFR-1). FGFR-1 can be stimulated by different ligands including NCAM [14,15,16], which has led us to examine in more detail the expression of NCAM molecules in interstitial cells, in different stages of interstitial fibrosis.

In the interstitium of healthy kidneys, NCAM-expressing cells are very rare, but during the course of certain pathological conditions their number can increase [17]. The results of our study showed that a greater number of NCAM-expressing cells almost exclusively appears in the initial stages of interstitial fibrosis, in etiologically different kidney diseases, while in advanced stages the expression is significantly lower. The results of other researchers suggested that the extent of NCAM expression in the interstitium is closely related to the degree of interstitial damage, both in humans and animals [4,18]. Thus, a sudden increase of NCAM cells was observed in the early phase of the regeneration process after ischemic tubule damage in rats [19]. Also, Luo et al proved a significant presence of NCAM in advanced stages of liver fibrosis, in patients with non-alcoholic steatosis of the liver [20]. In an in vitro model of kidney interstitial fibrosis, a strong induction of the expression of NCAM isoforms together with FGFR1 was observed, 24 hours after stimulation of the fibrogenesis process under the influence of transforming growth factor beta 1 (TGF-β1), although, at that moment, morphological changes were not visible. After 48 hours, a decrease in NCAM and FGFR1 mRNA levels was observed, indicating the key role of these molecules in the initiation of the fibrogenesis process. Also, by blocking the FGFR1 signaling pathway after exposure to TGF-β1, morphological reversion of the fibrogenesis process was observed, thus confirming the significant role of NCAM/FGFR1 in the initial stage of kidney fibrosis [10]. The discovery of molecular mechanisms of fibrogenesis, important in the initial phase of fibrosis, is significant due to the application of new, targeted therapeutic modalities, which would reduce the need for dialysis and kidney transplantation in patients suffering from various, etiologically heterogeneous, non-tumor kidney diseases.

The expression of NCAM, as a pathological substrate, apart from kidney fibrosis, has also been found in the heart, the lungs, and the hepatobiliary system. Studies also indicate the potential development of

produkujuće ćelije [7], ispitivali smo odnos distribucije pacijenata koji eksprimiraju *NCAM* ćelije i vrednosti eritrocita, hemoglobina, hematokrita i srednje zapremine eritrocita, međutim, nismo uočili povezanost.

Studije koje se bave određivanjem kliničkih i patoloških prediktora pogoršanja bubrežne funkcije imaju veliki praktični značaj. Među kliničkim parametrima, značajni prediktori pogoršanja funkcije bubrega su povišene vrednosti kreatinina i uree u serumu pacijenata, kao i visoke vrednosti proteinurije, naročito one nefrotskog ranga [19,26,27]. Među ispitivanim kliničkim parametrima u našoj studiji, kao prediktori pogoršanja bubrežne funkcije takođe su se izdvojile povišene vrednosti serumskog kreatinina i uree. U dosadašnjim istraživanjima je uočeno da proteinurija predstavlja prediktor lošeg ishoda [26,28,29]. Mi smo primetili da pacijenti koji su imali proteinuriju manju od 3 g/24 h, duže održavaju normalnu bubrežnu funkciju, međutim, proteinurija se nije izdvojila kao značajan prediktor pogoršanja bubrežne funkcije. Poznato je i da verovatnoća progresije bolesti bubrega u uznapredovale *CKD* stadijume značajno zavisi od patohistološke dijagnoze i stadijuma intersticijske fibroze [30], što zbog malog broja pacijenata u našoj studiji nije statistički ispitivano.

ZAKLJUČAK

Prisustvo *NCAM* ćelija u intersticijumu bubrega je karakteristika ranih faza hroničnih bolesti bubrega sa početnom intersticijskom fibrozom i blažim stepenom proteinurije. Vrednosti serumskog kreatinina i uree značajno su uticale na verovatnoću pogoršanja funkcije bubrega, te predstavljaju važne kliničke prediktore ulaska pacijenata u uznapredovale *CKD* stadijume.

Sukob interesa: Nije prijavljen.

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new therapeutic modalities in order to slow down the progression of fibrosis and suggest the possibility of reversing the process of fibrogenesis [21–25].

Our study was the only one to examine the clinical significance of the detection of NCAM cells in the kidney interstitium of nephrological patients, and it was established that patients with NCAM-expressing cells in the interstitium had significantly lower average proteinuria levels. Because of the assumption that there is a possibility that NCAM-expressing interstitial cells actually represent erythropoietin producing cells [7], we examined the relationship between the distribution of patients expressing NCAM cells and the erythrocyte count, the hemoglobin level, the hematocrit level, and the mean corpuscular volume (MCV). However, we did not observe any association.

Studies focused on determining clinical and pathological predictors of renal function deterioration are of great practical importance. Among the clinical parameters, significant predictors of the deterioration of kidney function are elevated levels of creatinine and urea in the serum of patients, as well as high levels of proteinuria, especially those in the nephrotic range [19,26,27]. Among the examined clinical parameters in our study, elevated levels of serum creatinine and urea also stood out as predictors of renal function deterioration. In previous studies, it has been observed that proteinuria is a predictor of poor outcome [26,28,29]. We observed that patients who had proteinuria below 3 g/24 h maintained normal renal function longer, however, proteinuria did not stand out as a significant predictor of declining renal function. It is also known that the probability of kidney disease progression to advanced CKD stages significantly depends on the pathohistological diagnosis and stage of interstitial fibrosis [30], which was not statistically investigated due to the small number of patients in our study.

CONCLUSION

The presence of NCAM cells in the renal interstitium is characteristic of the early stages of chronic kidney disease with incipient interstitial fibrosis and mild proteinuria. The levels of serum creatinine and urea significantly affected the probability of kidney function deterioration, which is why they represent important clinical predictors of patients progressing to advanced stages of CKD.

Conflict of interest: None declared.

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KONCENTRACIJA CITOKINA (IL-4, IL-12 I IFNγ) U PLAZMI I NJENA POVEZANOST SA APOPTOZOM LIMFOCITA PACIJENATA OBOLELIH OD HRONIČNE LIMFOCITNE LEUKEMIJE

ORIGINALNI RAD

ORIGINAL ARTICLE

CONCENTRATION OF CYTOKINES (IL-4, IL-12, IFNγ) IN THE BLOOD PLASMA AND ITS ASSOCIATION WITH LYMPHOCYTE APOPTOSIS IN PATIENTS SUFFERING FROM CHRONIC LYMPHOCYTIC LEUKEMIA

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SAŽETAK

Uvod: Hronična limfocitna leukemija (HLL) predstavlja malignu bolest hematopoetskog tkiva i najčešća je leukemija odraslih. Godinama je dominirao stav da je u patogenezi hronične limfocitne leukemije osnovni mehanizam nastanka i progresije bolesti poremećaj apoptoze i produženo preživljavanje malignih limfocita.

Cilj rada: Cilj našeg istraživanja je da se utvrdi povezanost procenta apoptotskih limfocita u perifernoj krvi pacijenta obolelih od hronične limfocitne leukemije sa koncentracijom antiapoptotskih citokina (IL-4, IL-12, IFNγ) u plazmi pacijenata.

Materijal i metode: U istraživanje je uključeno 29 pacijenata obolelih od hronične limfocitne leukemije (21 muškarac i 8 žena) koji u prethodnih 6 meseci nisu bili na hemioterapijskom režimu. Kod svih pacijenata su određivani klinički parametri (klinički stadijum bolesti, prisustvo limfadenopatije, splenomegalije), biohemijski parametri (LDH) i tip i procenat infiltracije koštane srži. Iz periferne krvi pacijenata određen je procenat apoptotskih limfocita i koncentracija citokina (IL-4, IL-12, IFNγ) u plazmi pacijenata.

Rezultati: U ispitivanoj grupi pacijenta su detektovane vrednosti plazmatske koncentracije IL-4 = 121,42 pg/ml (62,44 – 180,40), IL-12 = 7,62 pg/ml (4,36 – 10,87), IFNγ = 31,45 pg/ml (18,35 – 44,56). Među ćelijskom populacijom je detektovano ispod 1% apoptotskih ćelija, u rasponu od 0,03% do maksimalno 0,84%. Rezultati pokazuju da nema korelacije između koncentracije citokina i procenta apoptotskih limfocita u perifernoj krvi pacijenata, ali da koncentracija Il-12 pozitivno korelira sa stadijumom bolesti, kao i procentom infiltracije koštane srži malignim limfocitima. ($p < 0,001$ odnosno $p = 0,028$).

Zaključak: Plazmatske koncentracije IL-4, IL-12, IFNγ nisu u korelaciji sa procentom apoptotskih limfocita periferne krvi pacijenata obolelih od hronične limfocitne leukemije. Interleukin-12 ipak pokazuje pozitivnu korelaciju kod uznapredovale bolesti.

Ključne reči: hronična limfocitna leukemija, apoptoza, citokini

ABSTRACT

Introduction: Chronic lymphocytic leukemia (CLL) is a malignant disease of hematopoietic tissue and is the most common leukemia in adults. For years, the dominant view was that in the pathogenesis of chronic lymphocytic leukemia, the basic mechanism of the origin and progression of the disease is disruption in apoptosis and prolonged survival of malignant lymphocytes.

Aim: The aim of our study is to determine the association between the percentage of apoptotic lymphocytes in the peripheral blood of patients suffering from chronic lymphocytic leukemia and the concentration of antiapoptotic cytokines (IL-4, IL-12, IFNγ) in the patients' blood plasma.

Materials and methods: The study included 29 patients suffering from chronic lymphocytic leukemia (21 men and 8 women) who had not been on a chemotherapy regimen in the preceding 6 months. Clinical parameters (clinical stage of disease, presence of lymphadenopathy, splenomegaly), biochemical parameters (LDH), and the type and percentage of bone marrow infiltration were determined in all patients. The percentage of apoptotic lymphocytes and the concentration of cytokines (IL-4, IL-12, IFNγ) in the patients' plasma were determined from the patients' peripheral blood.

Results: In the studied group of patients, plasma concentration values of IL-4 = 121.42 pg/ml (62.44 – 180.40), IL-12 = 7.62 pg/ml (4.36 – 10.87), IFNγ = 31.45 pg/ml (18.35 – 44.56) were detected. In the cell population, less than 1% of apoptotic cells were detected, ranging from 0.03% to a maximum of 0.84%. The results show no correlation between the concentration of cytokines and the percentage of apoptotic lymphocytes in the patients' peripheral blood, however, they show that Il-12 concentration positively correlates with the stage of the disease, as well as with the percentage of bone marrow infiltration by malignant lymphocytes ($p < 0.001$ or $p = 0.028$).

Conclusion: Plasma concentrations of IL-4, IL-12, IFNγ are not correlated with the percentage of apoptotic lymphocytes in the peripheral blood of patients with chronic lymphocytic leukemia. Interleukin-12 nevertheless shows a positive correlation in advanced disease.

Keywords: chronic lymphocytic leukemia, apoptosis, cytokines

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Primljeno • *Received*: November 27, 2023; **Revidirano • *Revised*:** December 4, 2023; **Prihvaćeno • *Accepted*:** December 5, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47931

UVOD

Hronična limfocitna leukemija (HLL) predstavlja malignu bolest hematopoetskog tkiva koja nastaje proliferacijom i akumulacijom klona, malih, naizgled zrelih, imunološki izmenjenih limfocita u perifernoj krvi, koštanoj srži, limfnim nodusima, slezini i drugim organima, i ovo je najčešća leukemija kod odraslih pacijenata [1].

Godinama je dominirao stav da je u patogenezi hronične limfocitne leukemije osnovni mehanizam nastanka i progresije bolesti poremećaj apoptoze i produženo preživljavanje malignih limfocita [1]. Danas se zna da je produženo preživljavanje limfocita bitan parametar u patogenezi bolesti, ali da napredovanje bolesti takođe zavisi i od povećane proliferacije malignog klona [2,3]. Produženo preživljavanje malignih limfocita delom je posledica genetskih promena unutar samih ćelija, a delom i spoljašnjih uticaja, kao što su ćelijsko-ćelijske interakcije u ciljnim tkivima (koštana srž, limfni čvorovi) i cirkulišući citokini koji kao jednu od uloga imaju i inhibiciju apoptoze [3 – 6].

Cilj našeg istraživanja je bio da se utvrdi povezanost procenta apoptotskih limfocita u perifernoj krvi pacijenata obolelih od hronične limfocitne leukemije sa ekspresijom *Bcl-2* u malignim limfocitima, kao i koncentracijom antiapoptotskih citokina (IL-4, IL-12, IFNγ) u plazmi pacijenata. Takođe, cilj je bio i da se ispitivani parametri uporede sa dostupnim kliničkim i laboratorijski parametrima bolesti.

MATERIJALI I METODE

Istraživanje je sprovedeno na Klinici za hematologiju Univerzitetskog kliničkog centra Kragujevac, kao prospektivna studija, u periodu od oktobra 2017. godine do februara 2018. godine. U istraživanje je uključeno 29 pacijenata (21 muškog i 8 ženskog pola) obolelih od hronične limfocitne leukemije, koji u prethodnih 6 meseci nisu primali hemioterapiju. Kod svih pacijenata su određivani: klinički parametri (klinički stadijum bolesti, prisustvo limfadenopatije, splenomegalije), biohemijski parametri (laktat dehidrogeneza – LDH), tip i procenat infiltracije koštane srži (nodularni, intersticijalni i difuzni), kao i parametri krvne slike. Kod svih pacijenata je u jednom aktu uzorkovana periferna krv u količini od 5 ml sa EDTA antikoagulansom.

U perifernoj krvi je određivan procenat apoptotskih limfocita, a iz plazme pacijenata je metodom *microbeads* tehnike određivana koncentracija IL-4, IL-12, i IFNγ, na protočnom citometru *Beckman Coulter FC500*.

Ćelije pune krvi su centrifugirane na 3.000 obrtaja tokom 10 minuta, nakon čega je beli tepih prebačen u epruvetu sa 2 ml *Lymphoprep*-a i centrifugiran 22 minuta na 3.000 obrtaja. Posle izolacije, ćelije su oprane tri puta u *PBS*-u i resuspendovane u ledeno hladnom ve-

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a malignant disease of hematopoietic tissue that results from the proliferation and accumulation of clones, small, seeminlgy mature, immunologically altered lymphocytes in the peripheral blood, bone marrow, lymph nodes, spleen, and other organs, and this is the most common leukemia in adult patients [1].

For years, the predominant view was that in the pathogenesis of chronic lymphocytic leukemia, the basic mechanism of the onset and progression of the disease lay in the disruption of apoptosis and in the prolonged survival of malignant lymphocytes [1]. Nowdays, it is known that the prolonged survival of lymphocytes is an important parameter in the pathogenesis of the disease, but that the progression of the disease also depends on the increased proliferation of the malignant clone [2,3]. Prolonged survival of malignant lymphocytes is partly due to genetic changes within the cells themselves, and partly to external influences, such as cell-cell interactions in target tissues (bone marrow, lymph nodes) and circulating cytokines, which also play a role in inhibiting apoptosis [3 – 6].

The aim of our study was to determine the association between the percentage of apoptotic lymphocytes in the peripheral blood of patients suffering from chronic lymphocytic leukemia and the expression of Bcl-2 in malignant lymphocytes, as well as the concentration of antiapoptotic cytokines (IL-4, IL-12, IFNγ) in the patients' plasma. Also, the aim was to compare the analyzed parameters with the available clinical and laboratory parameters of the disease.

MATERIALS AND METHODS

The study was conducted at the Clinic for Hematology of the University Clinical Center Kragujevac, as a prospective study, in the period between October 2017 and February 2018. The study included 29 patients (21 male and 8 female patients) suffering from chronic lymphocytic leukemia, who had not received chemotherapy in the preceding 6 months. Clinical parameters (clinical stage of the disease, presence of lymphadenopathy, splenomegaly), biochemical parameters (lactate dehydrogenase - LDH), type and percentage of bone marrow infiltration (nodular, interstitial and diffuse), as well as blood count parameters were determined in all patients. Five milliliters of peripheral blood, with ETDA anticoagulant, were sampled at once from all patients.

The percentage of apoptotic lymphocytes was determined in the peripheral blood, and the concentration of IL-4, IL-12, and IFNγ was determined from the patients' blood plasma using the microbeads technique, on a Beckman Coulter FC500 Flow Cytometer.

zujućem puferu do finalne koncentracije od 1.000.000 ćelija/ml. Nakon toga, u 100 µl radnog rastvora dodato je 10 µl FITC obeleženog Aneksina V (engl. *Annexin V*) i 20 µl 7-AAD, a potom inkubirano u mraku 15 minuta. Nakon inkubacije, sadržaj je resuspendovan u 400 µl vezujućeg rastvora i analiziran na protočnom citometru do 20.000 događaja, na populaciji limfocita koja je određena na *FS/SS* dijagramu. Smatra se da su *Annexin V* (-); 7-AAD (-) ćelije vijabilne, da su *Annexin V* (+); 7-AAD (-) ćelije u ranoj fazi apoptoze, da se *Annexin V* (+); 7-AAD (+) ćelije nalaze u kasnoj fazi apoptoze, dok su *Annexin V* (-); 7-AAD (+) ćelije nekrotične. Procenat rane i kasne apoptoze, kao i nekroze, određivan je korišćenjem *CXP Cytometer* softvera. Statistička obrada podataka je urađena je uz pomoć komercijalnog statističkog programa – *SPSS*, verzija 20.

REZULTATI

Našu ispitivanu populaciju je činilo 70% pacijenata muškog pola i 30% pacijenata ženskog pola, prosečne starosti 66,9 godina (u rasponu od 53 – 87 godina). Što se tiče kliničkih parametara, 41% pacijenata je bilo u nižem kliničkom stadijumu bolesti (Rai 0 i 1), 28% je bilo u srednjem stadijumu (Rai 2), dok je 31% pacijenata bilo u uznapredovalom stadijumu bolesti (Rai 3 i 4). Pacijenti su većinom imali palpabilnu limfadenopatiju (oko 60%), dok je oko 43% pacijenata imalo palpabilnu slezinu. Što se infiltracije koštane srži tiče, ona je, po definiciji bolesti, bila prisutna kod svih pacijenata, ali je procenat infiltracije varirao od 25% – 95%. Prosečni broj leukocita kod pacijenata je bio 70,6 ± 47,1 x10^9/l, dok je koncentracija LDH bila 427,5 ± 216,5 U/l. Ostali ispitivani parametri su prikazani u Tabeli 1.

Iako je procenat ćelija u apoptozi bio u negativnoj korelaciji sa posmatranim parametrima (koncentracija IL-12, IFNγ i IL-4) nije bilo statističke značajnosti ($p > 0,05$). Pri analizi ćelija u pojedinačnim fazama apoptoze (rana apoptoza, kasna apoptoza i nekroza) takođe nije utvrđena statistička značajnost. Prilikom upoređivanja koncentracije citokina sa prisustvom limfadenopatije i uvećane slezine, takođe nije uočena korelacija. Ipak,

Whole blood cells were centrifuged at 3,000 rpm for 10 minutes, upon which the leukocyte precipitate was transferred to a test tube containing 2 ml of Lymphoprep and centrifuged for 22 minutes at 3,000 rpm. Upon isolation, cells were washed three times in PBS and resuspended in ice-cold binding buffer to a final concentration of 1,000,000 cells/ml. After that, 10 µl of FITC-labeled Annexin V and 20 µl of 7-AAD were added to100 µl of the working solution, and then incubated in the dark for 15 minutes. After incubation, the contents were resuspended in 400 µl of binding solution and analyzed on a flow cytometer at a maximum of up to 20,000 events, on a lymphocyte population determined on the FS/SS diagram. It is considered that Annexin V (-); 7-AAD (-) cells are viable, that Annexin V (+); 7-AAD (-) cells are in the early stage of apoptosis, that Annexin V (+); 7-AAD (+) cells are in the late stage of apoptosis, while Annexin V (-); 7-AAD (+) cells are necrotic cells. The percentage of early and late apoptosis, as well as necrosis, was determined using CXP Cytometer software. Statistical data processing was performed with commercial statistical software – SPSS, version 20.

RESULTS

Our study population consisted of 70% male patients and 30% female patients, of the average age of 66.9 years (range: 53 – 87 years). As to the clinical parameters, 41% of the patients had a lower clinical stage of the disease (Rai 0 and 1), 28% were in the intermediate stage (Rai 2), while 31% of the patients were in the advanced stage of disease (Rai 3 and 4). The majority of patients had palpable lymphadenopathy (about 60%), while the spleen was palpable in about 43% of patients. As far as bone marrow infiltration is concerned, it was, by virtue of the disease, present in all patients, but the percentage of infiltration varied from 25% – 95%. The average leukocyte count in patients was 70.6 ± 47.1 x 10^9/l, while the LDH concentration was 427.5 ± 216.5 U/l. Other tested parameters are presented in Table 1.

Although the percentage of cells in apoptosis was negatively correlated with the observed parameters

Tabela 1. Procenat apoptotskih limfocita u perifernoj krvi i koncentracija ispitivanih citokina

Table 1. The percentage of apoptotic lymphocytes in peripheral blood and the concentration of the analyzed cytokines

Parametar/ *Parameter*	**Srednja vrednost / *Mean value***
Procenat nekrotičnih limfocita / *Percentage of necrotic lymphocytes*	0.5 ± 0.5%
Procenat limfocita u ranoj apoptozi / *Percentage of lymphocytes in early apoptosis*	0.4 ± 0.3%
Procenat limfocita u kasnoj apoptozi / *Percentage of lymphocytes in early apoptosis*	1.0 ± 0.8%
Koncentracija IL-12 u plazmi / *Concentration of IL-12 in blood plasma*	70.6 ± 42.7 pg/ml
Koncentracija IFNγ u plazmi / *Concentration of IFNγ in blood plasma*	28.6 ± 16.4 pg/ml
Koncentracija IL-4 u plazmi / *Concentration of IL-4 in blood plasma*	121.4 ± 157.9 pg/ml

sva tri citokina pokazala su negativnu korelaciju sa procentom infiltracije koštane srži limfocitima (p = 0,028, p = 0,030, p = 0,042).

Što se tiče upoređivanja koncentracije citokina sa stadijumom bolesti pacijenata, IFNγ i IL-4 nisu pokazali statistički značajnu povezanost, dok je koncentracija Il-12 pokazala značajnu negativnu korelaciju sa stadijumom bolesti pacijenata (p < 0,01). Kod viših stadijuma bolesti pacijenata, detektovane su niže vrednosti koncentracije IL-12. Visok stepen pozitivne korelacije sa stadijumom bolesti pokazala je koncentracija LDH u serumu (p < 0,01).

DISKUSIJA

Studije koje su proučavale *in vitro* preživljavanje limfocita u kulturama kod pacijenata obolelih od hronične limfocitne leukemije, nedvosmisleno su pokazale da kultivisani maligni limfociti u monokulturi imaju viši stepen apoptoze od kultivisanih nemalignih B limfocita [7,8], što je doprinelo zaključku da inhibicija apoptoze limfocita hronične limfocitne leukemije nije urođeni mehanizam same ćelije, već je posledica interakcije malignih ćelija sa protektivnom mikrosredinom. Naše istraživanje je posmatralo perifernu krv kao jednu od mikrosredina u kojoj cirkulišu limfociti periferne krvi, i u njoj koncentraciju citokina (IL-12, IFNγ i IL-6), te njihovu povezanost sa procentom apoptotskih ćelija i napredovanjem bolesti.

Studije koje su se bavile efektom IL-12 *in vitro* pokazale su da IL-12 inhibira apoptozu ćelija hronične limfocitne leukemije i tako doprinosi napredovanju bolesti [9], ali da ovaj efekat nije dovoljno potentan kada se limfociti hronične limfocitne leukemije kultivišu samo sa IL-12, već svoj pun potencijal pokazuje u kombinaciji sa drugim citokinima [10]. Kao antiinflamatorni citokin, IL-12 pokazuje i antitumorsko dejstvo, pa njegova niža koncentracija može biti povezana sa napredovanjem bolesti [11].

Takođe, ovoj teoriji doprinose i novi radovi, koji navode da je kod pacijenata obolelih od psorijaznog artritisa lečenih ustekinumabom (inhibitorom IL-12) bilo veće učestalosti pojave hronične limfocitne leukemije. Među ovim studijama je i Rad Gediza i saradnika koji je u saglasnosti sa našim rezultatima, koji pokazuju da se niže koncentracije IL-12 javljaju kod pacijenata sa uznapredovalom bolešću [12]. Sa druge strane Parfienčik i saradnici su pokazali da je koncentracija IL-12 kao i IL-6 viša kod obolelih pacijenata, ali njihovo istraživanje je obuhvatalo samo pacijente u nižem stadijumu bolesti [13].

Što se tiče IL-4 i IFNγ, naši rezultati povezivanja koncentracije ovih citokina i parametara apoptoze i napredovanja bolesti nisu pokazali direktnu povezanost. Ovi citokini su ipak literaturno više ispitivani, i iako se

(concentrations of IL-12, IFNγ and IL-4), there was no statistical significance (p > 0.05). When analyzing cells in individual stages of apoptosis (early apoptosis, late apoptosis and necrosis) statistical significance was also not determined. When the concentration of cytokines was compared with the presence of lymphadenopathy and an enlarged spleen, no correlation was also observed. However, all three cytokines showed a negative correlation with the percentage of bone marrow infiltration by lymphocytes (p = 0.028, p = 0.030, p = 0.042).

With regards to the comparison of the cytokine concentration with the disease stage in patients, IFNγ and IL-4 did not show a statistically significant association, while the Il-12 concentration showed a significant negative correlation with the disease stage of patients (p < 0.01). In patients with more advanced disease stages, lower values of the concentration of IL-12 were detected. The concentration of LDH in the serum showed a high degree of positive correlation with the stage of disease (p < 0.01).

DISCUSSION

Studies analyzing in vitro survival of lymphocytes in cultures taken from patients with chronic lymphocytic leukemia, unequivocally showed that cultivated malignant lymphocytes in monoculture had a higher degree of apoptosis than cultivated non-malignant B lymphocytes [7,8], which led to the conclusion that inhibition of the apoptosis of lymphocytes in chronic lymphocytic leukemia is not an innate mechanism of the cell itself, but a consequence of the interaction of malignant cells with the protective microenvironment. Our study considered peripheral blood as one of the microenvironments wherein peripheral blood lymphocytes circulate, the concentration of cytokines (IL-12, IFNγ and IL-6) in peripheral blood, as well as the association of cytokines with the percentage of apoptotic cells and the progression of the disease.

Studies dealing with the in vitro effect of IL-12 showed that IL-12 inhibits the apoptosis of chronic lymphocytic leukemia cells and thus contributes to the progression of the disease [9], but that this effect is not potent enough when chronic lymphocytic leukemia lymphocytes are cultured only with IL-12, rather it shows its full potential in combination with other cytokines [10]. As an anti-inflammatory cytokine, IL-12 also exhibits an antitumor effect, therefore, its lower concentration may be associated with disease progression [11].

Recent studies also contribute to this theory, reporting that patients suffering from psoriatic arthritis who were treated with ustekinumab (IL-12 inhibitor) had a higher incidence of chronic lymphocytic leukemia. Amongst these studies is the one by Gediz et al., which is in agreement with our results showing that lower con-

literaturno same koncentracije u plazmi nisu pokazale kao statistički značajne, gustina receptora za IFNγ i IL-4, kako na samim leukemijskim limfocitima tako i na drugim imunim ćelijama, ukazuju da je imuni odgovor pomeren od Th1 prema Th2 odgovoru, (povećanje IL-4 a smanjenje IFNγ receptora), što otvara dovoljno mesta za postepeni razvoj hronične limfocitne leukemije [14,15].

ZAKLJUČAK

Plazmatske koncentracije IL-4, IL-12 i IFNγ nisu u korelaciji sa procentom apoptotskih limfocita periferne krvi pacijenata obolelih od hronične limfocitne leukemije, ali su u značajnoj negativnoj korelaciji sa infiltracijom koštane srži malignim limfocitima. Kao poseban parametar, IL-12 je u negativnoj korelaciji sa stadijumom bolesti, što ga izdvaja kao antiapoptotski citokin o kom treba razmišljati u patogenezi i toku hronične limfocitne leukemije i uvrstiti ga u dalja istraživanja u ovoj oblasti.

Sukob interesa: Nije prijavljen.

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centrations of IL-12 occur in patients with advanced disease [12]. On the other hand, Parfieńczyk et al. showed that the concentrations of IL-12 and of IL-6 were higher in patients suffering from CLL, but their study included only patients with lower stage of the disease [13].

Regarding IL-4 and IFNγ, our results linking the concentrations of these cytokines to parameters of apoptosis and disease progression did not show a direct association. These cytokines have, in fact, been studied to a greater extent in literature, and although the plasma concentrations themselves have not been shown to be statistically significant, the density of receptors for IFNγ and IL-4, both on the leukemic lymphocytes themselves as well as on other immune cells, indicate the shifting of the immune response from Th1 response to Th2 response, (increase in IL-4 and decrease in IFNγ receptors), which opens up enough room for gradual development of chronic lymphocytic leukemia [14,15].

CONCLUSION

Plasma concentrations of IL-4, IL-12 and IFNγ are not correlated with the percentage of apoptotic lymphocytes in the peripheral blood of patients with chronic lymphocytic leukemia, but they are significantly negatively correlated with bone marrow infiltration by malignant lymphocytes. As a separate parameter, IL-12 is negatively correlated with the stage of the disease, which distinguishes it as an antiapoptotic cytokine that should be considered in the pathogenesis and course of chronic lymphocytic leukemia and included in further research in this area.

Conflict of interest: None declared.

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KAKVA JE OBEZBEĐENOST CRNE GORE LEKARIMA SPECIJALISTIMA MEDICINE?

ORIGINALNI RAD

ORIGINAL ARTICLE

HOW AVAILABLE ARE SPECIALIST MEDICAL DOCTORS IN MONTENEGRO?

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SAŽETAK

Uvod: Zdravstveni radnici, a posebno visokostručni kadar, svojim znanjem, iskustvom i veštinama treba da omogućavaju sprovođenje zdravstvene politike, a sve sa ciljem očuvanja i poboljšanja zdravlja stanovništva. Cilj ove studije je bio da utvrdi obezbeđenost Crne Gore lekarima, specijalistima medicine, po vrstama specijalizacije, odnosno da utvrdi kakva je njihova starosna i polna struktura u odnosu na druge zemlje Evropskog regiona.

Materijali i metode: Jedinica posmatranja u istraživanju su bili lekari medicine (specijalisti, lekari na specijalizaciji i lekari bez specijalizacije). Osim primene deskriptivnih metoda (apsolutni i relativni brojevi) izračunavani su indeksi promene u broju lekara za period između 2009. i 2021. godine, indeksi promene u starosnoj strukturi lekara za period između 2008. i 2021. godine, indeksi promene u zastupljenosti lekara specijalista starosnog doba preko 55 godina (55+) po specijalnostima, kao i stope obezbeđenosti različitim profilima lekara specijalista na 100.000 stanovnika. Korišćeni su podaci koji se odnose na javni sektor, a koje prikuplja i publikuje Institut za javno zdravlje Crne Gore.

Rezultati: Ukupan broj lekara (specijalisti, lekari na specijalizaciji i lekari bez specijalizacije) je u Crnoj Gori, u 2021. godini, u javnom sektoru bio za trećinu veći u odnosu na 2009. godinu, dok se broj specijalista uvećao za četvrtinu. Porast broja specijalističkog lekarskog kadra je bio značajno veći u bolničkim delatnostima u odnosu na vanbolničke (povećanje broja lekara specijalista od 46% i lekara na specijalizaciji od 41%, u odnosu na 23% i 5% u vanbolničkim delatnostima). U 2021. godini, specijalistički kadar je bio u najvećem procentu u starosnoj grupi od 55 i više godina (oko 34%).

Zaključak: Navedene statističke serije podataka koje se odnose na lekare specijaliste, lekare bez specijalizacije i lekare na specijalizaciji, u vanbolničkoj i bolničkoj zdravstvenoj zaštiti, ukazuju na značajan manjak ovih lekara u Crnoj Gori, u odnosu na većinu zemalja Evropskog regiona, kao i na neadekvatnu starosnu strukturu, posebno za pojedine specijalnosti u kojima treba pažljivo planirati kadar. Kvalitetnije i efikasnije upravljanje ljudskim resursima trebalo bi da omogući ranije upućivanje mladih lekara na specijalizaciju.

Ključne reči: ljudski resursi, zdravstvena zaštita, lekari specijalisti

ABSTRACT

Introduction: Health workers, especially highly skilled and trained staff, with their knowledge, experience, and skills, should enable the implementation of health policy, with the aim of preserving and improving the health of the population. The aim of this study was to determine the availability of medical doctors and specialist medical doctors in Montenegro, by type of specialization, i.e., to determine their age and gender structure, as compared to other countries in the European Region (ER).

Materials and methods: Medical doctors (specialists, residents, and medical doctors without specialist training) represented the unit of observation in this study. In addition to the application of descriptive methods (absolute and relative numbers), indices of change in the number of doctors for the period between 2009 and 2021, indices of change in the age structure of doctors for the period between 2008 and 2021, indices of change in the prevalence of specialist doctors aged above 55 years (55+), by specialty, were calculated, as well as the density of different specialists per 100,000 population. Data related to the public sector, collected and published by the Institute of Public Health of Montenegro, were used.

Results: The total number of doctors (specialists, residents, and medical doctors without specialist training) in Montenegro, in 2021, in the public sector, was by a third higher than in 2009, while the number of specialists increased by a quarter. The increase in the number of specialist medical personnel was significantly higher in hospitals, as compared to outpatient facilities (increase in the number of specialist doctors by 46% and residents by 41%, compared to 23% and 5% in outpatient facilities). In 2021, the highest percentage of specialist staff was in the age group of 55 years and above (about 34%).

Conclusion: The aforementioned statistical series of data, related to specialist doctors, residents, and medical doctors without specialist training, in outpatient and inpatient health care, indicate a significant shortage of these doctors in Montenegro, as compared to most countries in the European Region, as well as an inadequate age structure, especially for certain specialties where careful human resources planning should be applied. Better and more efficient management of human resources should provide for young doctors to begin with specialist training sooner.

Keywords: human resources, health care, specialist medical doctors

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Primljeno • *Received*: Octobrer 31, 2023; **Revidirano • *Revised*:** December 7, 2023; **Prihvaćeno • *Accepted*:** December 14, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47454

UVOD

Performanse zdravstvenog sistema u mnogome zavise od njegovog najvažnijeg resursa – ljudskih resursa, njihovih znanja, veština i motivacije [1,2]. Zdravstveni radnici, a posebno visokostručni kadar, svojim znanjem, iskustvom i veštinama treba da omoguće sprovođenje zdravstvene politike, a sve sa ciljem očuvanja i poboljšanja zdravlja stanovništva. Na putu ka univerzalnoj zdravstvenoj dostupnosti, ljudski resursi moraju biti ne samo brojčano dostupni, već i adekvatno raspoređeni i kompetentni, a moraju imati i adekvatnu podršku [3].

Na tom putu su brojni izazovi, usled starenja populacije, loše geografske dostupnosti zdravstvenog kadra (medicinske pustinje) i povećane potražnje usluga. Sve evropske zemlje se suočavaju sa krizom ljudskih resursa. Nakon krize uzrokovane pandemijom KOVID-19 oboljenja, postojeći problemi su postali još vidljiviji i složeniji. Manjak angažovane radne snage je i dalje prisutan, a kadar odlazi iz zdravstvenog sistema pod teretom problema neadekvatnih uslova rada: izgaranje na poslu, preopterećenost, loši međuljudski odnosi, i drugo [4].

Male zemlje, u koje se ubraja i Crna Gora, susreću se sa velikim brojem izazova u obezbeđivanju kompetentnosti i neophodnih veština ljudskih resursa [5]. U proteklim decenijama su se ljudski resursi neravnomerno razvijali u Crnoj Gori. Velike razlike koje su se javljale među regionima, posledica su neadekvatnog planiranja broja i strukture kadra u prošlosti, kada se više ulagalo u pravcu bržeg razvoja specijalističke delatnosti sekundarnog i tercijarnog nivoa [6]. U novom milenijumu, reformske aktivnosti potencirale su značaj i ulogu specijalističkog kadra na primarnom nivou zdravstvene zaštite, što je za posledicu imalo veći broj lekara specijalista na ovom nivou zdravstvene zaštite.

Cilj ove studije je bio da se utvrdi obezbeđenost Crne Gore lekarima, specijalistima medicine po vrstama specijalizacije, odnosno da se ustanovi kakva je njihova starosna i polna struktura u odnosu na druge zemlje Evropskog regiona, koje svom stanovništvu obezbeđuju visoki standard zadovoljavanja potreba za specijalističkom zdravstvenom zaštitom.

MATERIJALI I METODE

Jedinica posmatranja u ovoj deskriptivnoj studiji su bili lekari specijalisti, lekari na specijalizaciji i lekari bez specijalizacije, za koje kategorije su, primenom deskriptivnih metoda (apsoluti i relativni brojevi) izračunavani indeksi promene u broju lekara za period između 2009. i 2021. godine, indeksi promene u starosnoj strukturi lekara za period između 2008. i 2021. godine, indeksi promene u zastupljenosti lekara specijalista starosnog doba preko 55 godina (55+) po specijalnostima,

INTRODUCTION

The performance of the healthcare system largely depends on its most important resource – human resources, their knowledge, skills and motivation [1,2]. Health workers, especially highly skilled and trained staff, should enable the implementation of health policy with their knowledge, experience and skills, all with the aim of preserving and improving the health of the population. On the road to universal health accessibility, human resources must be not only available in numbers, but also adequately distributed and competent, and they must also have adequate support [3].

This road is paved with numerous challenges, due to the ageing of the population, the poor geographical availability of health staff (medical deserts), and the increased demand for healthcare services. All European countries are facing a crisis regarding human resources. After the crisis caused by the COVID-19 pandemic, existing problems have become even more visible and complex. The lack of employed workforce is still present, and healthcare workers are leaving the healthcare system due to the burden of inadequate working conditions: burnout, overwork, poor interpersonal relations, and other [4].

Small countries, including Montenegro, face numerous challenges in securing the competence and necessary skills of human resources [5]. In the past decades, human resources have developed unevenly in Montenegro. The great differences occurring between regions are the result of inadequate planning of the number and structure of personnel in the past, when more was invested in the direction of faster development of specialist activities at the secondary and tertiary levels [6]. In the new millennium, reform activities emphasized the importance and role of specialist staff at the primary level of health care, which resulted in a greater number of specialist doctors at this level of health care.

The aim of this study was to determine the availability of doctors and medical specialists in Montenegro by type of specialization, i.e., to determine their age and gender structure, as compared to other countries in the European Region (ER), which offer their population a high standard in meeting the needs for specialist health care.

MATERIALS AND METHODS

Medical specialists, residents, and medical doctors without specialist training represented the unit of observation in this descriptive study, for which categories, using descriptive methods (absolute and relative numbers), indices of change in the number of doctors for the period between 2009 and 2021, indices of

kao i stope obezbeđenosti lekarima specijalistima na 100.000 stanovnika.

Na osnovu raspoloživih serija podataka o kretanju broja lekara, dobijene su linije trenda koje pokazuju njihovo prosečno kretanje za period između 2009. i 2021. godine. Obezbeđenost stanovništva doktorima medicine – specijalistima/specijalizantima (isključujući specijaliste/specijalizante hirurgije, ginekologije i akušerstva, pedijatrije, psihijatrije, i opšte medicine), na 100.000 stanovnika, predstavlja indikator koji obuhvata sledeće grupe specijalnosti/subspecijalnosti: interna medicina (uključujući i subspecijalnosti interne medicine), onkologija, pneumoftiziologija, neurologija, otorinolaringologija, radiologija, infektologija, dermatologija, mikrobiologija, biohemija, klinička imunologija, patologija, i medicina rada. Obezbeđenost stanovništva doktorima medicine, specijalistima/specijalizantima hirurških grana na 100.000 stanovnika čine sledeće grupe specijalnosti: opšta hirurgija (sa subspecijalizacijama), neurohirurgija, plastična hirurgija, ortopedija, oftalmologija, urologija, maksilofacijalna hirurgija, urgentna medicina, i anestezija. Prikazane su stope obezbeđenosti stanovništva doktorima medicine, specijalistima/specijalizantima pedijatrije i stope obezbeđenosti stanovništva doktorima medicine, specijalistima/specijalizantima ginekologije i akušerstva na 100.000 stanovnika.

Za dobijanje uporednih pokazatelja za zemlje Evropskog regiona i šire, korišćeni su podaci iz međunarodnih baza podataka kao što su: *OECD Health Statistics 2020*, *Eurostat Database*, baza podataka Svetske zdravstvene organizacije (SZO). Demografske odrednice koje su korišćene bile su pol (muški/ženski) i starost (starosne grupe: do 34 godine, 35 – 44 godine, 45 – 54 godine, 55 i više godina). Podaci o ljudskim resursima, koje prikuplja i objavljuje Institut za javno zdravlje Crne Gore, korišćeni su u izradi ove studije, i to ukupan broj lekara u javnom sektoru koji je obuhvatio lekare u vanbolničkim i bolničkim ustanovama. Za izračunavanje stopa su korišćeni podaci o stanovništvu koje objavljuje Uprava za statistiku MONSTAT.

REZULTATI

U 2021. godini, bilo je ukupno 1.736 lekara je u javnom sektoru, što je u poređenju sa 2009. godinom povećanje za 429 lekara, odnosno 32,77%. Broj lekara specijalista, u odnosu na 2009. godinu se povećao od 939 na 1.118, odnosno za 246 ili 26,20%, a lekara na specijalizaciji sa 263 na 363 ili za 26,20%. Broj lekara, doktora medicine bez specijalizacije, porastao je sa 107 na 184 ili za 71,96%.

U vanbolničkim delatnostima, postoji porast u broju sve tri kategorije lekara u periodu između 2009. i 2021.

change in the age structure of doctors for the period between 2008 and 2021, indices of change in the prevalence of specialist doctors aged above 55 years (55+), by specialty, were calculated, as well as the density of different specialists per 100,000 population.

Based on the available series of data regarding the trends in the number of doctors, trend lines were obtained showing the average trend for the period between 2009 and 2021. The availability of medical doctors – specialists/residents (excluding specialists/residents specializing in surgery, gynecology and obstetrics, pediatrics, psychiatry, and general medicine) per 100,000 population, is an indicator that includes the following groups of specialties/subspecialties: internal medicine (including subspecialties of internal medicine), oncology, pneumo-phthisiology, neurology, otorhinolaryngology, radiology, infectology, dermatology, microbiology, biochemistry, clinical immunology, pathology, and occupational medicine. The availability of medical doctors, specialists/residents specializing in surgical branches of medicine per 100,000 population consists of the following groups of specialties: general surgery (with subspecialities of general surgery), neurosurgery, plastic surgery, orthopedic surgery, ophthalmology, urology, maxillofacial surgery, emergency medicine, and anesthesia. The density of medical doctors – specialists/residents specializing in pediatrics and the density of medical doctors – specialists/residents specializing in gynecology and obstetrics per 100,000 population are presented in this study.

Data from international databases such as: OECD Health Statistics 2020, Eurostat Database, World Health Organization (WHO) database, were used for obtaining comparative indicators for the countries of the European Region and beyond. The demographic determinants used were gender (male/female) and age (age groups: 34 years and younger, 35 – 44 years, 45 – 54 years, 55 years and above). Data on human resources, collected and published by the Institute of Public Health of Montenegro, were used in the preparation of this study, namely the total number of doctors in the public sector, which included doctors in outpatient facilities and hospitals. Population data published by the Statistical Office of Montenegro MONSTAT were used to calculate the rates.

RESULTS

In 2021, there was a total of 1,736 doctors in the public sector, which, compared to 2009, is an increase by 429 doctors, or 32.77%. Compared to 2009, the number of specialist doctors increased from 939 to 1,118, i.e., by 246 or 26.20%, while the number of residents increased from 263 to 363, or by 26.20%. The number of

Tabela 1. Zastupljenost (broj i %) doktora medicine, po kategorijama, u Crnoj Gori, u periodu između 2009. i 2021. godine*

Table 1. Prevalence (number and %) of medical doctors, by category, in Montenegro, in the period between 2009 and 2021*

Doktori medicine / *Medical doctors*	2009. Broj / *Number* %	2013. Broj / *Number* %	2014. Broj / *Number* %	2015. Broj / *Number* %	2016. Broj / *Number* %	2017. Broj / *Number* %	2018. Broj / *Number* %	2019. Broj / *Number* %	2021. Broj / *Number* %
Specijalisti / *Specialists*	939	1,032	1,044	1,043	1,059	1,082	1,078	1,118	1,185
	71.74	76.61	76.26	70	65.53	65.22	62.31	65.46	68.18
Na specijalizaciji / *Residents*	263	197	199	305	405	404	463	413	364
	20.09	14.63	14.54	20.47	25.06	24.35	26.76	24.18	20.94
Bez specijalizacije / *Doctors without specialist training*	107	118	126	142	152	173	189	177	189
	8.17	8.76	9.2	9.53	9.41	10.43	10.93	10.36	10.88
UKUPNO / *Total*	**1,309**	**1,347**	**1,369**	**1,490**	**1,616**	**1,659**	**1,730**	**1,708**	**1,738**
	100	100	100	100	100	100	100	100	100

*Za navedeni period, obuhvaćene su godine: 2009, 2013, 2014, 2015, 2016, 2017, 2018, 2019. i 2021.

*For the observed period, the following years have been covered: 2009, 2013, 2014, 2015, 2016, 2017, 2018, 2019, and 2021.

godine, a najveći je bio porast broja lekara bez specijalizacije (71%), zatim na lekara na specijalizaciji (23%), dok je broj specijalista porastao za oko 5%.

U bolničkim delatnostima, broj lekara specijalista se, u periodu između 2009. i 2021. godine, uvećao za 243, odnosno za 46%, dok se broj lekara na specijalizaciji u ovom periodu uvećao za 68, odnosno 41%. Broj lekara bez specijalizacije u bolničkim delatnostima je bio zanemarljiv tokom celog perioda.

U Tabeli 2 su dati uporedni podaci o broju i učešću lekara (bez/sa specijalizacijom i na specijalizaciji) u

medical doctors without specialist training increased from 107 to 184, or by 71.96%.

In outpatient facilities, there is an increase in the number of all three categories of doctors in the period between 2009 and 2021, and the largest increase was in the number of doctors without specialist training (71%), followed by residents (23%), while the number of specialists increased by about 5%.

In hospitals, the number of specialists, in the period between 2009 and 2021, increased by 243, i.e., by 46%, while the number of residents increased by 68,

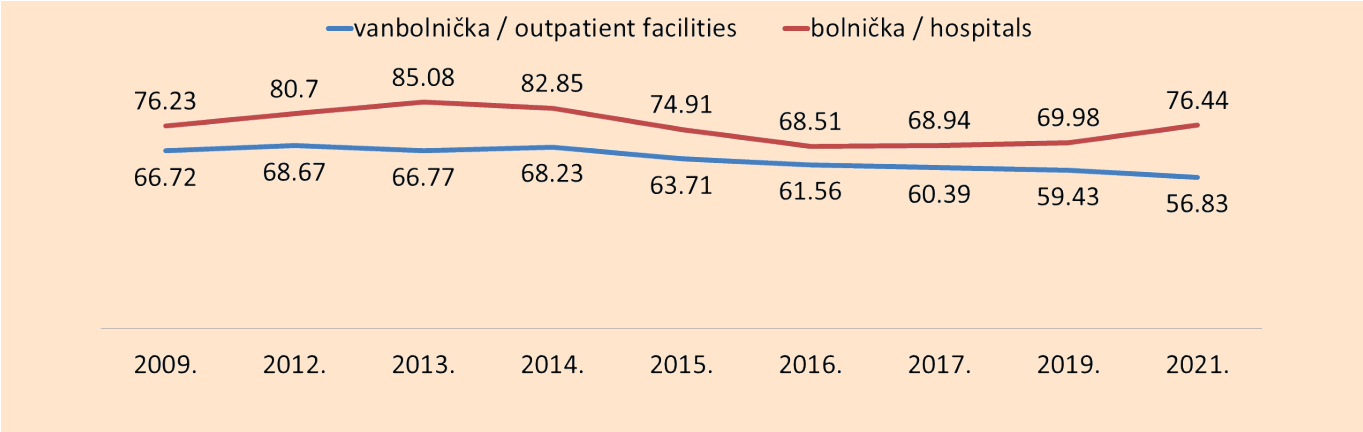
Tabela 2. Zastupljenost (broj i %) doktora medicine, bez specijalizacije, na specijalizaciji i specijalista, u vanbolničkim i bolničkim delatnostima, u Crnoj Gori, u periodu između 2009. i 2021. godine*

Table 2. Prevalence (number and %) of medical doctors without specialist training, residents, and specialists, in outpatient facilities and hospitals, in Montenegro, in the period between 2009 and 2021*

Doktori medicine / *Medical doctors*	Vanbolničke delatnosti / *Outpatient facilities*						Bolničke delatnosti / *Hospitals*					
	Godine / *Years*						Godine / *Years*					
	2009	2012	2015	2017	2019	2021	2009	2012	2015	2017	2019	2021
Specijalisti / *Specialists*	413	388	416	436	435	435	526	573	627	646	683	769
	66.72	68.67	63.7	60.39	59.43	56.83	76.23	80.7	74.91	68.94	69.98	76.44
Na specijalizaciji / *Residents*	99	73	98	113	122	122	164	137	207	291	291	232
	15.99	12.92	15.01	15.65	16.67	18.03	23.77	19.3	24.73	31.06	26.82	23.06
Bez specijalizacije / *Doctors without specialist training*	107	104	139	173	175	184	0	0	3	0	2	5
	17.29	18.41	21.29	23.96	23.9	25.14	0	0	0.36	0	0.2	0.5
Broj / *Number*	**619)**	**565**	**653**	**722**	**732**	**732**	**690**	**710**	**837**	**937**	**976**	**1,006**
%	100	100	100	100	100	100	100	100	100	100	100	100

*Za navedeni period, obuhvaćene su godine: 2009, 2012, 2015, 2017, 2019. i 2021.

*For the observed period, the following years have been covered: 2009, 2012, 2015, 2017, 2019, and 2021.



*Za navedeni period, obuhvaćene su godine 2009, 2012, 2013, 2014, 2015, 2016, 2017, 2019. i 2021.

Slika 1a. Zastupljenost (%) doktora medicine, specijalista, u vanbolničkoj i bolničkoj zaštiti, u Crnoj Gori, u periodu između 2009. i 2021. godine*

*For the observed period, the following years have been covered: 2009, 2012, 2013, 2014, 2015, 2016, 2017, 2019, and 2021.

Figure 1a. Prevalence (%) of specialist medical doctors in outpatient facilities and hospitals, in Montenegro, in the period between 2009 and 2021*

vanbolničkim i bolničkim delatnostima u Crnoj Gori, u periodu između 2009. i 2021. godine.

Zastupljenost navedenih kategorija lekara (bez specijalizacije, na specijalizaciji i specijalista) po navedenim godinama, prikazana je u Grafikonima 1. a, 1. b i 1. c.

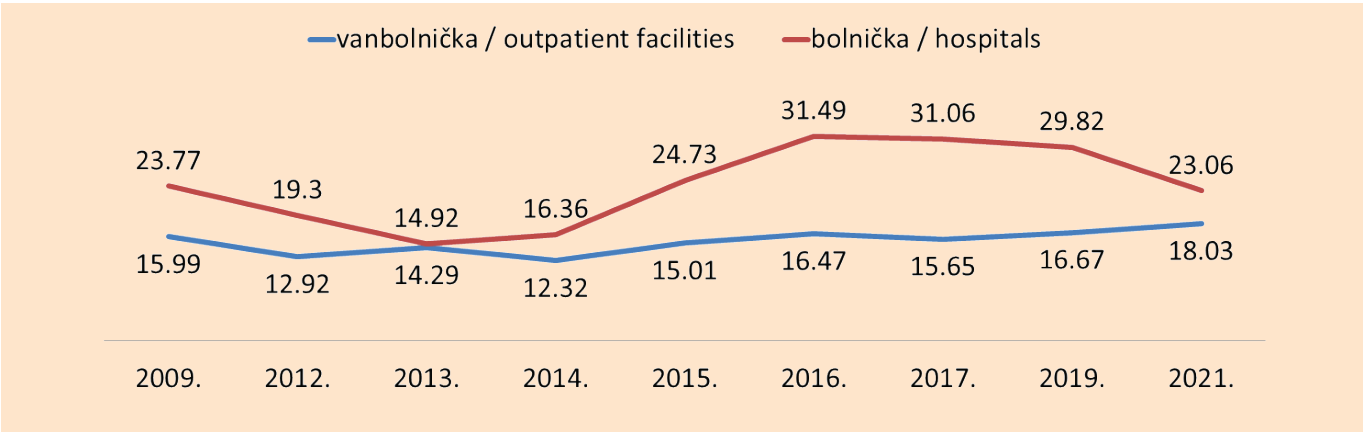
Posmatrajući zastupljenost (izraženu u procentima, Tabela 3.) lekara (specijalista, lekara na specijalizaciji i lekara bez specijalizacije), po starosnim grupama, u 2008. godini i 2021. godini, zaključuje se da je u 2008. godini specijalistički kadar bio dominantno skoncentrisan u starosnoj grupi od 45 – 54 godine (47%), dok je u 2021. godini specijalistički kadar bio u najvećem procentu u starosnoj grupi od 55 i više godina (oko 34%), a odmah zatim u starosnoj grupi od 35 – 44 godine (32%). Lekari na specijalizaciji su u 2008. godini bili najviše u starosnoj grupi do 34 godine (73%), dok je u 2021. godini taj udeo iznosio 57%. Lekara bez specija-

i.e., 41%, in this period. The number of doctors without specialist training in hospitals was negligible during the entire period.

Table 2 provides comparative data on the number and ratio of doctors (without specialist training/specialists/residents) in outpatient facilities and hospitals in Montenegro, in the period between 2009 and 2021.

The prevalence of the defined categories of doctors (doctors without specialist training/residents /specialists), by observed years, is presented in Graphs 1. a, 1. b, and 1. c.

Observing the prevalence (expressed in percentages, Table 3) of doctors (specialists/residents/doctors without specialist training), by age groups, in 2008 and 2021, it can be concluded that, in 2008, specialist medical doctors were predominantly concentrated in the 45 – 54 years age group (47%), while in 2021, specialist medical doctors were, in the highest percentage,

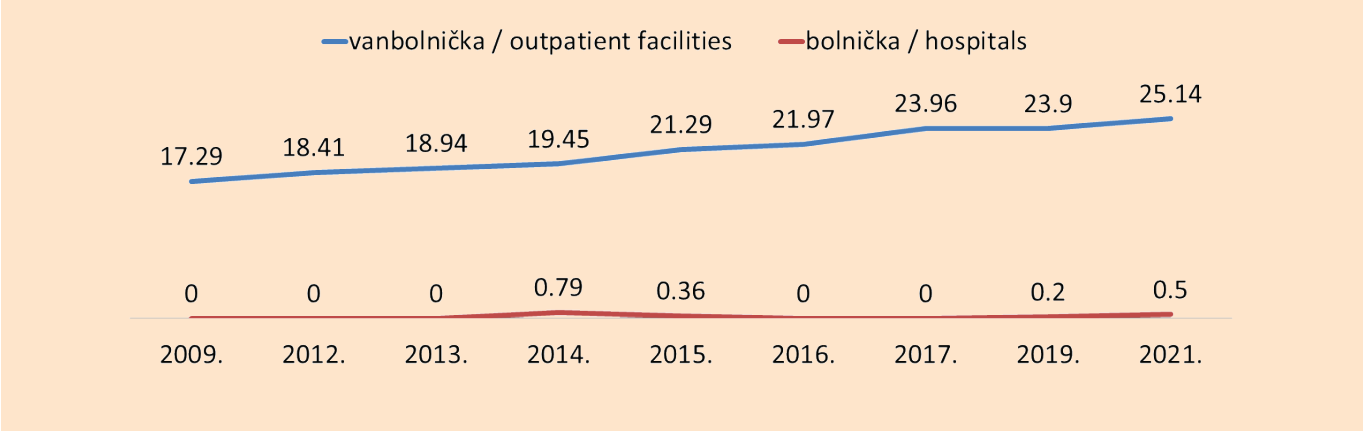


*Za navedeni period, obuhvaćene su godine 2009, 2012, 2013, 2014, 2015, 2016, 2017, 2019. i 2021.

Slika 1b. Zastupljenost (%) doktora medicine na specijalizaciji, u vanbolničkoj i bolničkoj zaštiti, u Crnoj Gori, u periodu između 2009. i 2021. godine *

*For the observed period, the following years have been covered: 2009, 2012, 2013, 2014, 2015, 2016, 2017, 2019, and 2021.

Figure 1b. Prevalence (%) of residents in outpatient facilities and hospitals, in Montenegro, in the period between 2009 and 2021*



*Za navedeni period, obuhvaćene su godine 2009, 2012, 2013, 2014, 2015, 2016, 2017, 2019. i 2021.

Slika 1c. Zastupljenost (%) doktora medicine bez specijalizacije, u vanbolničkoj i bolničkoj zaštiti, u Crnoj Gori, u periodu između 2009. i 2021. godine *

*For the observed period, the following years have been covered: 2009, 2012, 2013, 2014, 2015, 2016, 2017, 2019, and 2021.

Figure 1c. Prevalence (%) of medical doctors without specialist training in outpatient facilities and hospitals, in Montenegro, in the period between 2009 and 2021*

lizacije je u 2008. godini najviše bilo u starosnoj grupi do 34 godine (58%), dok je u 2021. godini lekara bez specijalizacije bilo više u starosnoj grupi od 35 – 44 godine (41%). U 2008. godini je blizu 20% lekara i dalje bilo bez specijalizacije, dok je u 2021. godini taj udeo iznosio 23%.

Od ukupnog broja lekara, broj lekara u starosnoj grupi od 35 – 54 godine je u 2021. godini bio za 6,63% manji nego u 2008. godini, dok je broj lekara starosti preko 55 godina porastao za 12,13%, u odnosu na 2008. godinu. Zastupljenosti lekara u Crnoj Gori, u 2008. godini i 2021. godini, po starosnim grupama, prikazana je u Grafikonu 2.

Od 1.185 specijalista, koji su obavljali zdravstvenu zaštitu stanovništva Crne Gore u vanbolničkim i bolničkim delatnostima (javni sektor), u 2021. godini je njih 407, odnosno 34,35%, bilo sa 55 i više godina starosti (Tabela 4.). Preko 50% angažovanog lekarskog kadra

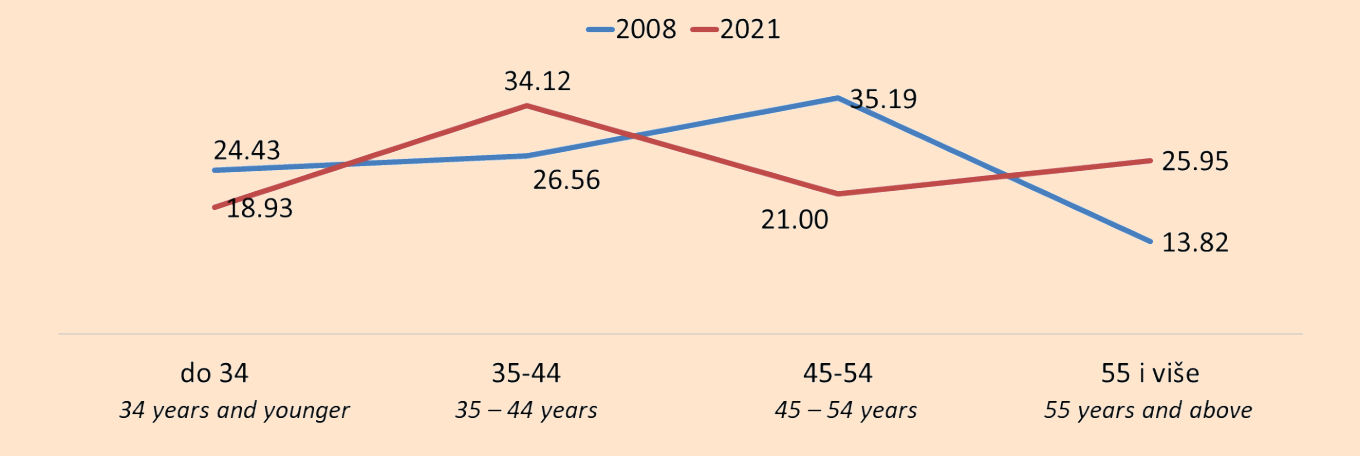
placed in the 55 years and above age group (about 34%), followed immediately by the 35 – 44 years age group (32%). In 2008, the majority of residents were in the 34 and younger age group (73%), while in 2021, this percentage was 57%. In 2008, the majority of medical doctors without specialist training were in the 34 years and younger age group (58%), while in 2021, there were more doctors without specialist training in the 35 – 44 years age group (41%). In 2008, almost 20% of doctors were still without specialist training, while in 2021, this percentage was 23%.

Out of the total number of doctors, the number of doctors in the 35 – 54 years age group in 2021 was by 6.63% lower than in 2008, while the number of doctors above the age of 55 years increased by 12.13%, as compared to 2008. The prevalence of doctors in Montenegro, in 2008 and 2021, by age group, is shown in Graph 2.

Tabela 3. Zastupljenost (%) doktora medicine, bez specijalizacije, na specijalizaciji i specijalista, u Crnoj Gori, u 2008. godini i 2021. godini

Table 3. Prevalence (%) of medical doctors without specialist training, residents, and specialists, in Montenegro, in years 2008 and 2021

Starosne grupe / *Age groups*	2008			2021		
	Specijalisti / *Specialists*	*Na specijalizaciji / Residents*	*Bez specijalizacije / Medical doctors without specialist training*	Specijalisti / *Specialists*	*Na specijalizaciji / Residents*	*Bez specijalizacije / Medical doctors without specialist training*
do 34 godine / *34 years and younger*	4.13	73.29	58.39	5.65	56.59	29.63
35 – 44* godine / *years	29.35	24.54	12.41	32.32	40.94	32.28
45 – 54* godine / *years	46.76	2.17	26.28	27.68	2.47	14.81
55 i više godina / *55 years and above*	19.76	0	2.92	34.35	0	23.28
Ukupno / *Total*	100.00	100.00	100.00	100.00	100.00	100.00



Slika 2. Zastupljenost (%) lekara po starosnim grupama, u Crnoj Gori, u 2008. i 2021. godini

Figure 2. Prevalence (%) of doctors, by age groups, in Montenegro, in years 2008 and 2021

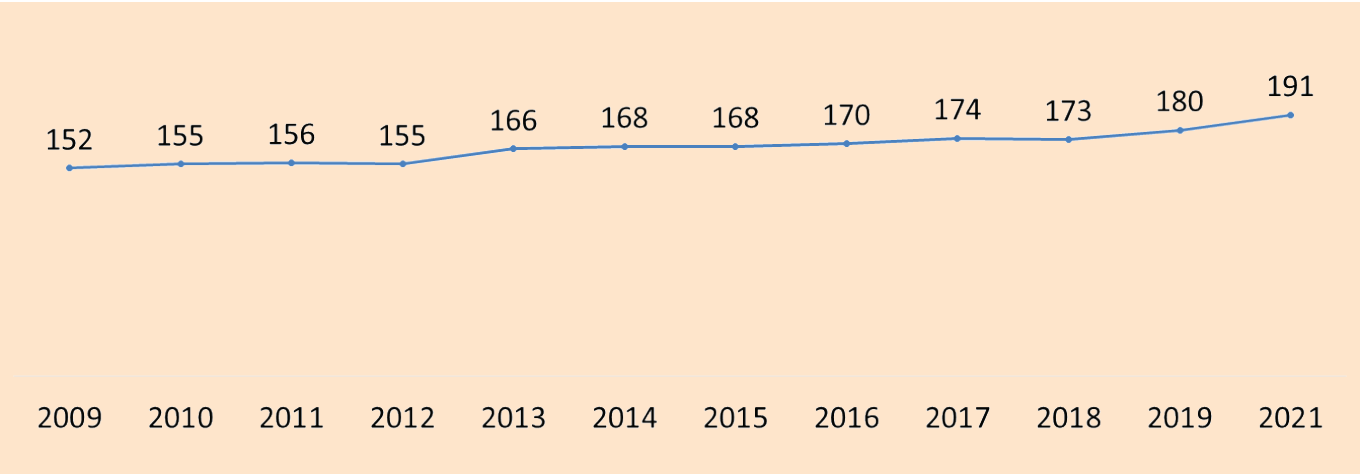
starijeg od 55 godina, bili su lekari specijalisti sledećih specijalnosti: pneumoftiziologija (71%), neuropsihijatrija (82%), fizikalna medicina (50%), transfuziologija (56%), sportska medicina (75%), medicina rada (75%), opšta medicina (60%), kao i plastična i rekonstruktivna hirurgija (60%). U 2021. godini, najveći broj lekara specijalista imao je specijalizaciju iz pedijatrije (148 lekara).

Na osnovu distribucije broja lekara specijalista u periodu između 2009. i 2021. godine i procenjenog broja stanovnika Crne Gore, procenjena je stopa obezbeđenosti lekarima specijalistima na 100.000 stanovnika (Grafikon 3). U poređenju sa 2009. godinom, kada je ta stopa iznosila 152 lekara na 100.000 stanovnika, u 2021. godini, taj indikator je dostigao vrednost od 191 lekara na 100.000 stanovnika.

U Crnoj Gori je obezbeđenost stanovništva doktorima medicine, specijalistima/specijalizantima (isključujući specijaliste/specijalizante hirurgije, ginekologije i akušerstva, pedijatrije, psihijatrije, i opšte medicine), u 2020. godini, na 100.000 stanovnika, iznosila 109, dok

Of 1,185 specialists, who were involved in the health care of the population of Montenegro, in outpatient facilities and hospitals (public sector), in 2021, 407 of them, or 34.35%, were 55 years old or above (Table 4). More than 50% of the employed medical staff above the age of 55 were medical doctors specializing in following medical fields: pneumo-phthisiology (71%), neuropsychiatry (82%), physical medicine (50%), transfusiology (56%), sports medicine (75%), occupational medicine (75%), general medicine (60%), as well as plastic and reconstructive surgery (60%). In 2021, the highest number of specialist doctors were pediatricians (148 doctors).

The density of specialist doctors per 100,000 population was estimated based on the distribution of the number of specialist medical doctors in the period between 2009 and 2021 and the estimated population of Montenegro (Graph 3). Compared to 2009, when the density was 152 doctors per 100,000 population, in 2021, this indicator reached the value of 191 doctors per 100,000 population.



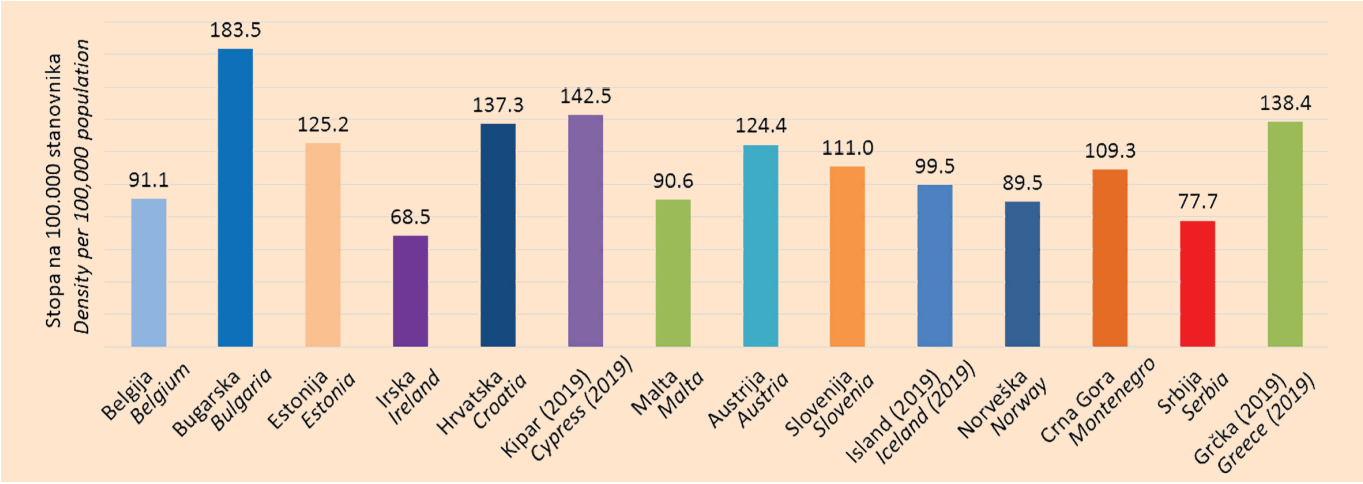
Slika 3. Distribucija (broj) doktora medicine, specijalista, na 100.000 stanovnika, u Crnoj Gori, u periodu između 2009. i 2021. godine

Figure 3. Distribution (number) of specialist medical doctors per 100,000 population, in Montenegro, in the period between 2009 and 2021

Tabela 4. Zastupljenost (broj i %) doktora medicine, specijalista, starosti od 55 i više godina, u Crnoj Gori, u 2021. godini

Table 4. Prevalence (number and %) of specialist medical doctors, aged 55 years and above, in Montenegro, in 2021

SPECIJALNOSTI LEKARA / SPECIALTIES	**Ukupan broj lekara specijalista** */ Total number of specialist medical doctors*	**Starosti od 55 i više godina** */ Aged 55 years and above*	
		Broj lekara / *Number of doctors*	**% lekara** */ of doctors*
Interna medicina / *Internal medicine*	131	47	35.88
Infektologija / *Infectology*	19	8	42.11
Pneumoftiziologija / *Pneumo-phthisiology*	24	17	70.83
Pedijatrija / *Pediatrics*	148	60	40.54
Psihijatrija / *Psychiatry*	47	12	25.53
Neuropsihijatrija / *Neuropsychiatry*	11	9	81.82
Neurologija / *Neurology*	18	6	33.33
Fizikalna medicina / *Physical medicine*	16	8	50.00
Dermatovenerologija / *Dermatovenereology*	20	6	30.00
Radiologija / *Radiology*	88	13	14.77
Hirurgija / *Surgery*	67	23	34.33
Urologija / *Urology*	19	8	42.11
Ortopedija / *Orthopedic surgery*	37	9	24.32
Neurohirurgija / *Neurosurgery*	7	1	14.29
Dečija hirurgija / *Pediatric surgery*	3	1	33.33
Ginekologija i akušerstvo / *Gynecology and obstetrics*	93	32	34.41
Oftalmologija / *Ophthalmology*	32	5	15.63
Otorinolaringologija / *Otorhinolaryngology*	29	6	20.69
Anesteziologija / *Anesthesiology*	64	23	35.94
Transfuziologija / *Transfusiology*	16	9	56.25
Patohistologija / *Pathohistology*	13	2	15.38
Sudska medicina / *Forensic medicine*	4	0	0.00
Epidemiologija / *Epidemiology*	49	6	12.24
Mikrobiologija / *Microbiology*	18	5	27.78
Higijena / *Hygiene*	10	4	40.00
Socijalna medicina / *Social medicine*	7	3	42.86
Nuklearna medicina / *Nuclear medicine*	3	0	0.00
Sportska medicina / *Sports medicine*	4	3	75.00
Urgentna medicina / *Emergency medicine*	26	8	30.77
Medicina rada / *Occupational medicine*	20	15	75.00
Opšta medicina / *General medicine*	60	36	60.00
Imunologija / *Immunology*	3	0	0.00
Klinička biohemija / *Clinical biochemistry*	23	6	26.09
Maksilofacijalna hirurgija / *Maxillofacial surgery*	7	0	0.00
Plastična i rekonstruktivna hirurgija / *Plastic and reconstructive surgery*	5	3	60.00
Porodična medicina / *Family medicine*	42	13	30.95
Zdravstvena statistika / *Health statistics*	1	0	0.00
Dečija psihijatrija / *Child psychiatry*	1	0	0.00
Ukupno lekara specijalista / *Total number of specialist medical doctors*	1,185	407	34.35



U grafikonu su prikazani radno aktivni lekari, osim u Crnoj Gori (profesionalno aktivni) i Grčkoj (lekari koji imaju licencu iz prakse); Izvor: *OECD Health Statistics 2020; Eurostat Database.*

Slika 4. Obezbeđenost stanovništva doktorima medicine, specijalistima/specijalizantima (isključujući specijaliste/specijalizante hirurgije, ginekologije i akušerstva, pedijatrije, psihijatrije i opšte medicine), na 100.000 stanovnika, u Crnoj Gori i u zemljama Evrope, u 2020. godini (ili poslednji dostupni podaci)

The graph shows working doctors, except in Montenegro (professionally active) and Greece (doctors who have a license to practice); Source: OECD Health Statistics 2020; Eurostat Database

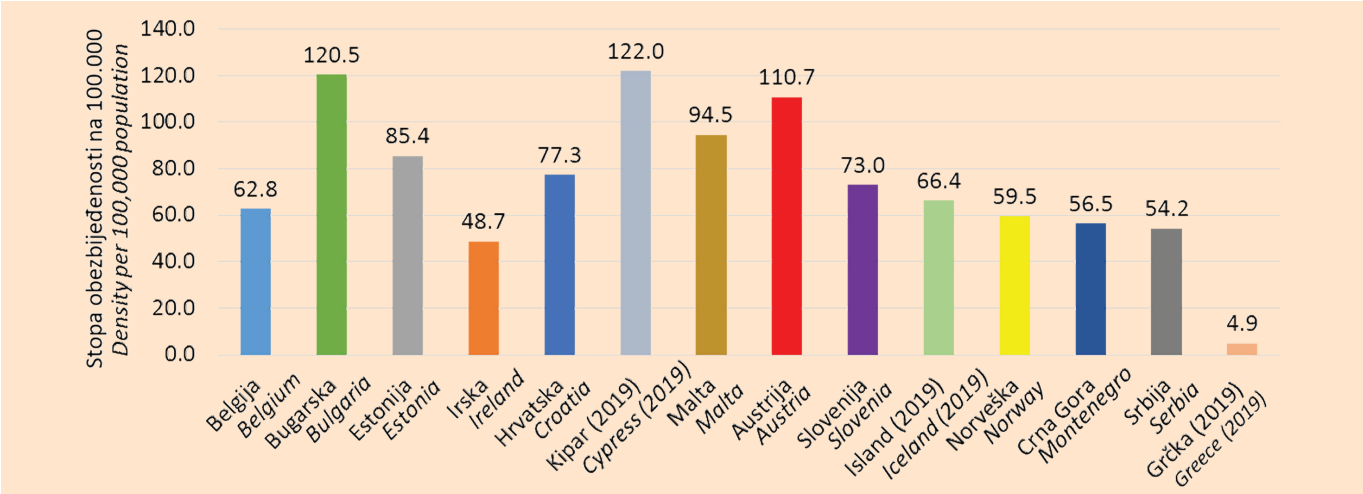
Figure 4. Availability of medical doctors – specialists/residents (excluding specialists/residents specializing in surgery, gynecology and obstetrics, pediatrics, psychiatry, and general medicine), per 100,000 population, in Montenegro and in other European countries, in 2020 (or latest available data)

je u Grčkoj iznosila 138 (2019. godina), u Sloveniji 111, a Srbiji 78 (Grafikon 4). Prosek u Evropskom regionu, prema poslednjim dostupnim podacima (SZO, 2014. godina), iznosi 90.

Stopa doktora medicine, specijalista/specijalizanata hirurških grana, na 100.000 stanovnika, u Crnoj Gori, u 2020. godini, iznosila je 57, u Grčkoj je iznosila 49 (2019. godina), a u istom periodu je u Sloveniji iznosila 73, dok je u Srbiji bila 54 (Grafikon 5). U Evropskom regionu (ER) je prosek, prema poslednjim dostupnim podacima (SZO, 2014. godina), iznosio 70.

In Montenegro, the availability of medical doctors – specialists/residents (excluding specialists/residents specializing in surgery, gynecology and obstetrics, pediatrics, psychiatry, and general medicine), in 2020, per 100,000 population, was 109, while in Greece it was 138 (2019), in Slovenia 111, and in Serbia 78 (Graph 4). The average availability per 100,000 population in the European Region, according to the latest available data (WHO, 2014), is 90.

The density of medical doctors – specialists/residents specializing in surgical branches per 100,000



U grafikonu su prikazani radno aktivni lekari, osim u Crnoj Gori (profesionalno aktivni) i Grčkoj (lekari koji imaju licencu iz prakse); Izvor: *OECD Health Statistics 2020; Eurostat Database*

Slika 5. Obezbeđenost stanovništva doktorima medicine, specijalistima/specijalizantima hirurških grana na 100.000 stanovnika, u Crnoj Gori i u zemljama Evrope, u 2020. godini (ili poslednji dostupni podaci)

The graph shows working doctors, except in Montenegro (professionally active) and Greece (doctors who have a license to practice); Source: OECD Health Statistics 2020; Eurostat Database

Figure 5. Availability of medical doctors – specialists/residents specializing in surgical branches per 100,000 population, in Montenegro and in other European countries, in 2020 (or latest available data)

DISKUSIJA

Ova studija je analizirala specijalistički lekarski kadar između dve velike krize, i to ekonomske krize, koja je zahvatila Evropski region 2008. godine, i krize uzrokovane pandemijom KOVID-19 oboljenja, u 2020. godini, kao i u 2021. godini. U periodu krize uzrokovane pandemijom KOVID-19 oboljenja, u 2020. godini, u velikom broju zemalja je zabeležen privremeni porast broja ljudskih resursa do kojeg je došlo usled odgovora na krizu [3,4]. Uzimajući u obzir objektivne okolnosti i složeni uticaj društveno-političko-ekonomskih faktora, koji su uticali na mogućnosti zemlje da jača i razvija zdravstveni sistem u navedenim okolnostima, veliki je uspeh što je osnažen kadrovski potencijal u Crnoj Gori. Ukupan broj lekara (specijalisti, lekari na specijalizaciji i lekari bez specijalizacije) je povećan za oko trećinu, dok je broj specijalista porastao za četvrtinu, u posmatranom periodu. Ipak, značajno veći broj lekara se u 2021. godini našao bez specijalizacije, što treba tumačiti, ne samo u kontekstu navedenih uticaja iz okruženja, već i iz aspekta upravljanja ljudskim resursima. To se posebno odrazilo na mladi kadar u vanbolničkim delatnostima, koji je duže vremena čekao da bude upućen na specijalizaciju nego što je to bio slučaj u 2009. godini.

Nasuprot tome, u bolničkim delatnostima je došlo do značajnijeg porasta broja lekara koji su upućivani na specijalizaciju (za dve trećine više), što se odrazilo na veći broj specijalističkog kadra u bolnicama. Ovo nam ukazuje na to da je upravljanje ljudskim resursima, iako u okolnostima manje obezbeđenosti lekarima specijalistima u odnosu na druge evropske zemlje, imalo veću usmerenost ka jačanju bolničkog potencijala nasuprot vanbolničkog. Iako Crna Gora u ovom trenutku nema strateški okvir kojim se usmerava razvoj zdravstvenog sistema ili ljudskih resursa (budući da su se ranija dokumenta odnosila na period do 2020. ili 2022. godine), potrebno je navesti da su raniji okviri usmeravali sistem ka primarnom nivou zdravstvene zaštite [6,7] kao okosnici zdravstvenog sistema. Nacrtom Strategije razvoja zdravstva, koja je dostupna na veb stranici Ministarstva zdravlja, a koja obuhvata period između 2023. i 2027. godine [8], navodi se da će donosioci odluka istrajati na reformskom opredeljenju iz 2005. godine, kojim se primarna zdravstvena zaštita prepoznaje kao "prioritetna oblast u razvoju zdravstvenog sistema, a u okviru nje i promovisanje zdravih stilova života i preventivne zdravstvene zaštite". Ovaj strateški dokument (nacrt) prepoznao je, u delu strateških ciljeva koji se odnose na ljudske resurse, potrebu povećanja broja specijalista iz oblasti medicine rada.

Specijalistički kadar u Crnoj Gori je relativno star, budući da je, u 2021. godini, bilo najviše lekara specijalista (trećina) koji su stariji od 55 godina. Veliki broj

population, in Montenegro, in 2020, was 57, in Greece it was 49 (2019), it was 73 in Slovenia, in the same period, while in Serbia it was 54 (Graph 5). In the European Region, the average, according to the latest available data (WHO, 2014), was 70.

DISCUSSION

This study analyzed specialist medical staff between two major crises, namely the economic crisis, which affected the European region in 2008, and the crisis caused by the COVID-19 pandemic in 2020 and continuing into 2021. In the period of the crisis caused by the COVID-19 pandemic in 2020, a large number of countries recorded a temporary increase in human resources numbers, which occurred as the result of response to the crisis [3,4]. Taking into account the objective circumstances and the complex influence of socio-political and economic factors, which affected the country's ability to strengthen and develop the health system in the aforementioned circumstances, the fact that human resources potential in Montenegro has been strengthened is quite a success. The total number of doctors (specialists/residents/medical doctors without specialist training) increased by about a third, while the number of specialists increased by a quarter, in the observed period. Nevertheless, in 2021, a significantly larger number of doctors found themselves lacking specialist training, which should be interpreted, not only in the context of the aforementioned impact of external factors, but also from the aspect of human resources management. This particularly affected younger health professionals in outpatient facilities, who waited longer to be enrolled in specialist training than was the case in 2009.

In contrast, in hospitals, there was a significant increase in the number of doctors who were enrolled in specialist training (by two thirds), which was reflected in the greater number of specialist medical doctors in hospitals. This indicates that the management of human resources, although in circumstances of lesser availability of specialists, as compared to other European countries, was more focused on strengthening inpatient potential as opposed to the potential of outpatient health facilities. Although Montenegro does not currently have a strategic framework directing the development of the healthcare system or the development of human resources (since earlier documents referred to the period until 2020 or 2022), it should be noted that earlier frameworks directed the system towards the primary health care level [6,7] as the backbone of the health system. The draft of the Health Development Strategy, which is available on the website of the Ministry of Health, and which covers the period

zemalja Evropske unije (EU) susreće se sa problemom izrazito starog lekarskog kadra. Tako je u Italiji čak 60% svih lekara starije od 55 godina [9]. Ipak, uočava se da je orjentacija ka jačanju bolničkih kadrovskih resursa u Crnoj Gori u prethodnom periodu dala pozitivne rezultate po pitanju zanavljanja kadra, pa se broj lekara koji su starosnog doba od 35 – 44 godine povećao i čini skoro trećinu specijalističkog kadra. Među najmlađim lekarima se smanjilo učešće onih koji su bili upućeni na specijalizaciju, pa je i broj lekara koji su na specijalizaciji bio veći u starijoj starosnoj grupi. Blago je povećan broj lekara koji su bez specijalizacije u starosnoj grupi od preko 55 godina života. Kvalitetnije i efikasnije upravljanje ljudskim resursima trebalo bi da omogući ranije upućivanje mladih lekara na specijalizaciju. Upravljanje je ključno, ne samo za jačanje radne snage, nego i za održavanje kompetencija koje su neophodne za pružanje zdravstvenih usluga [10].

U ukupnom broju lekara, uočava se da brže raste broj lekara u starosnoj grupi od 55 i više godina, nego što se povećava broj najmlađih lekara koji ulaze u sistem. Ovakvo upravljanje ljudskim resursima, i to lekarima, neće dugoročno poboljšati obezbeđenost lekarima, već može da dovede sistem u još nepovoljniji položaj. To će svakako zavisiti i od dejstva velikog broja drugih faktora iz okruženja (migracije, jačanje privatnog sektora, i slično).

Ova studija je prepoznala oblasti u kojima je posebno ugroženo funkcionisanje i pružanje usluga u budućem periodu, usled visokog udela kadra koji je starijeg doba, a koje su obuhvatile sledeće specijalnosti: pneumoftiziologija, neuropsihijatrija, fizikalna medicina, transfuziologija, sportska medicina, medicina rada, opšta medicina, kao i plastična i rekonstruktivna hirurgija.

U poređenju sa drugim zemljama regiona i Evrope, obezbeđenost stanovništva doktorima medicine, specijalistima/specijalizantima (isključujući specijaliste/specijalizante hirurgije, ginekologije i akušerstva, pedijatrije, psihijatrije, i opšte medicine) na 100.000 stanovnika, u Crnoj Gori, bila je blizu obezbeđenosti ovim kadrom u Sloveniji, a bolja nego u drugim malim zemljama, kao što su Malta ili Island [11]. Međutim, stopa doktora medicine, specijalista/specijalizanata hirurških grana na 100.000 stanovnika je, u Crnoj Gori, u 2020. godini, bila među najnižim u Evropi, i bila je značajno ispod standarda koji se odnosi na zemlje Evropske unije [11]. Bolja je situacija ako se uporedi obezbeđenost stanovništva doktorima medicine, specijalistima/ specijalizantima pedijatrije i obezbeđenost stanovništva doktorima medicine, specijalistima/ specijalizantima ginekologije i akušerstva na 100.000 stanovnika, u Crnoj Gori i u zemljama Evrope.

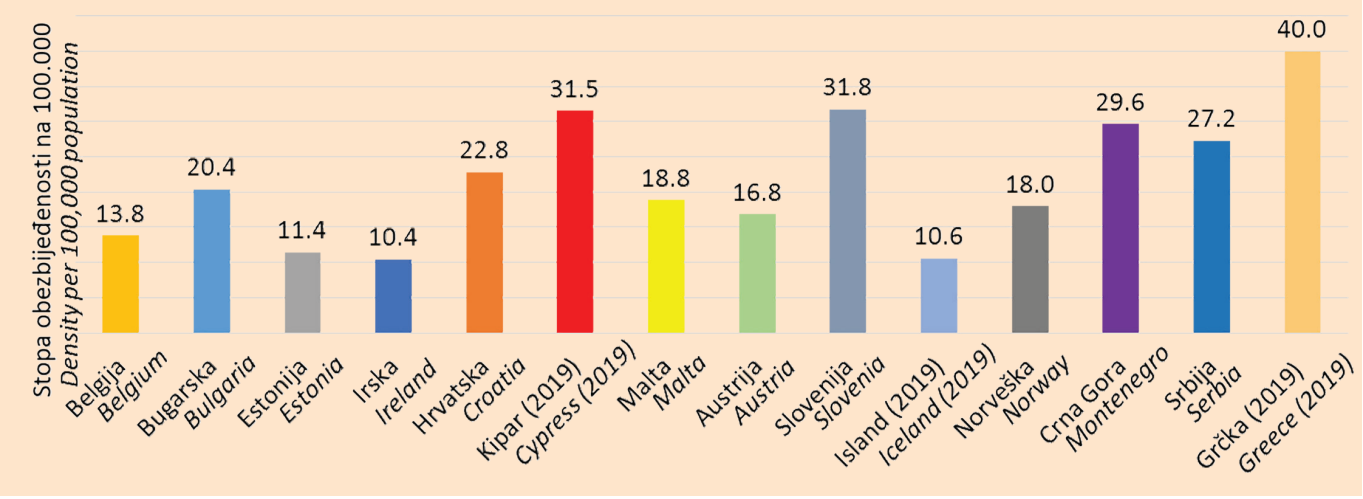
between 2023 and 2027 [8], states that decision-makers will stay on the course of reform commitments from 2005, which recognize primary health care as a "priority area in the development of the health system, and within it also the promotion of healthy lifestyles and preventive health care". This strategic document (draft) recognized, in the part of the strategic goals related to human resources, the need to increase the number of specialists in the field of occupational medicine.

In Montenegro, specialist medical personnel are relatively old, since in 2021, the majority of specialists (one third) are above the age of 55 years. A large number of European Union (EU) countries are facing the problem of very old medical staff. In Italy, as many as 60% of all doctors are older than 55 years [9]. Nevertheless, it is evident that the orientation towards strengthening hospital personnel resources in Montenegro in the previous period has yielded positive results in terms of staff recruitment, whereby the number of doctors aged 35 – 44 years has increased, making up almost a third of the specialist staff. Among the youngest doctors, the ratio of those enrolled in specialist training decreased, so the number of residents was higher in the older age group. The number of doctors without specialist training in the 55 years and above age group slightly increased. Better and more efficient management of human resources should enable earlier enrolment of young doctors in specialist training. Management is crucial, not only for strengthening the workforce, but also for maintaining the competencies necessary to provide health services [10].

In the total number of doctors, it can be seen that the number of doctors in the 55 years and above age group is growing faster than the number of the youngest doctors entering the system. This kind of human resources management, particularly doctors, will not improve the availability of doctors in the long term, rather it can drive the system into an even more unfavorable situation. This will certainly depend on the effect of a large number of other external factors (migration, strengthening of the private sector, etc.).

This study has identified areas where the future functioning and provision of services are particularly threatened, due to the high ratio of older staff. These areas included the following specialties: pneumophthisiology, neuropsychiatry, physical medicine, transfusiology, sports medicine, occupational medicine, general medicine, as well as plastic and reconstructive surgery.

As compared to other countries in the region and in Europe, the availability of medical doctors – specialists/residents (excluding specialists/residents specializing in surgery, gynecology and obstetrics, pediatrics,



U grafikonu su prikazani radno aktivni lekari, osim u Crnoj Gori (profesionalno aktivni) i Grčkoj (lekari koji imaju licencu iz prakse); Izvor: *OECD Health Statistics 2020; Eurostat Database*

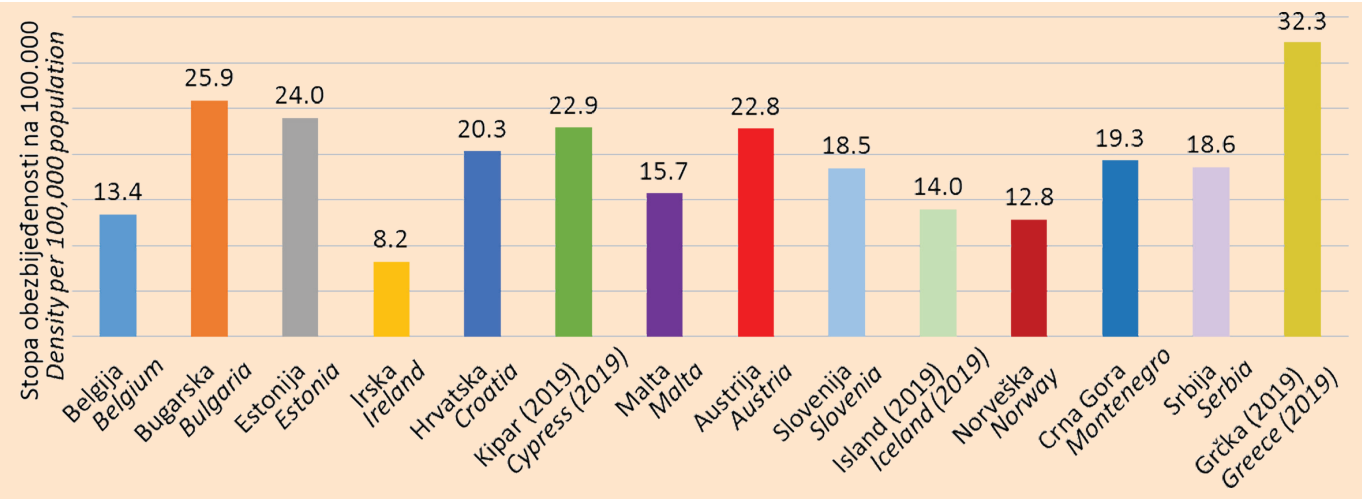
Slika 6. Obezbeđenost stanovništva doktorima medicine, specijalistima/specijalizantima pedijatrije na 100.000 stanovnika, u Crnoj Gori i u zemljama Evrope, u 2020. godini (ili poslednji dostupni podaci)

The graph shows working doctors, except in Montenegro (professionally active) and Greece (doctors who have a license to practice); Source: OECD Health Statistics 2020; Eurostat Database

Figure 6. Availability of medical doctors – specialists/residents specializing in pediatrics per 100,000 population, in Montenegro and in other European countries, in 2020 (or latest available data)

Budući da se, prema podacima SZO, udeo žena u ukupnoj radnoj snazi povećao u Evropskom regionu, važno je posebno analizirati podatke koji se odnose na polnu strukturu kadra, kako bi zdravstveni sistem prepoznao doprinos žena, kao i nejednakosti koje postoje u svetu [12] u kojem „muškarci vode, a žene pružaju usluge globalnog zdravlja" [13]. Trend feminizacije medicine u Crnoj Gori je od ranije prepoznat. Kao što je slučaj i u mnogim zemljama Evropskog regiona i zemljama u okruženju, zapaža se tendencija porasta udela žena među specijalističkim lekarskim kadrom, a

psychiatry, and general medicine) per 100,000 population, in Montenegro, was close to the availability of this personnel in Slovenia, and was better than in other small countries, such as Malta or Iceland [11]. However, the density of medical doctors – specialists/residents specializing in surgical branches per 100,000 population, in Montenegro, in 2020, was among the lowest in Europe, and was significantly below the standard applied in European Union countries [11]. The situation is better if the availability of medical doctors – specialists/residents specializing in pediatrics and the availability of medical doctors - specialists/residents specializing

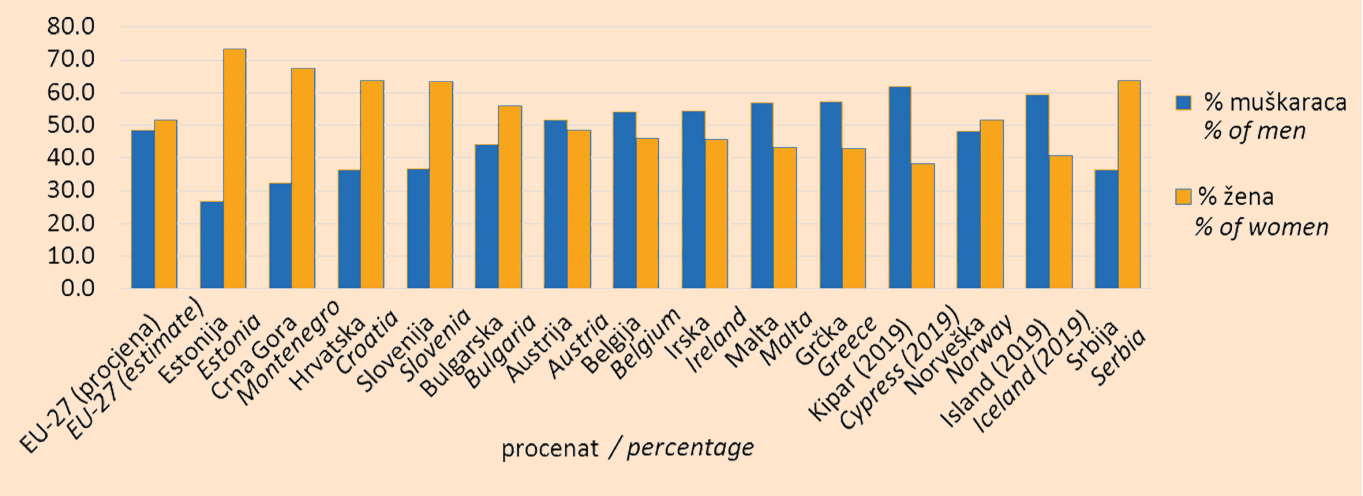


U grafikonu su prikazani radno aktivni lekari, osim u Crnoj Gori (profesionalno aktivni) i Grčkoj (lekari koji imaju licencu iz prakse); Izvor: *OECD Health Statistics 2020; Eurostat Database*

Slika 7. Obezbeđenost stanovništva doktorima medicine, specijalistima/specijalizantima ginekologije i akušerstva na 100.000 stanovnika, u Crnoj Gori i u zemljama Evrope, u 2020. godini (ili poslednji dostupni podaci)

The graph shows working doctors, except in Montenegro (professionally active) and Greece (doctors who have a license to practice); Source: OECD Health Statistics 2020; Eurostat Database

Figure 7. Availability of medical doctors – specialists/residents specializing in gynecology and obstetrics per 100,000 population, in Montenegro and in other European countries, in 2020 (or latest available data)



U grafikonu su prikazani radno aktivni lekari, osim u Crnoj Gori (profesionalno aktivni) i Grčkoj (lekari koji imaju licencu iz prakse); Izvor: *OECD Health Statistics 2020; Eurostat Database*

Slika 8. Odnos lekara prema polu, u 2020. godini (%), u Evropskoj uniji i regionu (procena/poslednji dostupni podaci)

The graph shows working doctors, except in Montenegro (professionally active) and Greece (doctors who have a license to practice); Source: OECD Health Statistics 2020; Eurostat Database

Figure 8. Ratio of doctors in relation to gender, in 2020 (%), in the European Union and in the region (estimate/latest available data)

to je posebno karakteristično za bivše jugoslovenske zemlje.

Glavno ograničenje naše studije je to što su obuhvaćeni samo podaci koji se odnose na javni sektor, budući da još uvek u Crnoj Gori nije razvijen registar kadrova, a zakonska regulative nije prepoznala nagli razvoj privatnog sektora u kojem je angažovan značajni deo specijalističkog kadra. Nadalje, iako se prepoznaje uticaj migracija na raspoloživost lekarskog kadra, usled nedostupnosti podataka, nije bilo moguće analizirati kretanje lekara sa ovog aspekta. Pitanje emigracije već duži vremenski period ostaje nerešeno, a gubljenjem kadrova, posebno specijalističkog kadra koji je visoko obrazovan, zemlja gubi velika sredstva i vreme koje je uloženo u izgradnju tih kadrova [14]. Ova studija nije ispitala kadrovsku obezbeđenost i dostupnost lekarima specijalistima po regionima u Crnoj Gori, već samo na nacionalnom nivou, budući da se Crna Gora ubraja u zemlje sa malim brojem stanovnika. Takva istraživanja u budućem periodu bi pružila detaljniji prikaz kadrovske obezbeđenosti lekarima specijalistima. Uporedivost podataka je jedno od ograničenja, jer neke zemlje prijavljuju licencirane zdravstvene radnike bez obzira na to gde su zaposleni ili ako su nezaposleni, a druge zemlje samo zdravstvene radnike koji aktivno rade u zdravstvenom sektoru.

ZAKLJUČAK

Prikazane statističke vremenske serije podataka o ljudskim resursima, kako ukupno za Crnu Goru, tako posebno za vanbolničku i bolničku zdravstvenu zaštitu, omogućavaju da se sagledaju stanje, struktura i dina-

in gynecology and obstetrics per 100,000 population, is compared between Montenegro and other European countries.

Since, according to WHO data, the ratio of women in the total labor force has increased in the European Region, it is important to analyze the data related to the gender structure of the staff separately, so that the health system may recognize the contribution of women, as well as the inequalities that exist in the world [12], where "men lead and women provide global health services" [13]. The trend of feminization of medicine in Montenegro has long been recognized. As is the case in many countries of the European Region and in the surrounding area, there is a tendency to increase the proportion of women among the specialist medical staff, and this is especially characteristic of former Yugoslav countries.

The main limitation of our study is that only data related to the public sector has been included in the analysis, since the human resources register has not yet been developed in Montenegro, and the laws and regulations have not as yet recognized the rapid development of the private sector, where a significant number of the specialist staff is employed. Furthermore, although the impact of migration on the availability of medical staff has been recognized, due to the unavailability of data, it was not possible to analyze the migration of doctors from this aspect. The issue of emigration has been unresolved for a long period of time, and by losing staff, especially highly trained specialist staff, the country loses considerable funds and time invested in educating this staff [14]. This study did not examine the availability and accessibility of specialist

mika njihovih promena u navedenom periodu. Podaci će u narednim godinama omogućiti uporedivost kadra raznih profila u Crnoj Gori sa drugim evropskim zemljama prema stopama opterećenosti. Navedene statističke serije podataka koje se odnose na lekare specijaliste, lekare bez specijalizacije i lekare na specijalizaciji, u vanbolničkoj i bolničkoj zdravstvenoj zaštiti, ukazuju na značajan manjak ljudskih resursa – lekara u Crnoj Gori, u odnosu na većinu zemalja Evropske unije ili Evropskog regiona, kao i na neadekvatnu starosnu strukturu, posebno za pojedine specijalnosti u kojima treba pažljivo planirati kadar, kako bi se poboljšala njihova obezbeđenost u budućem periodu.

Sukob interesa: Nije prijavljen.

medical doctors, by individual regions, in Montenegro, but only at the national level, since Montenegro is one of the countries with a small population. Such future research would provide a more detailed account of the availability of medical specialists. Comparability of data is one limitation, as some countries report licensed health workers regardless of where they are employed or if they are unemployed, and other countries only report health workers who are actively working in the health sector.

CONCLUSION

The presented statistical time series of data regarding human resources, both for Montenegro as a whole, and especially for outpatient and inpatient health care, allow us to see the state, structure and dynamics of their changes in the specified period. In the coming years, new data will enable comparability of human resources of various profiles in Montenegro with other European countries, according to workload rates. The aforementioned statistical series of data related to specialists, doctors without specialist training, and residents, in outpatient and hospital health care, indicate a significant shortage of human resources – doctors in Montenegro, as compared to most countries of the European Union or the European Region, as well as the inadequate age structure, especially for certain specialties, where personnel should be carefully planned, in order to improve their availability in the future.

Conflict of interest: None declared.

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OBUHVAT OBAVEZNOM VAKCINACIJOM NA TERITORIJI MAČVANSKOG OKRUGA U PERIODU IZMEĐU 2011. I 2021. GODINE

ORIGINALNI RAD

ORIGINAL ARTICLE

MANDATORY VACCINATION COVERAGE IN THE TERRITORY OF THE MAČVA DISTRICT IN THE PERIOD BETWEEN 2011 AND 2021

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SAŽETAK

Uvod: Vakcina je jedan od najstarijih i najkorisnijih pronalazaka u medicini. Ovo je jednostavan, bezbedan i efikasan način zaštite od zaraznih bolesti i dokazana, isplativa strategija javnog zdravlja, koja štiti i pojedinca i celu zajednicu. Sa druge strane, vakcina je postala žrtva svog uspeha, jer su mnoge bolesti koje se mogu sprečiti vakcinama postale toliko retke, da neki ljudi veruju kako su zauvek iskorenjene, pa ne shvataju korist od vakcinacije i opasnost ukoliko se ona ne sprovodi. Cilj rada je bio da se analizira obuhvat obaveznom vakcinacijom na teritoriji Mačvanskog okruga, u periodu od 2011. do 2021. godine.

Materijali i metode: U radu je korišćena retrospektivna analiza sekundarnih podataka godišnjih izveštaja domova zdravlja na teritoriji Mačvanskog okruga, za period od 2011. do 2021. godine. Za potrebe ovog istraživanja, obuhvat vakcinacijom je izračunat na osnovu broja novorođene dece u datoj godini. Podaci iz domova zdravlja dostavljaju se nadležnom Zavodu za javno zdravlje Šabac. Svaki izveštaj sadrži: broj lica koja podležu obaveznoj imunizaciji, broj lica koja su vakcinisana, kao i procenat vakcinisanih u odnosu na broj lica koja je trebalo vakcinisati. Za analizu trenda vakcinacije korišćen je metod korelacije i regresije, odnosno tumačena je vrednost Pirsonovog koeficijenta korelacije i određena je jednačina regresione prave.

Rezultati: Na teritoriji Mačvanskog okruga, posmatran je obuhvat dece obaveznom vakcinacijom u periodu od 2011. do 2021. godine. Uočen je negativni trend u obuhvatu vakcinacije za sve posmatrane vakcine, izuzev trenda koji se odnosi na vakcinaciju protiv *Haemophilus influenzae*.

Zaključak: Posmatrano za sve vakcine zajedno, obuhvat vakcinacijom tokom posmatranog perioda opada. Tokom 2021. godine, nijedna vakcina nije postigla obuhvat od 95%. Opadajući trend ukazuje na potrebu promovisanja vakcinacije, kao najbezbednije i najdelotvornije zaštite od zaraznih bolesti.

Ključne reči: vakcinacija, obuhvat vakcinacijom, trend, javno zdravlje

ABSTRACT

Introduction: The vaccine is one of medicine's oldest and most valuable inventions. It is a simple, safe, and effective way to protect against infectious diseases, a proven and cost-effective public health strategy that safeguards both individuals and the entire community. On the other hand, it has become a victim of its own success, as many vaccine-preventable diseases have become so rare that some people believe they have been eradicated forever, and do not understand the benefits of vaccination nor the risks of it not being conducted. This study aimed to analyze vaccination coverage throughout the Mačva District, in the period between 2011 and 2021.

Materials and methods: The study used a retrospective analysis of secondary data from annual reports submitted by community health centers, in the territory of the Mačva District, for the period between 2011 and 2021. For the purpose of this study, vaccination coverage was calculated based on the number of newborn babies in a given year. Data from community health centers are submitted to the Institute of Public Health Šabac, which is in charge of these issues for this district. Each report contains the number of individuals subject to mandatory immunization, the number of persons who have been vaccinated, as well as the percentage of vaccinated persons as compared to the number of persons who should have been vaccinated. The correlation and regression method was used to analyze the vaccination trend, i.e., the value of the Pearson correlation coefficient was interpreted and the equation of the regression line was calculated.

Results: In the Mačva District, mandatory vaccination coverage of children was observed in the period between 2011 and 2021. A negative trend was registered in vaccination coverage for all observed vaccines, except the trend related to vaccination for *Haemophilus influenzae*.

Conclusion: When all of the vaccines are observed together, vaccination coverage has been declining during the observed period. During 2021, not a single vaccine achieved 95% coverage. The declining trend indicates the need to promote vaccination as the safest and most effective protection against infectious diseases.

Keywords: vaccination, vaccination coverage, trend, public health

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Primljeno • *Received*: October 2, 2023; **Revidirano • *Revised*:** October 31, 2023; **Prihvaćeno • *Accepted*:** November 8, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-46880

UVOD

Vakcina je jedan od najstarijih pronalazaka u medicini, a sam proces vakcinacije predstavlja jedan od najkorisnijih izuma koje je medicina podarila čovečanstvu. Od njenog uvođenja, u 18. veku, pa do danas, brojne prednosti vakcinacije su dokumentovane i naučno dokazane. Vakcinacija predstavlja jednostavan, bezbedan i efikasan način zaštite od određenih bolesti, ona spašava više miliona života svake godine. To je dokazana, isplativa strategija javnog zdravlja koja štiti i pojedinca i celu zajednicu. Istovremeno, vakcinacija je postala žrtva svog uspeha, jer su mnoge bolesti koje se mogu sprečiti vakcinom postale toliko retke, da neki ljudi veruju kako su zauvek iskorenjene, pa ne shvataju koristi od vakcinacije i opasnosti, ukoliko se ona ne sprovodi. Sadašnje stope pokrivenosti vakcinacijom u Evropskom regionu Svetske Zdravstvene Organizacije (SZO) nisu dovoljne da se osigura imunitet i zaustavi širenje bolesti koje se mogu sprečiti vakcinama. Prethodnih godina, stope pokrivenosti vakcinacijom, posebno pojedinim vakcinama, opale su i u Srbiji.

Zakonska regulativa koja se odnosi na vakcinaciju i kalendar vakcinacije

U Srbiji, vakcinacija je regulisana Zakonom o zaštiti stanovništva od zaraznih bolesti („Službeni glasnik Republike Srbije", br. 15/2016, 68/2020 i 136/2020), Pravilnikom o imunizaciji i načinu zaštite lekovima („Službeni glasnik Republike Srbije", br. 88/2017, 11/2018, 14/2018, 45/2018, 48/2018, 58/2018, 104/2018, 6/2021, 52/2021 i 66/2022), Pravilnikom o Programu obavezne i preporučene imunizacije stanovništva protiv određenih zaraznih bolesti („Službeni glasnik Republike Srbije", br. 65/2020), Zakonom o lekovima i medicinskim sredstvima („Službeni glasnik Republike Srbije", br. 30/2010, 107/2012, 113/2017 – dr. zakon i 105/2017 – dr. zakon), Stručnim metodološkim uputstvom za sprovođenje imunizacije stanovništva protiv određenih zaraznih bolesti, Pravilnikom o prijavljivanju zaraznih bolesti i posebnih zdravstvenih pitanja („Službeni glasnik RS", br. 44/2017 i 58/2018) i Uputstvom za nadzor nad neželjenim događajem nakon imunizacije.

Na teritoriji Mačvanskog okruga, vakcinacija se obavlja u Domovima zdravlja u Loznici, Krupnju, Vladimircima, Bogatiću, Šapcu, Koceljevi, Ljuboviji i Malom Zvorniku.

Zarazne bolesti protiv kojih se sprovodi obavezna aktivna imunizacija lica određenog uzrasta su: tuberkuloza, difterija, tetanus, dečija paraliza, veliki kašalj (pertusis), male boginje, *rubella*, zauške, hepatitis B, oboljenja izazvana bakterijom *Haemophilus influenzae* tip b, oboljenja izazvana bakterijom *Streptococcus pneumoniae* (od januara 2018.).

INTRODUCTION

The vaccine is one of the oldest discoveries in medicine, and the vaccination process itself is one of the most useful inventions that medicine has given to mankind. Since its introduction, in the 18th century, until today, numerous benefits of vaccination have been documented and scientifically proven. Vaccination is a simple, safe and effective of protection against certain diseases, it saves millions of lives every year. It is a proven, cost-effective public health strategy that protects both the individual and the entire community. At the same time, vaccination has become a victim of its own success, as many vaccine-preventable diseases have become so rare that some people believe they have been eradicated forever, and do not understand the benefits of vaccination nor the dangers of not being vaccinated. Current vaccination coverage rates in the WHO European Region are insufficient to ensure immunity and prevent the spread of vaccine-preventable diseases. In previous years, the rates of vaccination coverage, especially with certain vaccines, have declined in Serbia as well.

Legislation related to vaccination and the vaccination schedule

In Serbia, vaccination is regulated by the Law on Protection of the Population from Infectious Diseases ("Official Gazette of the Republic of Serbia", No. 15/2016, 68/2020, and 136/2020), Rulebook on immunization and chemoprophylaxis ("Official Gazette of the Republic of Serbia", No. 88/2017, 11/2018, 14/2018, 45/2018, 48/2018, 58/2018, 104/2018, 6/2021, 52/2021, and 66/2022), Rulebook on the Program of mandatory and recommended immunization of the population against certain infectious diseases ("Official Gazette of the Republic of Serbia", No. 65/2020), Law on Medicine and Medical Devices ("Official Gazette of the Republic of Serbia", No. 30/2010, 107/2012, 113/2017 – other law and 105/2017 – other law), Expert methodological instructions for the immunization of the population against certain infectious disease, Rulebook on reporting communicable diseases and special health issues ("Official Gazette of the Republic of Serbia", No. 44/2017 and 58/2018), and the Manual on the monitoring of adverse events following immunization.

In the territory of the Mačva District, vaccination is carried out in community health centers in Loznica, Krupanj, Vladimirci, Bogatić, Šabac, Koceljeva, Ljubovija, and Mali Zvornik.

Infectious diseases against which mandatory active immunization of persons of a particular age is carried out are as follows: tuberculosis, diphtheria, tetanus, polio, whooping cough (pertussis), measles, rubella, mumps, hepatitis B, diseases caused by *Haemophilus*

Redosled davanja vakcina u odnosu na uzrast, sprovodi se prema kalendaru obavezne vakcinacije (Tabela 1)

Tabela 1. Redosled davanja vakcina u odnosu na uzrast

Vakcina / *Vaccine*	Na rođenju / *At birth*	Sa navršenih mesec dana života / *At 1 month old*	Sa navršenih 2 meseca života / *At 2 months old*	Sa navršenih 3,5 meseci života / *At 3.5 months old*	U 6. Mesecu života / *Between month 5 and month 6*	Sa navršenih 6 meseci života / *At 6 months old*	Sa navršenih 12 meseci života / *At 12 months old*	Sa navršenih 18 meseci života / *At 18 months old*	U 7. godini života (pred polazak u školu) / *Between year 6 and year 7 (before starting school)*	U 12. godini života (u 6. razredu) / *Between year 11 and year 12 (in 6th grade)*	U 14. godini života / *Between year 13 and year 14*
Vakcina protiv tuberkuloze / *Vaccine for tuberculosis*	*BCG*										
Vakcina protiv hepatitisa B u prvoj ili 12. godini života / *Vaccine for hepatitis B, at one or 12 years of age*	***Hep B 1st dose***	***Hep B 2nd dose***				***Hep B 3rd dose***				***Hep B 1st, 2nd, and 3rd dose (in unvaccinated children)***	
Vakcina protiv difterije, tetanusa i velikog kašlja / *Vaccine for diphtheria, tetanus, and whooping cough*			***DTaP 1st dose***	***DTaP 2nd dose***	***DTaP 3rd dose***			***DTaP 1st booster***			
Vakcina protiv dečije paralize / *Polio vaccine*			***IPV 1st dose***	***IPV 2nd dose***	***IPV 3rd dose***			***IPV 1st booster***	***bOPV (IPV) 2nd booster***		***bOPV (IPV) 3rd booster***
Vakcina protiv oboljenja izazvanih hemofilusom influence tip b / *Vaccine for diseases caused by Haemophilus influenzae type b*			***HiB 1st dose***	***HiB 2nd dose***	***HiB 3rd dose***			***HiB 1st booster***			
Vakcina protiv oboljenja izazvanih streptokokom pneumonije / *Vaccine for diseases caused by Streptococcus pneumoniae*			***PCV 1st dose***	***PCV 2nd dose***	***PCV 3rd dose***		***PCV booster***				
Vakcina protiv malih boginja, zaušaka I rubele / *Vaccine for measles, mumps, and rubella*							**MMR 1. doza / *MMR 1st dose***		**MMR revakcina / *MMR booster***		
Vakcina protiv difterije, tetanusa i velikog kašlja / *Vaccine for diphtheria, tetanus, and whooping cough*									**TdaP (DT) 2. revakcina / *TdaP (DT) 2nd booster***		
Vakcina protiv difterije, tetanusa i velikog kašlja / *Vaccine for diphtheria, tetanus, and whooping cough*											**TdaP (Td) 3. revakcina / *TdaP (Td) 3rd booster***

1) *imunoglobulin protiv hepatitisa B (HBIG) se daje novorođenčadi HbsAg pozitivnih majki (novorođenčad HbsAg pozitivnih majki prima i IV dozu vakcine, u skladu sa pravilnikom)

V - vakcinacija; **R** revakcinacija; BCG – vakcina protiv tuberkuloze; HB – vakcina protiv akutnog virusnog hepatitisa B; DTP – vakcina protiv difterije, tetanusa i velikog kašlja; OPV – vakcina protiv dečije paralize; MMR – vakcina protiv malih boginja, zaušaka i crvenke-rubele; HiB – vakcina protiv oboljenja izazvanih bakterijom *Haemophilus influenzae* tip b; DT – vakcina protiv difterije i tetanusa; dT – vakcina protiv difterije i tetanusa; TT – vakcina protiv tetanusa [3].

Sequence of administering vaccines, according to age, implemented in line with the mandatory vaccination schedule (Table 1)

1) *hepatitis B immunoglobulin (HBIG) is given to newborns of HbsAg-positive mothers (newborns of HbsAg-positive mothers also receive a 4th dose of the vaccine, in keeping with the regulations)

V = vaccination; B = booster; BCG – vaccine for tuberculosis; HB – vaccine for acute viral hepatitis B; DTP – vaccine for diphtheria, tetanus, and whooping cough; OPV – polio vaccine; MMR –vaccine for measles, mumps, and rubella; HiB – vaccine for diseases caused by Haemophilus influenzae type b; DT – vaccine for diphtheria and tetanus; dT – vaccine for diphtheria and tetanus; TT – vaccine for tetanus [3].

Vakcinacija se sprovodi vakcinama i/ili imunoglobulinima humanog porekla, imunobiološkim preparatima koji u sebi sadrže specifična antitela i monoklonskim antitelima.

Za sprovođenje obavezne vakcinacije nije potreban pismeni pristanak lica, zakonskog zastupnika deteta, odnosno lica lišenog poslovne sposobnosti. Obavezna vakcinacija se ne može odbiti, osim u slučaju postojanja privremene ili trajne kontraindikacije, koju utvrđuje doktor medicine odnosno stručni tim za kontraindikacije.

Organizaciju i sprovođenje vakcinacije sprovode nadležne zdravstvene ustanove i zdravstveni radnici, prema planu potreba.

Pregled lica koje treba vakcinisati kao i samu vakcinaciju, zatim vođenje propisane evidencije o izvršenim vakcinacijama, vrši doktor medicine. Za nadzor nad sprovođenjem vakcinacije je zadužen teritorijalno nadležni institut, odnosno Zavod za javno zdravlje.

Deca predškolskog i mlađeg školskog uzrasta, kao i adolescenti uzrasta 10 – 18 godina, vakcinišu se kontinuirano u okviru sistematskih i kontrolnih pregleda, u skladu sa Pravilnikom o imunizaciji [4].

Javnozdravstveni značaj vakcinacije

Vakcinacija je, prema Centru za kontrolu i prevenciju bolesti (engl. *Centers for disease control and prevention – CDC*), stavljena na listu kao prvo od deset velikih dostignuća javnog zdravlja u dvadesetom veku. Vakcinacija je jedna od najefektivnijih, najefikasnijih i najisplativijih mera javnozdravstvene intervencije. Vakcinacija sprečava između dva i tri miliona smrti godišnje. Vakcinisanje beba do druge godine je najbolji način zaštite od ozbiljnih dečjih bolesti, kao i smanjenja smrtnosti dece.

Vakcinacija je smanjila prekomernu upotrebu i otpornost na antibiotike. Njome se produžava životni vek stanovništva i smanjuje odsustvo sa posla zbog bolesti. Vakcinacija promoviše jednakost za sve, jer je dostupna svim slojevima društva.

CILJ RADA

Cilj rada je analiza obuhvata obaveznom vakcinacijom na teritoriji Mačvanskog okruga u jedanaestogodišnjem periodu, od 2011. do 2021. godine.

MATERIJALI I METODE

U radu je korišćena retrospektivna analiza sekundarnih podataka godišnjih izveštaja domova zdravlja na teritoriji Mačvanskog okruga, za period od 2011. do 2021. godine. Analizirani su podaci koji se odnose na obuhvat obaveznom vakcinacijom za posmatrani period.

Vaccination is carried out with vaccines and/or immunoglobulins of human origin, immunobiological preparations containing specific antibodies, and monoclonal antibodies.

The implementation of mandatory vaccination does not require the written consent of the person who is the legal representative of the child/person deprived of legal capacity. Mandatory vaccination cannot be refused, except in the case of a temporary or permanent contraindication, which is determined by a medical doctor or an expert team competent for making decisions on contraindications.

The organization and implementation of vaccination is carried out by the competent health institutions and health workers, according to the plan made on the basis of needs assessment.

The examination of the person that is to be vaccinated, the vaccination itself, as well the required record keeping of the administered vaccinations, is carried out by a medical doctor. The Institute of Public Health, i.e., its branch competent for the particular territory/region is in charge of supervising the implementation of vaccination.

Children of preschool and younger school age, as well as adolescents aged 10 – 18 years, are continuously vaccinated as part of regular wellness check-ups and follow-up examinations, in accordance with the Rulebook on immunization [4].

Public health benefits of vaccination

According to the Centers for Disease Control and Prevention (CDC), vaccination has been listed as the first among the ten major public health achievements of the twentieth century. Vaccination is one of the most effective, efficient, and cost-effective measures of public health intervention. Vaccination prevents between two and three million deaths per year. Vaccinating babies by the age of two is the best way to protect against serious childhood diseases, as well as to reduce child mortality.

Vaccination has reduced the overuse of antibiotics and the resistance to these drugs. It increases the life expectancy of the population and reduces absenteeism from work due to illness. Vaccination promotes equality for all, as it is accessible to all classes of society.

STUDY AIM

The aim of this study is to analyze coverage of mandatory vaccination throughout the Mačva District in the eleven-year period, from 2011 to 2021.

MATERIALS AND METHODS

Retrospective analysis of secondary data presented in the annual reports of the community health centers located in the Mačva District, for the period between

Na teritoriji Mačvanskog okruga nalazi se osam Domova zdravlja: Dom zdravlja Šabac, Dom zdravlja Loznica, Dom zdravlja Bogatić, Dom zdravlja Vladimirci, Dom zdravlja Koceljeva, Dom zdravlja Krupanj, Dom zdravlja Mali Zvornik, Dom zdravlja Ljubovija. Podaci iz domova zdravlja se dostavljaju nadležnom Zavodu za javno zdravlje Šabac. Svaki izveštaj treba da sadrži:

- broj lica koja podležu obaveznoj imunizaciji
- broj lica koja su vakcinisana
- procenat vakcinisanih u odnosu na broj lica koja je trebalo vakcinisati.

Za potrebe ovog istraživanja, obuhvat vakcinacijom izračunat je na osnovu broja novorođene dece u datoj godini.

Posmatran je obuhvat za sledeće vakcine: vakcina protiv tuberkuloze, vakcina protiv dečije paralize, vakcina protiv difterije tetanusa i pertusisa (Di-Te-Per), vakcina protiv *Haemophilus influenzae*, vakcina protiv hepatitisa B i MMR vakcina.

Statistička obrada podataka urađena je u programu *IBM SPSS Statistics version 23*. Podaci su prikazani tabelarno i grafički.

Za analizu trenda vakcinacije je korišćen metod korelacije i regresije, odnosno tumačena je vrednost Pirsonovog koeficijenta korelacije i određena je jednačina regresione prave. Za grafički prikaz ovih rezultata je korišćen dijagram rasturanja na kom je ucrtana regresiona prava.

Rezultati su smatrani statistički značajnim ukoliko je značajnost (p-vrednost) bila manja ili jednaka 0,05.

REZULTATI

Tuberkuloza

U posmatranom periodu, najveći obuhvat vakcinacijom protiv tuberkuloze na celokupnoj teritoriji Mačvanskog okruga je bio 2017. godine, i iznosio je 98,26%, a najmanji procenat vakcinisanih je bio 2015. godine, i iznosio je 94,82%, što pokazuje da u ovom periodu nije bilo velikih oscilacija (Grafikon 1).

U opštini Bogatić, najbolji odziv je bio 2018. godine, kada je zabeležen obuhvat vakcinacijom od 100%, dok je najmanje vakcinisanih bilo 2016. godine, kada je vakcinisano 92,90%.

Opština Vladimirci je imala najviše vakcinisanih 2013. i 2017. godine, kada je odziv bio 100%, a najmanji obuhvat je bio 2019. godine, i iznosio je 90,91% .

U opštini Koceljeva je, 2018. godine, obuhvat bio 100%, a najmanji obuhvat je bio 2021. godine, i iznosio je 84,00%.

Opština Krupanj nijedne godine nije imala potpuni obuhvat, najveći obuhvat beleži 2014. godine (99,09%) a najmanji obuhvat je bio 2020. godine, 91,53%.

2011 and 2021, were used in the study. Data related to mandatory vaccination coverage for the observed period were analyzed.

There are eight community health centers located in the Mačva District: Community Health Center Šabac, Community Health Center Loznica, Community Health Center Bogatić, Community Health Center Vladimirci, Community Health Center Koceljeva, Community Health Center Krupanj, Community Health Center Mali Zvornik, Community Health Center Ljubovija. Data from community health centers are submitted to the Institute of Public Health Šabac, which is in charge of these issues for this district. Each report needs to include the following:

- number of persons subject to mandatory immunization
- number of vaccinated persons
- percentage of vaccinated persons as compared to the number of persons who should have been vaccinated.

For the purpose of this study, vaccination coverage was calculated based on the number of newborns in a given year.

Coverage was observed for the following vaccines: vaccine for tuberculosis, polio vaccine, vaccine for diphtheria, tetanus, and pertussis (Di-Te-Per), vaccine for *Haemophilus influenzae*, Hepatitis B vaccine, and the MMR vaccine.

Statistical data processing was performed using the IBM SPSS Statistics version 23 software. The data are presented in tables and graphs.

The correlation and regression method was used to analyze the vaccination trend, i.e., the value of the Pearson correlation coefficient was interpreted and the equation of the regression line was calculated. For the graphic display of these results, a scatter diagram was used, wherein the regression line was drawn.

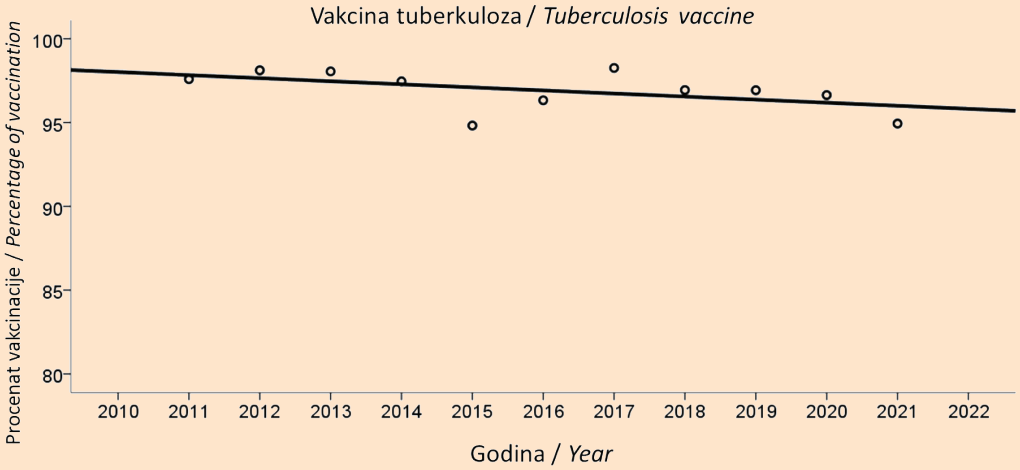
The results were considered statistically significant if the significance (p-value) was less than or equal to 0.05.

RESULTS

Tuberculosis

In the observed period, the highest vaccination coverage for tuberculosis throughout the Mačva District territory was achieved in 2017 and was 98.26%, while the lowest percentage of vaccination was in 2015, amounting to 94.82%, which shows that there were no great oscillations in this period (Graph 1).

In the Bogatić municipality, the best compliance was in 2018, when a 100% vaccination coverage was recorded, while the lowest vaccination coverage was in 2016, amounting to 92.90%.



Grafikon 1. Trend obuhvata vakcinacijom protiv tuberkuloze 2011 – 2021

Graph 1. Trend of vaccination coverage for tuberculosis in the period between 2011 and 2021

Opština Loznica je imala najveći obuhvat vakcinacijom 2015. godine i on je iznosio 98,97%, a najmanji obuhvat od 96,01% je bio 2018. godine.

Opština Ljubovija je imala obuhvat vakcinacijom od 100% u šest godina tokom posmatranog perioda, i to: 2011, 2012, 2013, 2017, 2019. i 2020. godine. Najmanji obuhvat je iznosio 87,21% i zabeležen je 2015. godine.

U opštini Mali Zvornik, kompletni obuhvat vakcinacijom je zabeležen 2012, 2014, 2016. i 2019. godine. Najmanji obuhvat je bio 2017. godine, i iznosio je 96,00%.

Opština Šabac je imala najbolji obuhvat vakcinacijom 2017. godine, koji je iznosio 100%, a najmanji procenat vakcinisanih je zabeležen 2020. godine i to od 96,64%.

Utvrdili smo da postoji osrednji negativni trend (r = - 0,513) ali da nije statistički značajan (p = 0,107), (Grafikon 1).

Jednačina: **procenat vakcinacije = - 0,183 * godina + 465,844**

Dečija paraliza

Najveći obuhvat vakcinacijom protiv dečije paralize, u periodu koji smo posmatrali za teritoriju Mačvanskog okruga, zabeležen je 2012. godine, i iznosio je 99,37%, dok je najmanji procenat vakcinisanih bio 2021. godine, i iznosio je 84,74%, što nije predstavljalo značajnu razliku u broju vakcinisanih (Grafikon 2).

Opština Bogatić je u prvom delu posmatranog perioda imala visok procenat vakcinisanih, 2011. godine i 2018. godine je obuhvat bio čak 100%, ali poslednje dve godine beleži se značajni pad broja vakcinisanih – 2020. godine je iznosio 48,62%, a 2021. godine je bilo 41,49 % vakcinisanih, što je ispod polovine predviđenog broja.

The Vladimirci municipality had the highest number of vaccinated persons in 2013 and 2017, when the compliance was 100%, and the lowest coverage was in 2019, when it was 90.91%.

In the Koceljeva municipality, in 2018, coverage was 100%, and the lowest coverage was in 2021, amounting to 84.00%.

The Krupanj municipality did not have full coverage in any year, the highest coverage was recorded in 2014 (99.09%) and the lowest coverage was in 2020, 91.53%.

The Loznica municipality had the highest vaccination coverage in 2015, when it was 98.97%, while the lowest coverage in this municipality was of 96.01%, recorded in 2018.

The Ljubovija municipality had 100% vaccination coverage in six years of the observed period, namely: 2011, 2012, 2013, 2017, 2019, and 2020. The lowest coverage was 87.21%, and it was recorded in 2015.

In the Mali Zvornik municipality, complete vaccination coverage was recorded in 2012, 2014, 2016 and 2019. The lowest coverage was in 2017, and it was 96.00%.

The Šabac municipality had the best vaccination coverage in 2017, when it was 100%, while the lowest percentage of vaccination was recorded in 2020, at 96.64%.

We found a strong negative trend (r = - 0.513), but it is not statistically significant (p = 0.107), (Graph 1).

Equation: **Vaccination percentage = - 0.183 * year + 465.844**

Polio

The highest vaccination coverage for polio, in the period we observed for the territory of the Mačva Dis-

U posmatranom periodu od jedanaest godina, opština Vladimirci šest godina beleži kompletni obuhvat vakcinacijom protiv dečije paralize, a najmanje vakcinisanih je bilo 2014. godine, ukupno 88,82% vakcinisanih.

Opština Koceljeva je imala 100% vakcinisanih prve i poslednje posmatrane godine, 2011. godine i 2021. godine, a najmanje vakcinisanih je zabeleženo 2017. godine, u obuhvatu od 94,12%.

Opština Krupanj je imala vrlo diskretna odstupanja i to: 2016. godine kada je obuhvat vakcinacijom bio 99,36%, 2018. godine kada je obuhvat bio 99,45% i 2021. godine kada je obuhvat bio 99,22%, a svih ostalih godina posmatranog perioda obuhvat vakcinacijom je bio 100%.

U opštini Loznica, u toku dve godine se beleži kompletni obuhvat vakcinacijom, 2011. i 2021. godine. Najmanji obuhvat je bio 2020. godine, kada je vakcinisano 96,06% od planiranog broja.

Opština Ljubovija je imala maksimalni obuhvat vakcinacijom tokom pet godina, 2011, 2012, 2019, 2020. i 2021. godine. Najmanji obuhvat je bio 2017. godine, i iznosio je 96,50% vakcinisanih.

Opština Mali Zvornik beleži kompletni obuhvat vakcinacijom tokom 2013, 2017, 2018, 2019. i 2021. godine. Pad u broju vakcinisanih je zabeležen 2016. godine, i iznosio je 84,92%.

Tokom posmatranog perioda, opština Šabac nijedne godine nije imala obuhvat vakcinacijom od 100%. Najbolji rezultat je zabeležen 2012. godine kada je bilo 99,54% vakcinisanih, a najmanje je bilo vakcinisanih 2021. godine i to 84,74%.

Utvrdili smo da postoji osrednji negativni trend (r = - 0,633), koji je statistički značajan (p = 0,035), (Grafikon 2).

Jednačina: **procenat vakcinacije = - 0,829 * godina + 1768,259**

trict, was recorded in 2012 and it amounted to 99.37%, while the lowest percentage of vaccination was in 2021 amounting to 84.74%, which was not a significant difference in the number of vaccinations (Graph 2).

During the first part of the observed period, the Bogatić municipality had a high percentage of vaccinations, in 2011 and 2018 the coverage was as high as 100%, but in the last two years there has been a significant decrease in the number of vaccinations – in 2020 it amounted to 48.62%, while in 2021, there were 41.49% of vaccinations, which is less than half of the planned vaccinations.

The Vladimirci municipality recorded complete vaccination coverage for polio in six out of the eleven years of the observation period, and the lowest vaccination percentage was in 2014, a total of 88.82%.

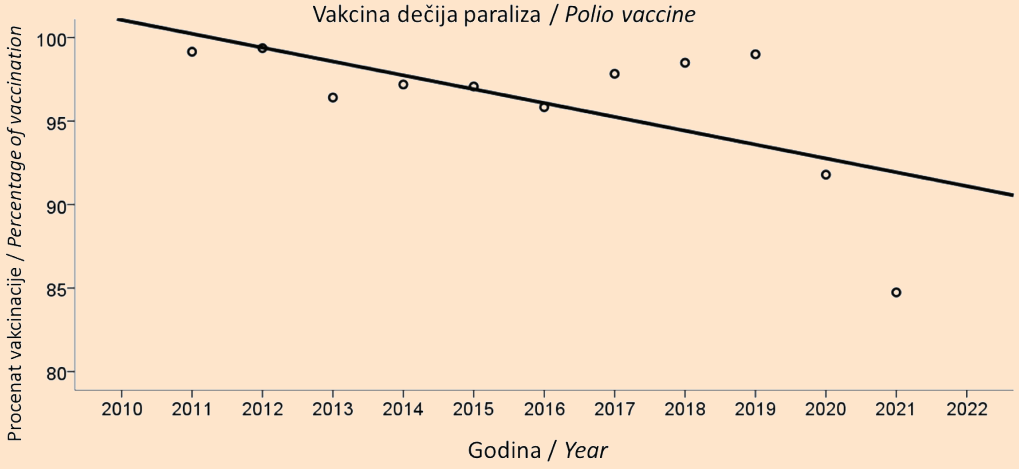
The Koceljeva municipality had a 100% coverage in the first and last of the observed years, 2011 and 2021, while the lowest number of vaccinations was recorded in 2017, at 94.12%.

The Krupanj municipality had very slight deviations: in 2016, when vaccination coverage was 99.36%, in 2018, when the coverage was 99.45%, and in 2021, when the coverage was 99.22%, while in all other years of the observed period, vaccination coverage was 100%.

In the Loznica municipality, complete vaccination coverage was recorded for two years, in 2011 and 2021. The lowest coverage was in 2020, when 96.06% of the planned number of vaccinations was carried out.

The Ljubovija municipality had maximum vaccination coverage in years: 2011, 2012, 2019, 2020, and 2021. The lowest coverage was in 2017 amounting to 96.50%.

The Mali Zvornik municipality recorded complete vaccination coverage in 2013, 2017, 2018, 2019, and



Grafikon 2. Trend obuhvata populacije vakcinom protiv dečije paralize, Mačvanski okrug po opštinama, 2011 – 2021.

Graph 2. Trend of vaccination coverage for polio, in the Mačva District by municipality, 2011 – 2021

Di-Te-Per

Obuhvat vakcinacijom protiv difterije tetanusa i pertusisa (Di-Te-Per), u posmatranom periodu, za Mačvanski okrug, bio je najbolji 2011. godine, i iznosio je 99,15%, a najmanji procenat je zabeležen 2021. godine, kada je iznosio 88,00%, što ne predstavlja značajno odstupanje (Grafikon 3).

Na teritoriji opštine Bogatić, zabeležen je obuhvat vakcinacijom od 100% tokom 2011, 2014. i 2018. godine, a najmanji obuhvat je zabeležen 2021. godine, i bio je 80,91% .

Opština Vladimirci imala je maksimalni obuhvat vakcinacijom tokom 2011, 2012, 2016, 2017, 2018. i 2019. godine. Godine 2014, bilo je najmanje vakcinisanih i to 89,36%.

Opština Koceljeva je u prvoj i poslednjoj godini posmatranog perioda imala obuhvat vakcinacijom od 100%, a najmanji procenat vakcinisanih je bio 2013. godine, i iznosio je 87,50%.

U opštini Krupanj, tokom posmatranog perioda od jedanaest godina, kompletni obuhvat vakcinacijom je zabeležen tokom šest godina, i to: 2011, 2012, 2014, 2015, 2017. i 2019. godine. Najmanji obuhvat vakcinacijom je zabeležen 2022. godine, i iznosio je 72,81%.

U opštini Loznica, 2011, 2013. i 2014. godine je zabeležen obuhvat vakcinacijom od 100%, dok je najmanji broj vakcinisanih zabeležen 2021. godine, kada je iznosio 94,13%.

U opštini Ljubovija je u šest godina, i to: 2011, 2012, 2013, 2019, 2020. i 2021. godine, zabeležen maksimalni obuhvat vakcinacijom, dok je 2017. godine zabeležena najniža vrednost od 96,50%.

U opštini Mali Zvornik je u pet godina zabeležen obuhvat vakcinacijom od 100%, i to: 2013, 2014, 2017, 2018. i 2019. godine. Najniži rezultat je zabeležen 2021. godine, i iznosio je 80,65%.

2021. A decrease in the number of vaccinations was recorded in 2016 and it amounted to 84.92%.

During the observed period, the Šabac municipality did not record a 100% vaccination coverage in any of the years. The best result was recorded in 2012, when the vaccination percentage was 99.54%, while coverage was the lowest in 2021 with a vaccination percentage of 84.74%.

We found a moderate negative trend (r = - 0.633), which is statistically significant (p = 0.035), (Graph 2).

Equation: **Vaccination percentage = - 0.829 * year + 1768.259**

Di-Te-Per

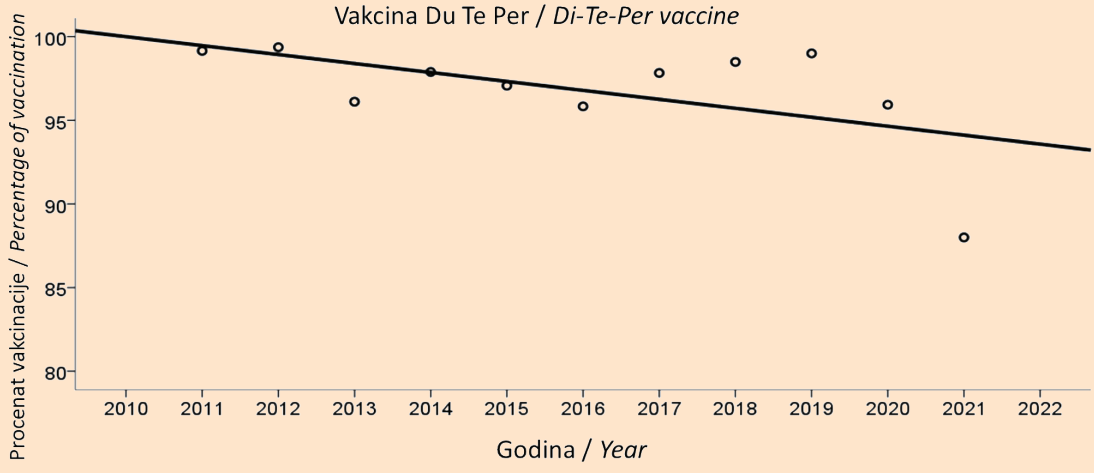
The vaccination coverage for diphtheria, tetanus and pertussis (Di-Te-Per), in the observed period, for the Mačva District, was the best in 2011 and it amounted to 99.15%, while the lowest percentage was recorded in 2021, when it was 88.00%, which does not represent a significant deviation (Graph 3).

In the Bogatić municipality, 100% vaccination coverage was recorded in 2011, 2014 and 2018, and the lowest coverage was recorded in 2021, amounting to 80.91%.

The Vladimirci municipality had maximum vaccination coverage in 2011, 2012, 2016, 2017, 2018 and 2019. In 2014, the coverage was the lowest, amounting to 89.36%.

In the first and the last year of the observed period, the Koceljeva municipality had a 100% vaccination coverage, while the lowest percentage of vaccination was registered in 2013, and it was 87.50%.

In the Krupanj municipality, during the eleven-year observation period, complete vaccination coverage was recorded for six years, namely: 2011, 2012, 2014,



Grafikon 3. Trend obuhvata populacije vakcinom protiv difterije, tetanusa i pertusisa, Mačvanski okrug po opštinama, 2011 – 2021.

Graph 3. Trend of vaccination coverage for diphtheria, tetanus and pertussis, in the Mačva District by municipality, 2011 – 2021

Opština Šabac nijedne godine nije zabeležila obuhvat vakcinacijom od 100%. Najveći obuhvat je bio 2012. godine, i iznosio je 99,37%, dok je najmanji obuhvat zabeležen 2021. godine, kada je bio 88,00% .

Utvrdili smo da postoji osrednji negativni trend (r = - 0,557), ali da nije statistički značajan (p = 0,075), (Grafikon 3).

Jednačina: **Procenat vakcinacije = - 0,535 * godina + 1175,898**

Haemophilus influenzae

U periodu od 2011. do 2021. godine, obuhvat vakcinacijom protiv *Haemophilus influenzae*, na teritoriji Mačvanskog okruga, bio je najbolji 2019. godine, kada je iznosio 99,34%. Najmanji odziv je zabeležen 2012. godine, i iznosio je 79,18%, dok u svim ostalim godinama rezultat nije silazio ispod 94,81% (Grafikon 4).

U opštini Bogatić, najmanji obuhvat vakcinacijom je zabeležen 2012. godine, iznosio je 78,22%, a najveći procenat vakcinisanih je zabeležen tokom tri godine, i to: 2011, 2019. i 2021. godine, i iznosio je 100%.

Opština Vladimirci je imala najbolji rezultat vakcinacije 2014. godine, kada je obuhvat bio 100%, a najmanje vakcinisanih je zabeleženo 2012. godine, i to 82,71%.

U opštini Koceljeva je tokom sedam godina, od ukupno jedanaest, obuhvat vakcinacijom bio 100%, u periodu između 2014 i 2019. godine, kao i 2021. godine. Najmanje vakcinisanih je bilo 2011. godine, i to 92,63%.

Opština Krupanj je 2011, 2017. i 2021. godine imala maksimalni broj vakcinisanih, a 2012. je obuhvat vakcinacijom bio najmanji, i iznosio je 81,03%.

U opštini Loznica, kompletni obuhvat je zabeležen 2013, 2014, 2015, 2017. i 2018. godine, a najmanje vakcinisanih je bilo 2012. godine, kada je zabeležen obuhvat od 68,36%.

Opština Ljubovija je, osim 2012. godine, kada je vakcinisano 77,53% planirane populacije, svih ostalih godina posmatranog perioda imala obuhvat vakcinacijom od 100%.

U opštini Mali Zvornik je 2011, 2013, 2016. i 2019. godine vakcinacija kompletno sprovedena, a najmanje vakcinisanih je bilo 2012. godine, i to 77,63%.

U opštini Šabac, 2016. godine je zabeležen najveći obuhvat vakcinacijom od 100%, a najmanji je bio 2012. godine, i to 74,70%.

Utvrdili smo da postoji umeren pozitivni trend (r = 0,281), ali da nije statistički značajan (p = 0,402), (Grafikon 4).

Jednačina: **Procenat vakcinacije = 0,479 * godina + 870,293**

2015, 2017, and 2019. The lowest vaccination coverage was recorded in 2022, and it was 72.81%.

In the Loznica municipality, a 100% vaccination coverage was recorded in 2011, 2013, and 2014, while the lowest vaccination percentage was 94.13%, recorded in 2021.

In the Ljubovija municipality, in years: 2011, 2012, 2013, 2019, 2020, and 2021, maximum vaccination coverage was recorded, while in 2017, the lowest value of 96.50% was recorded.

In the Mali Zvornik municipality, 100% vaccination coverage was recorded for years: 2013, 2014, 2017, 2018, and 2019. The lowest result was recorded in 2021, amounting to 80.65%.

The municipality of Šabac did not record a 100% vaccination coverage in any year. The highest coverage was in 2012, and it was 99.37%, while the lowest coverage was recorded in 2021, when it was 88.00%.

We found a moderate negative trend (r = - 0.557), but it is not statistically significant (p = 0.075), (Graph 3).

Equation: **Vaccination percentage = - 0.535 * year + 1175.898**

Haemophilus influenzae

In the period between 2011 and 2021, vaccination coverage for *Haemophilus influenzae* in the territory of the Mačva District, was the best in 2019, when it amounted to 99.34%. The lowest compliance was recorded in 2012, when it was 79.18%, while in all other years the result did not drop below 94.81% (Graph 4).

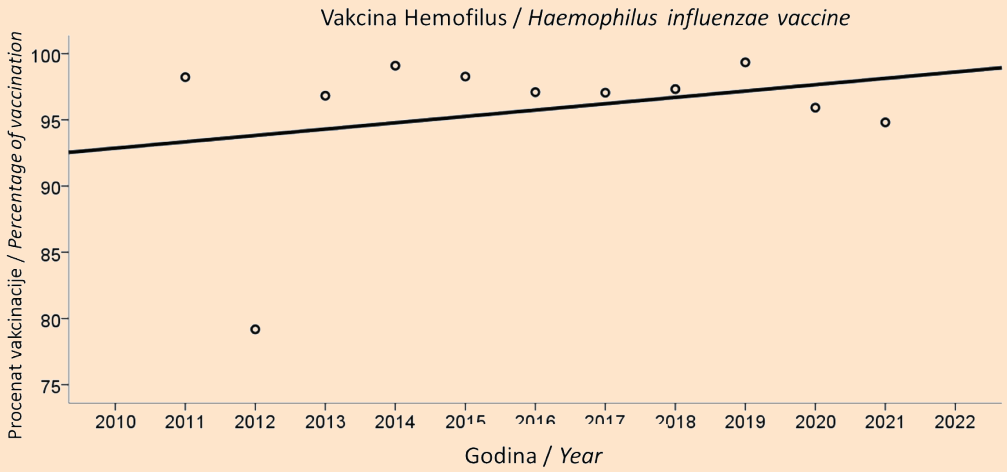
In the Bogatić municipality, the lowest vaccination coverage was recorded in 2012, at 78.22%, and the highest percentage of vaccination was recorded in years: 2011, 2019, and 2021, and it was 100%.

The Vladimirci municipality had the best vaccination result in 2014, when the coverage was 100%, while the lowest number of vaccinations was recorded in 2012, namely 82.71%.

In the Koceljeva municipality, during seven years, out of a total of eleven, vaccination coverage was 100%, i.e., in the period between 2014 and 2019, as well as in 2021. The smallest number of vaccinations was registered in 2011, amounting to 92.63%.

In 2011, 2017, and 2021, the Krupanj municipality had the maximum number of vaccinations, and in 2012, the vaccination coverage was the lowest, amounting to 81.03%.

In the Loznica municipality, complete coverage was recorded in 2013, 2014, 2015, 2017, and 2018, while the smallest number of vaccinations, amounting to a coverage of 68.36% was recorded in 2012.



Grafikon 4. Trend obuhvata populacije vakcinom protiv Haemophilus influenzae, Mačvanski okrug po opštinama, 2011 – 2021

Graph 4. Trend of vaccination coverage for Haemophilus influenzae, in the Mačva District by municipality, 2011 – 2021

Hepatitis B

Kada je vakcina protiv hepatitisa B u pitanju, tokom posmatranog perioda, na teritoriji Mačvanskog okruga, obuhvat vakcinacijom je bio najbolji 2013. godine, kada je iznosio 98,70% planirane populacije, dok je najmanji obuhvat vakcinacijom zabeležen 2021. godine, i bio je 93,83% (Grafikon 5).

U opštini Bogatić, tokom četiri godine od posmatranih jedanaest, zabeležen je stoprocentni obuhvat vakcinacijom i to: 2011, 2013, 2014, i 2015. godine, dok je najmanji obuhvat vakcinacijom zabeležen 2017. godine, kada je iznosio 81,85%.

U opštini Vladimirci, 2020. godine je obuhvat bio celih 100%, a najmanji broj vakcinisanih je bio 91,07%, tokom 2014. godine.

Opština Koceljeva je 2012, 2013, 2014, 2015, 2018, 2020. i 2021. godine imala obuhvat vakcinacijom od 100%, dok je 2016. godine zabeležen najmanji obuhvat vakcinacijom od 86,52%.

U opštini Krupanj, kompletna vakcinacija je obavljena 2012, 2013, 2017. i 2021. godine, a najmanji procenat vakcinisanih je zabeležen 2020. godine, i to 77,50%.

U opštini Loznica, najveći procenat vakcinisanih je bio 2014, 2016. i 2018. godine, i tada je ostvaren obuhvat od 100%, a najmanji procenat vakcinisanih je bio 2021. godine, kada je vakcinisano 95,40% planirane populacije.

U opštini Ljubovija je tokom posmatranog perioda, svih jedanaest godina obuhvat vakcinacijom bio 100%.

Opština Mali Zvornik je 2011, 2013, 2015. i 2017. imala obuhvat vakcinacijom od 100%, a najmanji obuhvat vakcinacijom imala je poslednje godine posmatranog perioda, 2021, kada je vakcinisano 80,77% od planiranog broja.

Except for 2012, when 77.53% of the planned population was vaccinated, the Ljubovija municipality had a 100% vaccination coverage in all other years of the observed period.

In the Mali Zvornik municipality, vaccination was carried out completely in 2011, 2013, 2016, and 2019, while in 2012, 77.63% of the planned population was vaccinated, which was the lowest percentage for this municipality in the observed period.

In the Šabac municipality, the highest vaccination coverage of 100% was recorded in 2016, and the lowest was in 2012, at 74.70%.

We found a moderate positive trend ($r = 0.281$), but it is not statistically significant ($p = 0.402$), (Graph 4).

Equation: **Vaccination percentage = 0.479 * year + 870.293**

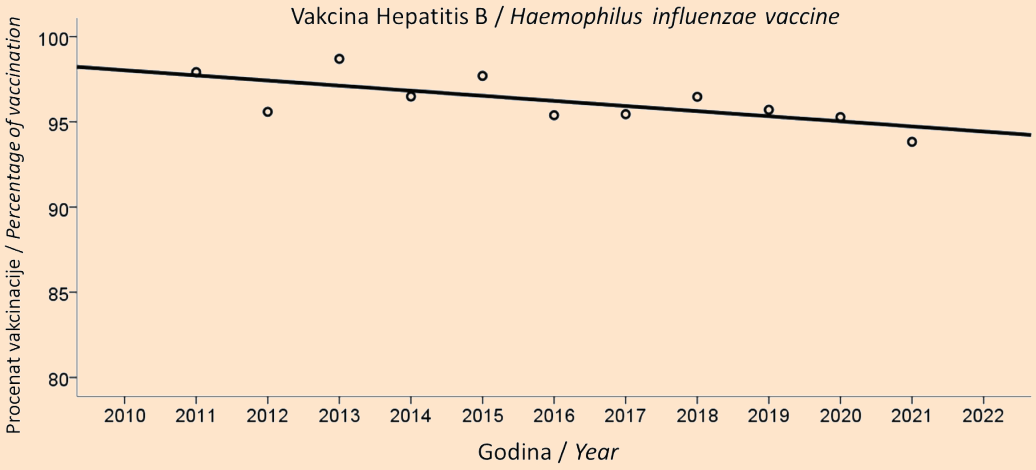
Hepatitis B

During the observed period, in the territory of the Mačva District, vaccination coverage for the hepatitis B vaccine was the best in 2013, when it was 98.70% of the planned population, while the lowest vaccination coverage was recorded in 2021, and it was 93.83% (Graph 5).

In the Bogatić municipality, in four years out of the observed eleven, a one hundred percent vaccination coverage was recorded, namely in: 2011, 2013, 2014, and 2015, while the lowest vaccination coverage was recorded in 2017, when it was 81.85%.

In the Vladimirci municipality, in 2020, coverage was 100%, while the lowest percentage of vaccination was 91.07%, in 2014.

The Koceljeva municipality had a 100% vaccination coverage in 2012, 2013, 2014, 2015, 2018, 2020, and 2021, while the lowest vaccination coverage was recorded in 2016, at 86.52%.



Grafikon 5. Trend obuhvata populacije vakcinom protiv Haemophilus influenzae, Mačvanski okrug po opštinama, 2011 – 2021

Graph 5. Trend of vaccination coverage for Haemophilus influenzae, in the Mačva District by municipality, 2011 – 2021

U opštini Šabac, kompletni obuhvat vakcinacijom zabeležen je 2016. godine, a 2021. je obuhvat iznosio 82,17%.

Utvrdili smo da postoji jak negativni trend (r = - 0,704), koji je statistički značajan (p = 0,016), (Grafikon 5).

Jednačina: **Procenat vakcinacije = - 0,300 * godina + 700,114**

MMR

U periodu koji je praćen, obuhvat vakcinacijom protiv MMR-a je bio najmanji 2021. godine, i iznosio je 87,50%, a najveći obuhvat zabeležen je 2011. godine, kada je vakcinisano 99,34% planirane populacije (Grafikon 6) .

U opštini Bogatić, najbolji rezultat vakcinacije je bio 2013, 2020, i 2021. godine, kada je obuhvat vakcinacijom iznosio 100%, dok je najmanji obuhvat bio 2015. godine, i iznosio je 77,06%.

U opštini Vladimirci, najbolji obuhvat vakcinacijom je bio 2011. godine, kada je vakcinisano 99,17% planirane populacije, a najmanji obuhvat je bio 2021. godine, kada je vakcinisano njih 70,00%.

U opštini Koceljeva, tokom posmatranog perioda od jedanaest godina, u toku devet godina je obuhvat vakcinacijom bio kompletan. To su godine: 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2019. i 2021. Godine 2018. je vakcinisano 90,59%, a 2020. godine 98,30% od planirane populacije.

U opštini Krupanj, 2011, 2012. i 2018. godine je obuhvat vakcinacijom bio najveći, odnosno 100%, a 2016. je bio najmanji, i iznosio je 85,61%.

Opština Loznica je imala stopostotni obuhvat vakcinacijom tokom pet godina posmatranog perioda, i to su godine: 2011, 2014, 2016, 2018. i 2020. Najmanji

In the Krupanj municipality, complete vaccination was carried out in 2012, 2013, 2017 and 2021, and the lowest percentage of vaccination was recorded in 2020, namely 77.50%.

In the Loznica municipality, the highest percentage of vaccination was recorded in 2014, 2016, and 2018, when 100% coverage was achieved, and the lowest percentage of vaccination was recorded in 2021, when 95.40% of the planned population was vaccinated.

In the Ljubovija municipality, during the observed period, vaccination coverage was 100% for all eleven years.

The Mali Zvornik municipality had a 100% vaccination coverage in 2011, 2013, 2015, and 2017, and the lowest vaccination coverage was recorded in the last year of the observed period, 2021, when 80.77% of the planned population were vaccinated.

In the Šabac municipality, complete vaccination coverage was recorded in 2016, while in 2021, the coverage was 82.17%.

We found a strong negative trend (r = - 0.704), which is statistically significant (p = 0.016), (Graph 5).

Equation: **Vaccination percentage = - 0.300 * year + 700.114**

MMR

In the observed period, MMR vaccination coverage was the lowest in 2021, amounting to 87.50%, while the highest coverage was recorded in 2011, when 99.34% of the planned population was vaccinated (Graph 6).

In the Bogatić municipality, the best vaccination result was achieved in 2013, 2020, and 2021, when vaccination coverage was 100%, while the lowest coverage was in 2015, and it was 77.06%.

obuhvat je zabeležen 2019. godine, kada je vakcinisano 94,41% planirane populacije.

U opštini Ljubovija, vakcinacija je obavljena kompletno 2015, 2019, 2020. i 2021. godine, a najmanje vakcinisanih je bilo 2014. godine, kada je obuhvat vakcinacijom bio 94,83%.

Opština Mali Zvornik je imala obuhvat vakcinacijom od 100% tokom četiri godine, i to: 2011, 2012, 2013. i 2016. godine, a najmanji obuhvat je zabeležen 2021. godine, i iznosio je 81,52%.

U Šabačkoj opštini, najviše vakcinisanih je bilo 2011. godine, i to 99,69% od planirane populacije, a najmanje vakcinisanih je bilo 2021. godine, i to 67,19%.

Utvrdili smo da postoji osrednji negativni trend (r = - 0,598), ali da nije statistički značajan (p = 0,052, (Grafikon 6).

Jednačina: **Procenat vakcinacije = - 0,593 * godina + 1289,995**

DISKUSIJA

U toku posmatranog perioda, od 2011. do 2021. godine, na teritoriji Mačvanskog okruga je zabeležen negativni trend u obuhvatu vakcinacije za sve posmatrane vakcine, izuzev trenda koji se odnosi na vakcinaciju protiv *Haemophilus influenzae* [8–17].

Analizom trenda vakcinacije protiv tuberkuloze (BCG), utvrđeno je postojanje negativnog trenda, ali ne i statistički značajne promene trenda vakcinacije od 2011. do 2021. godine. Za vakcinaciju protiv dečije paralize utvrđeno je da je postojao osrednji negativni trend, koji je bio statistički značajan. Vakcinacija protiv difterije, tetanusa i pertusisa (Di-Te-Per), imala je osrednji negativni trend, ali on nije bio statistički značajan. Analizirajući trendove vakcinacije protiv *Haemophilus influenzae*, utvrđeno je da je ovaj obuhvat imao pozitivni trend, ali on nije bio statistički značajan. Vakcinacija protiv hepatitisa B je zabeležila negativni trend, koji je bio statistički značajan. Kada se sagledaju rezultati vakcinacije protiv malih boginja, zauški i crvenke (MMR), i ovde je, u posmatranom periodu, bio prisutan osrednji negativni trend ali on nije bio statistički značajan.

Kada uporedimo sprovođenje planirane vakcinacije u Mačvanskom okrugu u odnosu na sprovođenje vakcinacije na teritoriji Republike Srbije, dobijamo sledeće rezultate:

Obuhvat vakcinacijom protiv tuberkuloze u Mačvanskom okrugu, tokom svih posmatranih godina, bio je manji u odnosu na republički prosek [8–17].

U toku 2021. godine, u Republici Srbiji, imunizacija novorođenčadi protiv tuberkuloze je sprovedena BCG vakcinom. Obuhvat ovom vakcinacijom je bio 98,2%, pri čemu je jedino u Borskom okrugu obuhvat bio ispod 95%, dok je u svim ostalim okruzima bio iznad te vrednosti.

In the Vladimirci municipality, the best vaccination coverage was in 2011, when 99.17% of the planned population was vaccinated, and the lowest coverage was in 2021, when 70.00% of them were vaccinated.

In the Koceljeva municipality, during the observed eleven-year period, vaccination coverage was complete in years: 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2019 and 2021. In 2018, 90.59% of the planned population was vaccinated, and in 2020, the coverage was 98.30%.

In the Krupanj municipality, in 2011, 2012 and 2018, vaccination coverage was the highest, i.e., 100%, and in 2016, it was the lowest, at 85.61%.

The Loznica municipality had a 100% vaccination coverage during the five years of the observed period, namely the years: 2011, 2014, 2016, 2018 and 2020. The lowest coverage was recorded in 2019, when 94.41% of the planned population was vaccinated.

In the Ljubovija municipality, vaccination was carried out completely in 2015, 2019, 2020, and 2021, while the lowest percentage of vaccination was in 2014, amounting to 94.83%.

The Mali Zvornik municipality had a 100% vaccination coverage in years: 2011, 2012, 2013, and 2016, while the lowest coverage was recorded in 2021, amounting to 81.52%.

In the Šabac municipality, the highest percentage of vaccination was achieved in 2011, namely 99.69% of the planned population, while the lowest coverage was in 2021, namely 67.19%.

We found a moderate negative trend (r = - 0.598), but it is not statistically significant (p = 0.052), (Graph 6).

Equation: **Vaccination percentage = - 0.593 * year + 1289.995**

DISCUSSION

During the observed period, from 2011 to 2021, a negative trend was recorded in the coverage of vaccination for all of the observed vaccines, except for the trend related to vaccination for *Haemophilus influenzae* [8-17].

Analysis of tuberculosis vaccination (BCG) showed a moderate negative trend, but no statistically significant change in the trend of vaccination, from 2011 to 2021. For polio vaccination, a moderate negative trend was found, which was statistically significant. Vaccination against diphtheria, tetanus and pertussis (Di-Te-Per) had a moderate negative trend, but it was not statistically significant. Analyzing vaccination trends for *Haemophilus influenzae*, it was determined that the coverage had a positive trend, but it was not statistically significant. Vaccination for hepatitis B showed a strong negative trend, which was statistically signifi-

Vrednost obuhvata koji je postignut u Centralnoj Srbiji iznosio je 98%, a u Vojvodini 98,9% [5].

Obuhvat vakcinacijom protiv dečije paralize, sve do 2020. godine, bio je iznad republičkog proseka, nakon toga beleži se pad sa 99% na 91,79%, a još manji obuhvat je zabeležen 2021. godine, i iznosio je 84,74%. Godine 2021. je u Srbiji registrovan obuhvat vakcinacijom protiv dečije paralize od 90,8%, što je ispod ciljne vrednosti (95%) [8–17]. U slučaju obuhvata vakcinacijom kombinovanom petovalentnom vakcinom, posmatrajući rezultate po okruzima, u toku 2021. godine, samo je u oblasti četiri okruga (Kolubarski, Nišavski, Pirotski i Jablanički) dostignut ciljni obuhvat od 95% vakcinisane dece u odnosu na planirani broj [5].

Vakcinacija Di Te Per vakcinom je imala veći obuhvat od proseka u Republici Srbiji, ali je u poslednjoj godini posmatranog perioda taj obuhvat pao na 88% [8–17]. Vakcinacija planirane populacije kombinovanom petovalentnom vakcinom je, 2021. godine, sprovedena u Republici Srbiji sa obuhvatom od 90,8% (procenjeni 91,5%).

Obuhvat vakcinacijom petovalentnom vakcinom, koja je obavljena u centralnom delu Srbije, bio je 90,6% planirane dece, dok je procenjeni obuhvat, koji je baziran na broju živorođene dece u 2020. godini, iznosio 91,3%.

U Vojvodini je vakcinacija planirane populacije kombinovanom petovalentnom vakcinom sprovedena u 2021. godini imala obuhvat od 91,4% planirane dece [8]. Procenjeni obuhvat, prema broju živorođene dece, u Vojvodini, u 2020. godini, iznosio je 92% [9].

Posmatrano po okruzima, obuhvat vakcinacijom kombinovanom petovalentnom vakcinom u toku 2021. godine pokazuje da je on dostigao vrednost od 95% i više u samo četiri okruga (Pirotski, Kolubarski, Jablanički i Nišavski), dok je obuhvat manji od 90% registrovan u devet okruga (Raški, Zaječarski, Pčinjski, Braničevski, Rasinski, Šumadijski, Grad Beograd, Zapadnobački i Južnobački). Na teritoriji Raškog okruga je registrovan najniži obuhvat, koji je iznosio 81,3% [5].

Obuhvat vakcinacijom protiv *Haemophilus influenzae* na teritoriji Mačvanskog okruga, svake godine, osim 2012, bio je iznad proseka u Republici Srbiji. Analiza obuhvata vakcinacijom 2021. godine je obuhvaćena analizom petovalentne kombinovane vakcine [8 –17].

Vakcinacija protiv hepatitisa B, na teritoriji Mačvanskog okruga, ako izuzmemo 2012. godinu, imala je veći obuhvat od republičkog proseka. Imunizacija dece u prvoj godini života, koja se sprovodi protiv hepatitisa B, u 2021. godini je sprovedena sa obuhvatom od 89,1%, posmatrano na nacionalnom nivou, dok je procenjeni obuhvat iznosio 89,7% [8–17]. Obuhvat koji se odnosi na Centralnu Srbiju je bio 88,5%, dok je obuhvat u Vojvodini bio 90,6%. Kada se analizira obuhvat vakcinaci-

cant. The results of vaccination for measles mumps and rubella (MMR), in the observed period, also show that there was a moderate negative trend, but that it was not statistically significant.

When we compare the implementation of planned vaccination in the Mačva District in relation to the implementation of vaccination in the territory of the Republic of Serbia, we get the following results:

The vaccination coverage for tuberculosis in the Mačva District, during all the observed years, was lower, as compared to the national average [8–17].

During 2021, in the Republic of Serbia, the immunization of newborns against tuberculosis was carried out with the BCG vaccine. The coverage of this vaccination was 98.2%, with only the coverage in the Bor District being below 95%, while in all the other districts, it was above that percentage.

The coverage value achieved in Central Serbia was 98%, and in Vojvodina it was 98.9% [5].

Until 2020, polio vaccination coverage was above the national average, after which year it dropped from 99% to 91.79%, and an even lower coverage was recorded in 2021, amounting to 84.74%. In 2021, the vaccination coverage for polio was registered in Serbia at 90.8%, which is below the target value (95%) [8–17]. As for vaccination coverage with the combined pentavalent vaccine, looking at the results by district, in the course of 2021, only in four districts (Kolubara District, Nišava District, Pirot District, and Jablanica District) was the target coverage of 95% of vaccinated children, out of the planned number, achieved [5].

Vaccination with the Di-Te-Per vaccine had a higher coverage than the average recorded for the Republic of Serbia, but in the last year of the observed period, that coverage dropped to 88% [8–17]. Vaccination of the planned population with the combined pentavalent vaccine was carried out in the Republic of Serbia, in 2021, with a coverage of 90.8% (estimated 91.5%).

Vaccination coverage with the pentavalent vaccine, which was carried out in the central part of Serbia, was 90.6% of the planned children, while the estimated coverage, based on the number of live births in 2020, was 91.3%.

In Vojvodina, the vaccination of the planned population with the combined pentavalent vaccine, carried out in 2021, covered 91.4% of the planned children [8]. The estimated coverage, according to the number of live births, in Vojvodina, in 2020, was 92% [9].

Observed by districts, the vaccination coverage with the combined pentavalent vaccine in 2021 was 95% and above in only four districts (Pirot District, Kolubara District, Jablanica District, and Nišava District), while coverage of less than 90% was registered in nine

jom protiv hepatitis B, gledano po okruzima, obuhvat od 95% nije dostignut ni u jednom okrugu, a dvanaest okruga imalo je obuhvat niži od 90%. Zaječarski (77,9%) i Raški okrug (79,3%) su imali najniže obuhvate ovom vakcinacijom [5].

Na teritoriji Mačvanskog okruga, vakcinacija MMR vakcinom je pokazala smanjivanje obuhvata tokom poslednjih godina posmatranog perioda. Takođe, i na republičkom nivou se obuhvat konstantno smanjivao [8–17]. Vakcinacija protiv malih boginja, zaušaka i rubele, kombinovanom MMR vakcinom, na teritoriji Republike Srbije, u 2021. godini, sprovedena je sa obuhvatom od 74,8% (u 2020. godini je obuhvat bio 78,1%), odnosno sa procenjenim obuhvatom od 75,2%. Obuhvat vakcinacijom u Centralnoj Srbiji je iznosio 75,8%, dok je u Vojvodini bio još niži, i to 72,1% planirane dece. Kada obuhvat MMR vakcinacijom posmatramo po okruzima, ni u jednom okrugu nije postignut obuhvat od 95%, a obuhvat od 90% postignut je u samo tri okruga od ukupno dvadeset pet, i to u: Borskom okrugu u Centralnoj Srbiji, te Severnobanatskom i Severnobačkom okrugu u Vojvodini. Obuhvat niži od 80% je registrovan na teritoriji devet okruga, a najniži je bio u Južnobačkom okrugu (46,8%), Rasinskom okrugu (65,7%) i Raškom okrugu (66,4%) [5].

Uporedili smo obuhvate vakcinacijom za Mađarsku, Rumuniju, Bugarsku, kao i za dve ekonomski razvijene zemlje (Italija i Francuska), za period od 2009. do 2019. godine, sa obuhvatima na teritoriji Republike Srbije u ovom periodu, u cilju poređenja rezultata imunizacije u Srbiji sa drugim zemljama [6]. Podaci o obuhvatu vakcinama u regionu za sve zemlje u navedenoj publikaciji još uvek nisu dostupni za 2020. godinu, da bi bilo moguće poređenje, pa se isto odnosi na podatke za 2019. godinu. Prikazani obuhvat vakcinom protiv tuberkuloze pokazuje da Italija ne sprovodi rutinski imunizaciju, kao ni Francuska, od 2011. godine. U odnosu na prikazane zemlje, Srbija ima visok obuhvat novorođenčadi BCG vakcinom, koji je iznad proseka za Evropski region. Kretanje obuhvata OPV/IPV3 i DTP/DTaP3 u Srbiji je pokazivalo tendenciju kontinuiranog održavanja do 2012. godine, kada su zabeležene nešto niže vrednosti u posmatranom periodu, koje su varirale i tokom 2014. i 2015. godine, a potom su se održavale iznad prosečnih vrednosti za Evropski region. Dok je u Italiji zabeležen silazni trend, koji je bio oko proseka za Evropski region, Rumunija je u posmatranom periodu zabeležila najnižu vrednost od 88% za OPV/IPV3. U obuhvatu MMR vakcinom, Mađarska je prikazala kontinuirano izuzetno visok obuhvat, dok su vrednosti obuhvata u 2019. godini, u drugim zemljama, bile ispod evropskog proseka (95%), a najniži u Rumuniji i Francuskoj (90%). Srbija je registrovala obuhvat od 88%.

districts (Raška District, Zaječar District, Pčinja District, Braničevo District, Rasina District, Šumadija District, the City of Belgrade, West Bačka District, and South Bačka District). The lowest coverage was registered in the territory of the Raška District, which was 81.3% [5].

Vaccination coverage for *Haemophilus influenzae* in the territory of the Mačva District, every year, except for 2012, was above the average registered for the Republic of Serbia. The analysis of vaccination coverage in 2021 included an analysis of the pentavalent combined vaccine [8–17].

Vaccination for hepatitis B, in the territory of the Mačva district, if we exclude the year 2012, had a higher coverage than the national average. Immunization of children during the first year, which is carried out against hepatitis B, was implemented in 2021, with a coverage of 89.1%, observed at the national level, while the estimated coverage was 89.7% [8–17]. Coverage related to Central Serbia was 88.5%, while coverage in Vojvodina was 90.6%. When analyzing hepatitis B vaccination coverage by district, 95% coverage was not reached in any district, and twelve districts had a coverage lower than 90%. The Zaječar District (77.9%) and Raška district (79.3%) had the lowest coverage for this vaccination [5].

In the territory of the Mačva District, vaccination with the MMR vaccine showed a decrease in coverage during the last years of the observed period. Also, at the national level, coverage constantly decreased in the observed period [8–17]. Vaccination for measles, mumps and rubella with the combined MMR vaccine, in the territory of the Republic of Serbia, in 2021, was carried out with a coverage of 74.8% (in 2020, the coverage was 78.1%), i.e., with an estimated coverage of 75.2%. Vaccination coverage in Central Serbia was 75.8%, while in Vojvodina it was even lower, namely 72.1% of the planned children. When MMR vaccination coverage is observed by district, no district achieved 95% coverage, and 90% coverage was achieved in only three districts out of a total of twenty-five, namely: Bor in central Serbia, and North Banat District and North Bačka District in Vojvodina. Coverage lower than 80% was registered in the territory of nine districts, and the lowest was in the South Bačka District (46.8%), Rasina District (65.7%), and Raška District (66.4%) [5].

We compared vaccination coverage for Hungary, Romania, Bulgaria, as well as for two economically developed countries (Italy and France), for the period between 2009 and 2019, with the coverage in the territory of the Republic of Serbia in this period, in order to compare the results of immunization in Serbia with other countries [6]. Data on vaccine coverage in the region, for all countries in the aforementioned publication, are

U Republici Srbiji, imunizacija protiv hepatitisa B je otpočela sredinom 2005. godine, uz poteškoće. Izuzetno visok dostignti i održavani obuhvat beleže Mađarska i Italija. Registrovani obuhvat u Republici Srbiji od 91%, u 2019. godini, je bio u okviru prosečnih vrednosti za Evropski region. Imunizacija protiv oboljenja izazvanih bakterijom *Haemophilus influenzae* tip b je u Republici Srbiji otpočela krajem 2006. godine, uz poteškoće, i u 2019. godini je zabeležen obuhvat od 95%. Visoki obuhvat su zabeležile skoro sve zemlje, sa vrednostima iznad proseka za Evropski region (79%) [8–17].

ZAKLJUČAK

- Na teritoriji Mačvanskog okruga, posmatran je obuhvat dece obaveznom vakcinacijom u periodu od 2011. do 2021. godine.
- Za sve vakcine je zabeležen negativni trend u obuhvatu dece vakcinacijom tokom godina.
- Jedina vakcina čiji se obuhvat povećavao je vakcina protiv *Haemophilus influenzae*.
- Posmatrano za sve vakcine zajedno, obuhvat vakcinacijom tokom posmatranog perioda opada.
- Tokom 2021. godine, nijedna vakcina nije postigla obuhvat od 95%.
- Opadajući trend ukazuje na potrebu promovisanja vakcinacije kao najbezbednije i najdelotvornije zaštite od zaraznih bolesti.
- Potreban je aktivniji zdravstveno-vaspitni rad u lokalnoj zajednici, u savetovalištima prilikom planiranja porodice, praćen medijskom podrškom, u cilju podizanja svesti opšte populacije o značaju vakcinacije.

Sukob interesa: Nije prijavljen.

not as yet available for 2020, so as to make comparison possible, which is why comparison was made regarding data for 2019. The presented tuberculosis vaccine coverage shows that Italy does not routinely immunize, and neither does France, as of 2011. As compared to the presented countries, Serbia has a high coverage of newborns with the BCG vaccine, which is above the average for the European Region. The trend for OPV/IPV3 and DTP/DTaP3 in Serbia showed a tendency of having continuous values, until 2012, when slightly lower values were recorded in the observed period. They then varied during 2014 and 2015, and subsequently remained above the average values registered in the European Region. While a downward trend was recorded in Italy, which was around the average for the European Region, Romania recorded the lowest value of 88% for OPV/IPV3, in the observed period. Hungary showed a continuous, very high coverage of MMR vaccination, while coverage values for 2019 in other countries were below the European average (95%), with the lowest ones registered in Romania and France (90%). Serbia registered a coverage of 88%.

In the Republic of Serbia, immunization against hepatitis B started in mid-2005, with certain difficulties. Hungary and Italy recorded an exceptionally high coverage, which was maintained. The registered coverage in the Republic of Serbia of 91%, in 2019, was within the average values for the European Region. Immunization against diseases caused by *Haemophilus influenzae* type b began in the Republic of Serbia at the end of 2006, with certain difficulties, and in 2019, a 95% coverage was recorded. High coverage was recorded by almost all of the observed countries, with values that were above the average for the European Region (79%) [8–17].

CONCLUSION

- In the territory of the Mačva district, coverage of children with mandatory vaccination was observed in the period between 2011 and 2021.
- For all vaccines, a negative trend was recorded in the vaccination coverage of children over the years.
- The only vaccine whose coverage increased was the vaccine against *Haemophilus influenzae*.
- When all the vaccines are observed together, it can be seen that vaccination coverage has declined during the observed period.
- In 2021, no vaccine achieved a 95% coverage.
- The downward trend indicates the need for promoting vaccination as the safest and most effective protection against infectious diseases.

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- A more proactive health and educational approach is needed in the local community, as well as in counseling centers in the course of family planning, with accompanying media support, so as to raise the awareness of the general population about the importance of vaccination.

Conflict of interest: None declared.

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VANBOLNIČKI SRČANI ZASTOJ I MERE KARDIOPULMONALNE REANIMACIJE U SLUŽBI ZA HITNU MEDICINSKU POMOĆ PANČEVO – JEDNOGODIŠNJA ANALIZA

ORIGINALNI RAD

ORIGINAL ARTICLE

OUT-OF-HOSPITAL CARDIAC ARREST AND MEASURES OF CARDIOPULMONARY RESUSCITATION IN EMERGENCY MEDICAL SERVICE PANČEVO – ONE-YEAR ANALYSIS

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SAŽETAK

Uvod: Vanbolnički srčani zastoj (VSZ) predstavlja najurgentnije stanje sa kojim se susreću zdravstveni radnici. Primenjene mere kardiopulmonalne reanimacije (KPR) imaju za cilj uspostavljanje ROSC-a (Return of spontaneous circulation). Ciljevi ovog istraživanja su bili određivanje učestalosti VSZ, kao i demografskih karakteristika pacijenata.

Metode: Istraživanje je u vidu retrospektivne studije koja obuhvata period od 01.01.2022.-31.12.2022.godine u Službi za hitnu medicinsku pomoć Pančevo. Podaci su uzeti iz protokola kućnih poseta i poziva, a rezultati su prikazani deskriptivnom statistikom.

Rezultati: U ispitivanom jednogodišnjem periodu VSZ se javio kod 36 pacijenata. U većini su to bili muškarci (69,4%) starijeg uzrasta sa pikom u dobi 70-81 godina. Mesto zadesa je u većini slučajeva prebivalište (72,2%), a svedok laik (77,8%). Mere Basic Life Support-a (BLS) su započete kod 13,9%. Dominantni inicijalni ritam je nešokabilni kod 69,4%, a ROSC je uspostavljen kod 39%. Dispečer je prepoznao da se radi o VSZ u 75 % slučajeva. Etiologija je uglavnom kardiovaskularna kod 44,4% pacijenata. VSZ se najviše javljao tokom popodnevnih sati, a najviše slučajeva je bilo u oktobru.

Zaključak: Prebivalište kao najčešće mesto zadesa i mali broj započetih mera BLS-a, kao i deo neprepoznatih VSZ od strane dispečera ukazuju na neophodnost edukacije stanovništva, kao i uvođenja jedinstvenog protokola za dispečere.

Ključne reči: VSZ, KPR, ROSC

ABSTRACT

Introduction: Out-of-hospital cardiac arrest (OHCA) is the most urgent condition that medical professionals are faced with. The applied measures of cardiopulmonary resuscitation (CPR) aim to establish the return of spontaneous circulation (ROSC). This study aimed to determine the frequency of OHCA, as well as the demographic characteristics of patients.

Methods: The research is in the form of a retrospective study in the period from January 1. 2022 - December 31. 2022. in the Emergency Medical Service of Pančevo. The data were taken from protocols of home visits and calls, and descriptive statistics presented the results.

Results: In the one-year period, OHCA occurred in 36 patients. Most were men (69.4%) of older age, with a peak at the age of 70-81 years. The place of occurrence is mostly the residence (72.2%), and the bystander is a layman (77.8%). Basic Life Support (BLS) measures were initiated in 13.9%. The dominant initial rhythm was non-shockable in 69.4%, and ROSC was established in 39%. The dispatcher recognized that 75% of the cases were OHCA. The etiology is mainly cardiovascular in 44.4% of patients. The most frequent occurrences of OHCA were during the afternoon hours, and the highest number of cases occurred in October.

Conclusion: The place of residence, as the most common place where OHCA occurs, and a small number of initiated BLS, as well as a part of the unrecognized OHCA by dispatchers indicate the necessity of educating the population, but also introducing a unique protocol for dispatchers.

Keywords: OHCA, CPR, ROSC

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Primljeno • *Received*: November 10, 2023; **Revidirano • *Revised*:** November 27, 2023; **Prihvaćeno • *Accepted*:** December 17, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47636

UVOD

Akutni srčani zastoj (ASZ) je nagli i neočekivani prestanak cirkulacije krvi uzrokovan funkcionalnim prestankom rada srca, koji ima za posledicu gubitak svesti i prestanak disanja [1]. ASZ predstavlja najurgentnije i najdramatičnije stanje sa kojima se medicinski radnici susreću, kako u vanbolničkim, tako i u bolničkim uslovima. Na unesrećenima se primenjuje kardiopulmonalna reanimacija (KPR), koja predstavlja skup hitnih mera i postupaka kod srčanog i respiratornog zastoja sa ciljem ponovnog uspostavljanja cirkulacije i disanja [2]. Redosled i postupak radnji koji se primenjuju u tretmanu ASZ zajednički se nazivaju lanac preživljavanja, koji se sastoji iz 4 karika: rano prepoznavanje i pozivanje u pomoć, rana KPR, rana defibrilacija i rani postreanimacioni tretman. Svaka od ovih karika je podjednako važna za dobijanje pozitivnog ishoda [3]. Vreme je ključan faktor za uspešnost mera KPR. Rana primena mera KPR može utrostručiti preživljavanje kod vanbolničkog srčanog zastoja (VSZ) [4]. Uspešna reanimacija podrazumeva povratak prethodno privremeno izgubljenih životnih funkcija- disanja, svesti i srčanog rada. ROSC (return of spontaneous circulation), kao pozitivan ishod kod reanimiranih pacijenata se ispoljava palpabilnim pulsom, merljivom tenzijom, električnom aktivnosti srca spojivom sa životom ili prisustvom pokreta kod pacijenta [5]. Učestalost, etiologija i smrtnost od VSZ s jedne strane, zatim epidemiološke karakteristike unesrećenih sa druge strane su parametri koji variraju u odnosu na veličinu i karakteristike populacije koja se ispituje. Najčešći uzroci su kardiovaskularne bolesti (KVS), od kojih se posebno izdvajaju aritmije. Ostali uzroci su respiratorne, endokrinološke i metaboličke bolesti, traumatski faktori, intoksikacije, kao i niz drugih spoljašnjih faktora [6]. U EuReCa studiji po podacima iz Srbije u šestomesečnom periodu tokom 2017.godine, na populaciji od 902 970 osoba, rezultati pokazuju da je kod 446 osoba registrovan VSZ [7]. ASZ je jedan od vodećih smrtnih uzroka na globalnom nivou. Istraživanja na teritoriji Evropske unije govore da je srčani zastoj uzrok smrti kod oko 250 000 stanovnika godišnje [8]. VSZ je izazov za medicinske radnike, ali i za laike koji svedoče istom. Započete mere BLS-a (Basic Life Support) od strane očevica pokazuju veću šansu za preživljavanjem [3]. Postoji povezanost između zadesnih elemenata i ishoda VSZ, kao što su prisustvo svedoka, da li je svedok započeo mere reanimacije, kakav je bio inicijalni ritam, i drugi faktori [9]. Ciljevi rada su analiza učestalosti pojave VSZ i demografskih karakteristika reanimiranih pacijenata u Službi za hitnu medicinsku pomoć (SHMP) Pančevo u toku 2022. godine.

INTRODUCTION

Acute cardiac arrest (ACA) is a sudden and unexpected cessation of blood circulation caused by functional heart failure, resulting in loss of consciousness and cessation of breathing [1]. It is the most urgent and dramatic condition that medical workers encounter, both in out-of-hospital and hospital settings. Cardiopulmonary resuscitation (CPR) is a set of emergency measures and procedures for cardiac and respiratory arrest to restore circulation and breathing applied to the afflicted [2]. The sequence and procedure of actions applied in the treatment of ACA altogether are called a survival chain. It consists of 4 links - early recognition and call for help, early CPR, early defibrillation, and early post-reanimation treatment. Each of these links is equally important for obtaining a positive outcome [3]. Time is a key factor for the success of CPR measures. Early administration of CPR measures can triple the survival in out-of-hospital cardiac arrest (OHCA) [4]. Successful reanimation involves the return of previously temporarily lost life functions - breathing, consciousness, and heart work. ROSC (return of spontaneous circulation) as a positive outcome in reanimated patients is manifested by palpable pulse, measurable tension, the electrical activity of the heart compatible with life, or the presence of movement in the afflicted [5]. Frequency, etiology, and mortality from OHCA on the one hand, then the epidemiological characteristics of the afflicted on the other hand are parameters that vary according to the size and characteristics of the population being examined. The most common causes are cardiovascular diseases (CVD), where arrhythmia stands out in particular. Other causes include respiratory, endocrine, and metabolic diseases, traumatic factors, intoxication, as well as several other external factors [6]. In the EuReCa study, according to data from Serbia in the six-month period during 2017 on a population of 902,970 people, the results show that 446 people are registered with OHCA [7]. ACA is one of the leading causes of death globally. Research in the European Union shows that cardiac arrest is the cause of death in about 250,000 inhabitants per year [8]. OHCA is a challenge for medical workers, but also for laypeople who witness it. The BLS (Basic Life Support) measures initiated by a bystander show a likelihood of survival [3]. There is a correlation between the incidental elements and the outcome of the OHCA, such as the presence of bystanders, whether the bystander initiated resuscitation measures, what the initial rhythm was, and other factors [9]. The objectives of the paper are to analyze the frequency of occurrence of OHCA and demographic characteristics of resuscitated patients in the Emergency Medical Service (EMSP) Pančevo during 2022.

METODE

Istraživanje je u vidu retrospektivne studije koja obuhvata jednogodišnji period od 01.01.2022. do 31.12.2022. Podaci su prikupljeni iz protokola kućnih poseta (KP) i poziva (PP) SHMP Pančevo. U PP dispečer unosi podatke o imenu i prezimenu pacijenta, adresu i kontakt telefon pozivaoca, kratak opis tegoba, zatim vreme prijema poziva, vreme odlaska ekipe na teren kao i vreme povratka ekipe. Za primljene pozive koji spadaju u prvi red hitnosti, uključujući potvrđenu ili postavljenu sumnju na VSZ, ekipe se odmah šalju na teren, odnosno maksimalno minut od prijema poziva. U KP ekipe unose od medicinskih podataka kratku anamnezu, dijagnozu/e, fizikalni nalaz i terapiju, kao i eventualno upućivanje i transport pacijenta u Opštu bolnicu Pančevo (OBPVO). Parametri koji su prikupljani i analizirani su: broj pacijenata sa VSZ, pol, starost, mesto nastupanja, etiologija, podaci o očevicima, vreme i mesec nastupanja, započinjanje BLS-a od strane očevica, inicijalni ritam i ishod KPR. Za obradu podataka je korišćena deskriptivna statistika, a podaci su prikazani tekstualno, kao i putem grafikona i tabela.

REZULTATI

Tokom 2022. godine u SHMP Pančevo je bilo ukupno 6207 KP. Od toga je VSZ na terenu imalo ukupno 36 (0,6%) pacijenata. Kod svih je primenjena KPR od strane ekipa SHMP. U odnosu na pol, bilo je više muškaraca (69,4%) nego žena (30,6%) (Tabela 1). Najmlađi reanimirani pacijent je bio muškarac starosti 36 godina, a najstariji takođe muškog pola starosti 94 godina. U ženskoj populaciji, najmlađa pacijentkinja je imala 64 godina, a najstarija 87 godina. Nije bilo dece sa VSZ to-

Tabela 1. Pacijenti sa VSZ i distribucija po polu

Table 1. Patients with OHCA and distribution by sex

	N	Procenat/ Percentage %
Ukupan broj KP / **Total number of HV**	6207	100
Ukupan broj VSZ / *Total number of OHCA*	36	0.6%
Pol / *Sex*		
Muški / *Male*	25	69.4
Ženski / *Female*	11	30.6

Objašnjenje- Broj (procenat) pacijenata po polu je izveden iz ukupnog broja VSZ
Explanation- The number (percentage) of patients by sex is derived from the total number of OHCA
N- number
KP- kućne posete
HV- home visits
VSZ- vanbolnički srčani zastoj
OHCA- out of hospital cardiac arrest

METHODS

The research is in the form of a retrospective study covering a one-year period from 01.01.2022. to 31.12.2022. The data were collected from the protocol of home visits (HV) and calls (CP) EMSP Pančevo. In CP dispatcher enters information about the name and surname of the patient, the address and contact phone of the caller, a brief description of the problem, then the time of receiving the call, the time of departure of the team to the site, as well as the time of return. Receiving calls that fall into the first line of urgency, including confirmed or placed suspicion of OHCA, teams are immediately sent to the site, i.e. a maximum of a minute after receiving the call. HV teams enter in medical data a short history, diagnosis/es, physical findings, and therapy, as well as possible referral and transport of the patient to the General Hospital Pančevo (GHP). The parameters that were collected and analyzed are the number of patients with OHCA, gender, age, place of occurrence, etiology, eyewitness data, time and month of occurrence, initiation of BLS by bystanders, initial rhythm, and outcome of CPR. Descriptive statistics were used to process the data, and the data were presented textually, as well as through graphs and tables.

RESULTS

In 2022 there were a total of 6207 HV in EMSP Pančevo. OHCA had a total of 36 (0.6%) patients on the site. All of them had CPR applied by the EMSP team. Compared to gender, there were more men 69.4% than women 30.6% (Table 1). The youngest resuscitated patient was a 36-year-old male, and the oldest, also a male, was 94 years old. In the female population, the youngest patient was 64 years old and the oldest was 87 years old. There were no children with OHCA in 2022. Distribution by age shows that the most OHCA occurs in the elderly population, in the age group 71-80 years (12) and the group 61-70 years (8); while there are no resuscitated patients in age groups under 30 years (Chart 1). The distribution by month shows a peak in October when there were 6 patients with OHCA. There were no cases in September. The distribution by month is shown in Chart 2. In most cases, it happened in patients' residences, where 26 (72.2%) patients were resuscitated, and the least during medical transport from the site to GHP 2 (5.6%). The OHCA distribution by residential places is shown in Chart 3. When it comes to the initial rhythm, the afflicted most often manifested a non-shockable rhythm, recorded in 25 (69.4%) patients. Asystole was the dominant non-shocking rhythm (23-92%). Shockable rhythms were registered in 11 (30.6%) patients. 8 of these patients (72.7%) had ventricular fibrillation (VF). The distribution according to the initial rhythm is

Tabela 2. Distribucija pacijenata sa VSZ po inicijalnom ritmu

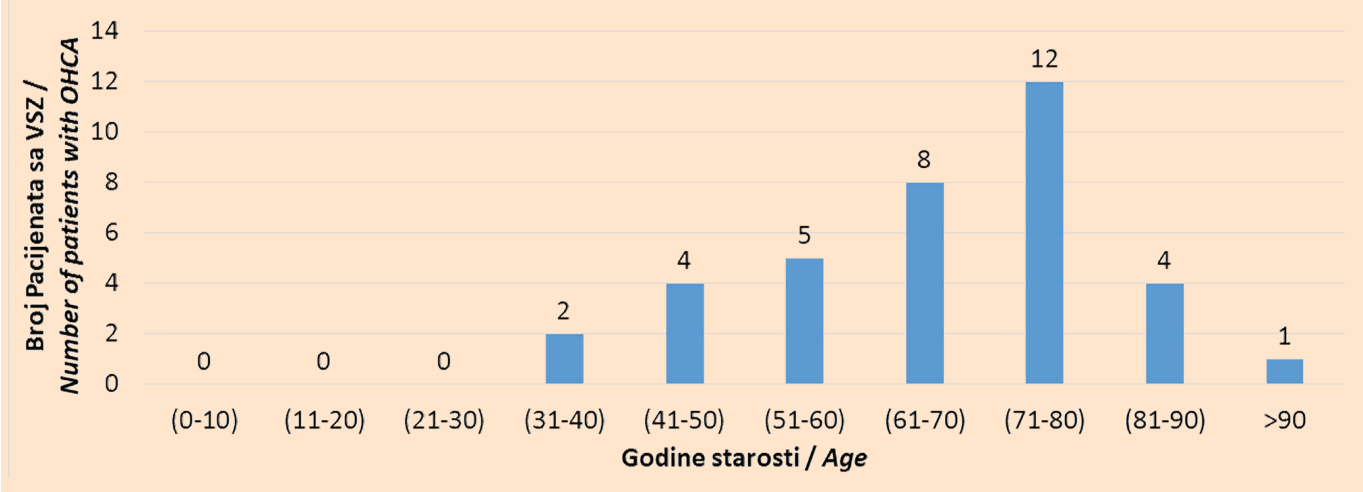
Table 2. Distribution of patients with OHCA by initial rhythm

Inicijalni ritam / *Initial rhythm*	**N**	**Procenat / *Percentage* %**
Šokabilni / *Shockable*	11	30.6
VT bez pulsa / *pVT*	3	27.3
Ventrikularna fibrilacija / *VF*	8	72.3
Nešokabilni / *Non-shockable*	25	69.4
Asistolija / *Asystole*	23	92
Elektromehanička disocijacija / *PEA*	2	8

Objašnjenje- Broj (procenat) pacijenata sa šokabilnim i nešokabilnim ritmom je izveden iz ukupnog broja pacijenata sa VSZ. Broj (procenat) pacijenata sa VF i VT bez pulsa je izveden iz ukupnog broja pacijenata sa šokabilnim ritmom. Broj (procenat) pacijenata sa PEA i asistolijom je izveden iz ukupnog broja pacijenata sa nešokabilnim ritmom.
Explanation- The number (percentage) of patients with shockable and nonshockable rhythm is derived from the total number of patients with OHCA. The number (percentage) of patients with VF and pVT is derived from the total number of patients with shockable rhythm. The number (percentage) of patients with PEA and asystole is derived from the total number of patients with non-shockable rhythm.
N- number
VSZ- Vanbolnički srčani zastoj; OHCA- out of hospital cardiac arrest;
VT- ventrikularna tehikardija; VF- ventricular fibrilation;
pVT- pulseless ventricular tachycardia; PEA- pulseless electrical activity;

kom 2022.godine. Distribucija po starosti pokazuje da se najviše VSZ dešava u starijoj populaciji, u starosnoj grupi 71-80 godina (12) i u grupi 61-70 godina (8), dok nema reanimiranih pacijenata u starosnim grupama ispod 30 godina (Grafikon 1). Raspodela po mesecima pokazuje pik u oktobru, kada je bilo 6 pacijenata sa VSZ. Tokom septembra nije bilo nijednog slučaja. Distribucija po mesecima je prikazana u Grafikonu 2. Mesto zadesa je u većini slučajeva bilo prebivalište, gde je reanimirano 26 (72,2%) pacijenata, a najmanje tokom sanitetskog transporta sa terena do OBPVO, svega 2 (5,6%). Distribucija VSZ po mestu zadesa je prikazana na Grafikonu 3. Kada je u pitanju inicijalni ritam, pacijenti su najčešće ispoljavali nešokabilni ritam, zabeležen kod 25 (69,4%) pacijenata. Asistolija je bila dominantan nešokabilni ritam (23-92%). Šokabilni ritmovi su registrovani kod 11 (30,6%) pacijenata. Od toga je 8

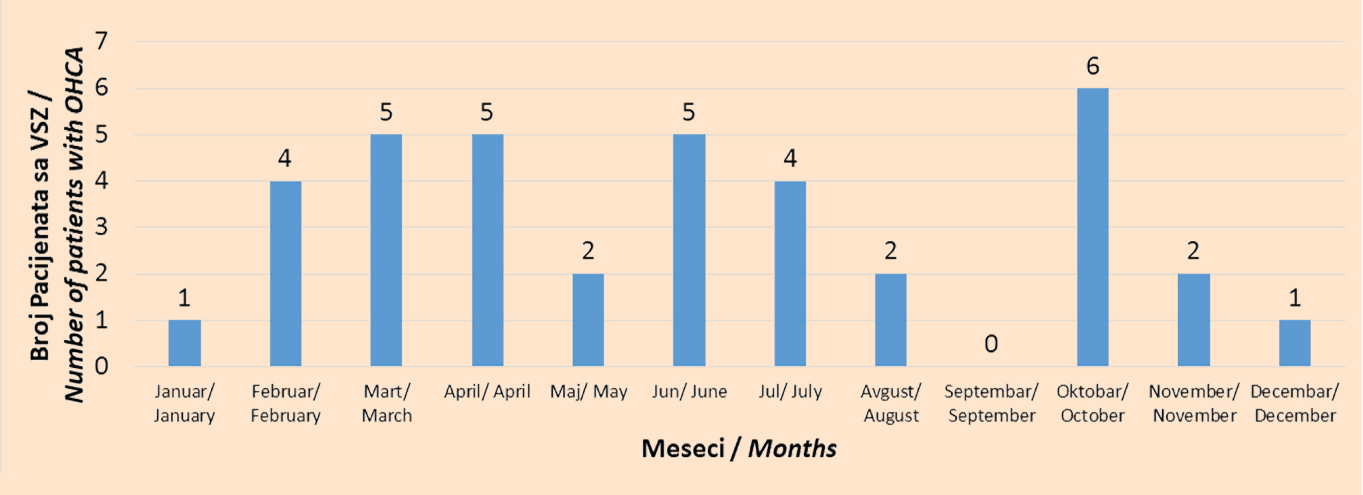
shown in Table 2. Etiological factors are primarily cardiovascular in 16 (44.4%) patients, and unknown cause in 10 (27.8%) patients. In the category of other causes are metabolic, endocrine, and malignant diseases. The distribution by etiology is shown in Chart 4. BLS measures were applied to only 5 (13.9%) patients (Table 3). In most cases, the bystander was a layman in 77.8% of them (Table 4). The time of the day in which OHCA most often occurred is in the period 15:00-15:59h in 4 (11.1%) patients, as well as in the period 19:00-19:59h also 4 (11.1%). The circadian rhythm distribution is shown in Chart 5. In relation to whether the dispatcher recognized/suspected that it was OHCA, two groups of patients are distinguished - the first consists of those in whom the OHCA is suspected or confirmed (recorded that the patient does not breathe, does not respond, or is unconscious), while in the second are those in whom



VSZ- Vanbolnički srčani zastoj/ OHCA- Out of hospital cardiac arrest

Slika 1. Distribucija pacijenata sa VSZ po godinama starosti

Figure 1. Distribution of patients with OHCA by age



VSZ – vanbolnički srčani zastoj/ OCHA- Out of hospital cardiac arrest

Slika 2. Distribucija pacijenata sa VSZ po mesecima

Figure 2. Distribution of patients with OHCA by months

Tabela 3. Distribucija u odnosu na primenjene mere BLS

Table 3. Distribution in terms of aplied BLS measures

	N	Procenat / *Percentage* %
Ukupan broj VSZ / *Total number of OHCA*	36	100
BLS da / *BLS yes*	5	13.9
BLS ne / *BLS no*	31	86.1

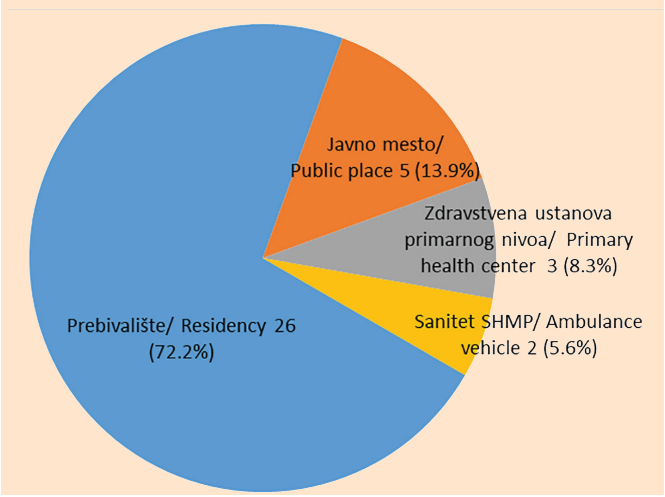
VSZ- vanbolnički srčani zastoj
OHCA- Out of hospital cardiac arrest
BLS- Basic life support

Tabela 4. Distribucija VSZ po svedoku

Table 4. Distribution of OHCA by witness

	N	Procenat / *Percentage* %
Ukupan broj VSZ / *Total number of OHCA*	36	100
Laik / *layman*	28	72.8
Zdravstveni radnik u ustanovi primarnog nivoa / *Health professional in primary health institution*	3	8.3
SHMP / EMS	5	13.9

VSZ- Vanbolnički srčani zastoj/ OHCA- Out of hospital cardiac arrest
SHMP- Služba hitne medicinske pomoći/ EMS- Emergency medical service

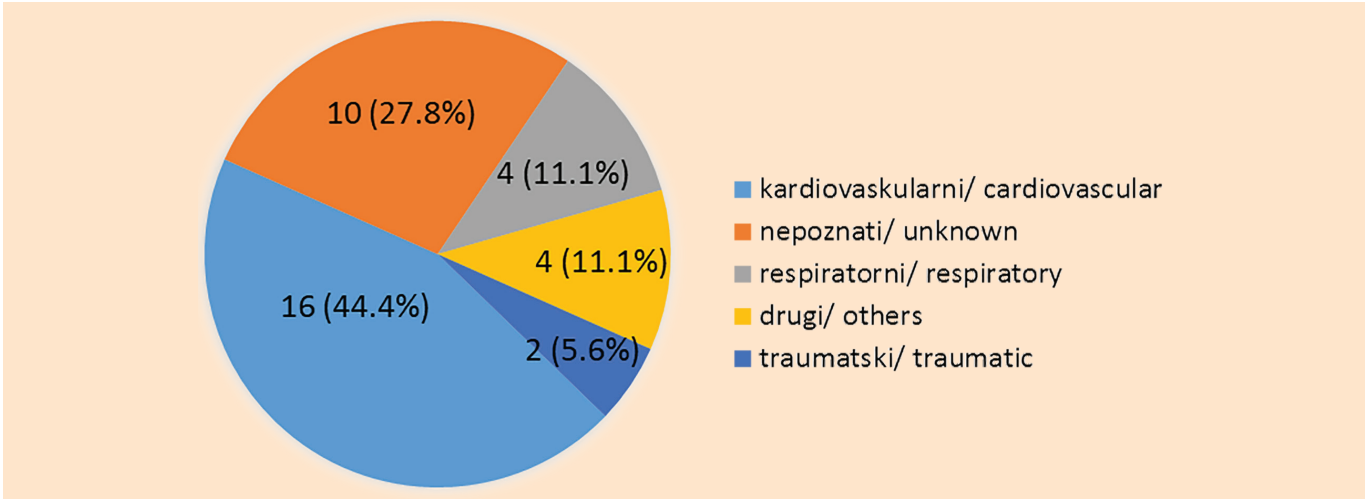


SHMP- Služba za hitnu medicinsku pomoć/ EMS- Emergency medical service
VSZ- Vanbolnički srčani zastoj/ OHCA- Out of hospital cardiac arrest

Slika 3. Distribucija VSZ po mestu zadesa

Figure 3. Distribution of OHCA by place of occurrence

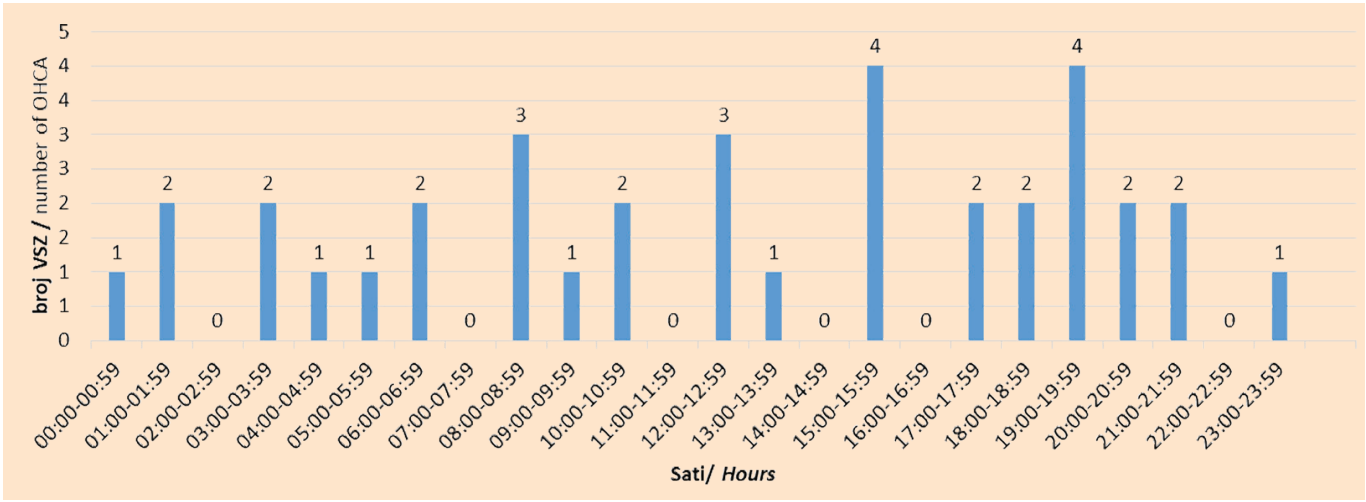
dispatchers did not recognize on the basis of available data from the caller. There are 27 (75%) patients in the first group and 9 (25%) in the second group. For patients who were not recognized as OHCA, unspecified problems were most often reported (the patient suddenly became ill) followed by choking and chest pain. Nevertheless, all patients in whom OHCA has occurred are perceived as urgent. No cases of telephone-guided CPR by dispatchers have been recorded. Distribution by dispatcher recognition OHCA is shown in Chart 6. ROSC was recorded in 14 (39%) patients. Established ROSC refers to those patients who are transported with a positive outcome of CPR and handed to the attending physician in the emergency service GHP. This number also includes the appearance of ROSC on the site, as well as ROSC during the resuscitation of patients who experienced OHCA during the transport from the site to the GHP. So, it applies only to those patients who survived until admission to the hospital. Further moni-



VSZ- Vanbolnički srčani zastoj/ OHCA- Out of hospital cardiac arrest

Slika 4. Distribucija VSZ po uzrocima

Figure 4. Distribution of OHCA by causes

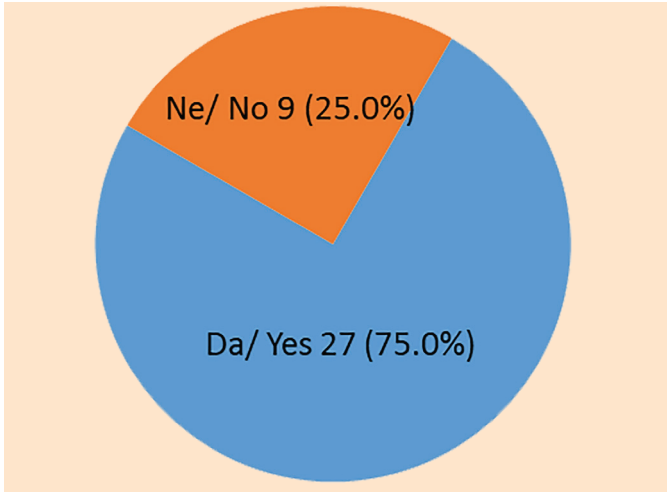


VSZ- Vanbolnički srčani zastoj/ OHCA- Out of hospital cardiac arrest

Slika 5. Distribucija VSZ po cirkadijalnom ritmu

Figure 5. Distribution of OHCA by circadian rhythm

(72,7%) pacijenata imalo ventrikularnu fibrilaciju (VF). Distribucija po inicijalnom ritmu je prikazana u Tabeli 2. Etiološki faktori su na prvom mestu kardiovaskularni kod 16 (44,4%) pacijenata, i nepoznatog uzroka kod 10 (27,8%) pacijenata. U kategoriji drugih uzroka su metaboličke, endokrinološke i maligne bolesti. Distribucija po etiologiji je prikazana na Grafikonu 4. Mere BLS-a su primenjene kod samo 5 (13,9%) pacijenata (Tabela 3). Očevidac je u najvećem broju slučajeva bio laik kod njih 77,8% (Tabela 4). Doba dana u kome se najčešće desio VSZ je u periodu od 15:00-15:59h kod 4 (11,1%) pacijenata, kao i u periodu od 19:00-19:59h takođe 4 (11,1%). Distribucija po cirkadijalnom ritmu je prikazana na Grafikonu 5. U odnosu na to da li je dispečer prepoznao/posumnjao da se radi o VSZ, izdvajaju se dve grupe pacijenata- prvu čine oni kod kojih je postavljena sumnja ili potvrđen VSZ (zabeleženo da pacijent ne diše, ne reaguje ili je bez svesti), dok su u

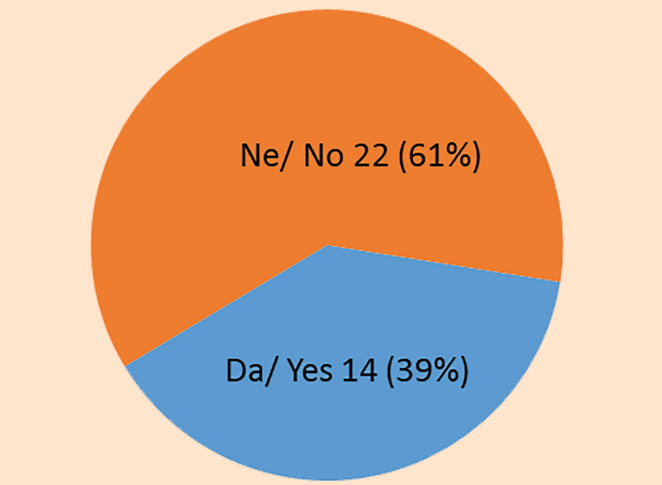


VSZ- Vanbolnički srčani zastoj/ OHCA- Out of hospital cardiac arrest

Slika 6. Distribucija VSZ po prepoznavanju od strane dispečera

Figure 6. Distribution of OHCA recognized by dispatchers

drugoj oni kod kojih dispečeri nisu prepoznali VSZ na osnovu dostupnih podataka od pozivaoca. U prvoj grupi se nalazi 27 (75%) pacijenata, a u drugoj 9 (25%). Za pacijente kod kojih se nije znalo da se radi o VSZ najčešće su prijavljivane neodređene tegobe (pacijentu odjednom pozlilo), potom gušenje i bol u grudima. Bez obzira na to, svi pacijenti kod kojih se desio VSZ su shvaćeni kao prvi red hitnosti. Nije zabeležen nijedan slučaj telefonski vođene KPR od strane dispečera. Distribucija po prepoznavanju VSZ od strane dispečera je prikazana na Grafikonu 6. ROSC je zabeležen kod 14 (39 %) pacijenata. Uspostavljeni ROSC se odnosi na one pacijente koji su sa pozitivnim ishodom KPR transportovani i predati dežurnom lekaru prijemne službe OBPVO. U taj broj je uračunata i pojava ROSC-a na samom terenu, kao i ROSC tokom reanimacije pacijenata koji su doživeli VSZ tokom transporta sa lica mesta do OBPVO. Dakle, odnosi se samo na one pacijente koji su preživeli do prijema u bolnicu. U ovom radu nije izvršeno dalje praćenje preživljavanja pacijenata po otpustu. Distribucija po uspostavljenom ROSC-u je prikazana na Grafikonu 7.



VSZ- Vanbolnički srčani zastoj/ OHCA- Out of hospital cardiac arrest

Slika 7. Distribucija VSZ po uspostavljenom ROSC-u

Figure 7. Distribution of OHCA by established ROSC

DISKUSIJA

U ovom istraživanju u periodu od godinu dana, VSZ je bio prisutan kod 36 pacijenata. Incidenca VSZ u drugim istraživanjima varira, pre svega u odnosu na veličinu posmatrane populacije i ukupan broj pacijenata kod kojih su intervenisale hitne službe, ali i u odnosu na dužinu posmatranog perioda. U novijim studijama u zemlji i regionu, podaci beleže razlike u broju pacijenata sa VSZ u toku jednogodišnjeg perioda, koji se kreću od 148 na teritoriji Novog Sada, do 7773 na teritoriji cele Hrvatske [10,11]. Incidenca u opštinama na teritoriji Srbije je raznolika; kreće se od oko 22 godišnje u Kanjiži [12], zatim 119 u Somboru [13], do 148 u Zrenjaninu [14]. Polna distribicija pokazuje predominaciju muškog pola, nešto manje od tri četvrtine, što je u skladu sa mnogim drugim istraživanjima u zemlji [10,15,16] i na globalnom nivou [17,18]. Kod njih se procentualno učešće kreće od nešto više od 50% do više od 70%. Kardiovaskularni uzroci su najčešći uzrok VSZ, što je u korelaciji sa podacima istraživanja na nivou cele Srbije, prikazanim u dvogodišnjoj analizi [19] i rezultatima novije studije u Kini [17]. To se može objasniti sve većom zastupljenošću KVS bolesti među domaćom i svetskom populacijom. Nepoznati uzroci zauzimaju drugo mesto u etilogiji VSZ, što je više nego u prospektivnoj studiji EuReCa Srbija [12,13,14,19]. Pacijenti u ovom istraživanju su uglavnom stariji; većina je starosti u rasponu od 60-80 godina. To se može dovesti u vezu sa najčešćim uzrokom VBS- KVS bolesti, koje su česte kod starije populacije, uz mnoge komorbiditete.

toring of patients' survival after discharge was not taken into account. The distribution for established ROSC is shown in Chart 7.

DISCUSSION

In this study, OHCA was present in 36 patients over a one-year period. The incidence of OHCA in other studies varies, primarily concerning the size of the observed population and the total number of patients in whom emergency services intervened, but also to the length of the observed period. In recent studies in the country and regions, data records differ in the number of patients with OHCA over a one-year period, ranging from 148 on the territory of Novi Sad, to 7773 on the territory of Croatia [10,11]. The incidence in municipalities on the territory of Serbia varies, ranging from about 22 per year in Kanjiža [12], then 119 in Sombor [13], to 148 in Zrenjanin [14]. Gender distribution shows male predominance, just under three-quarters, which is consistent with many other surveys in the country [10,15,16] and globally [17,18]. The percentage in males ranges from just over 50% to more than 70%. Cardiovascular causes are the most common cause of OHCA, which correlates with research data in the whole Serbia, presented in a two-year analysis [19] and the results of a recent study in China [17]. This can be explained by the increasing prevalence of CVS disease among the domestic and world population. Unknown causes occupy the second place in the etiology of OHCA, which is more than in the prospective study of EuReCa Serbia [12,13,14,19]. The patients in this study are mostly elderly, most of the ages from 60-80 years. This can be associated with the most common cause of VBS-CVS disease, which is common in the elderly population,

U poređenju sa sličnim istraživanjima, dobijeni rezultati takođe ukazuju na stariju populaciju, sa prosečnom starošću preko 65 godine [10,17,20]. Podaci iz svetske literature se slažu sa rezultatima ovog rada, pokazujući da je prebivalište ubedljivo na prvom mestu po lokaciji na kojoj se zadesio unesrećeni sa VSZ [17,21]. To ima višestruki značaj jer, pre svega, povlači za sobom pitanje izvodjenja BLS-a u datim uslovima; u većini slučajeva svedoci na toj lokaciji su laici, uglavnom članovi porodice ili poznanici. Potom ukazuje na značaj obuke opšteg građanstva, posebno onih koji nisu zdravstveni radnici, s obzirom da su oni u više od 75% slučajeva svedoci VSZ [22]. U ovom istraživanju su takođe laici najčešći svedoci (77,8%). Mere BLS-a se uglavnom primenjuju kod malog broja pacijenata [15,20,23]; rezultati se kreću od 3,7% do oko 17%, što se slaže sa ovim rezultatima (13,9%). Kada se posmatra distribucija po mesecima, pik je prisutan u oktobru, potom martu i aprilu. Podaci iz literature su sa sličnom distribucijom; jesenji i zimski meseci su uglavnom na prvom mestu [16,23]. Cirkadijalni ritam ukazuje na pik u dva vremenska perioda 15:00-15:59h i 19:00-19:59h (po 4 VSZ) i u periodu 08:00h-08:59h i 12:00h-12:59h. Druga istraživanja potvrđuju da se VSZ dešava uglavnom u toku dana, sa manjim brojem unesrećenih tokom noći [24]. To se može objasniti učestalijom pojavom aritmija tokom dana u odnosu na noć, kao najčešćim uzrokom VBS među kardiološkom etiologijom, ali i manjim brojem poziva koji se odnose na VSZ tokom noći obično zbog odsustva svedoka koji bi to prijavili [25]. Inicijalni ritam je jedan od značajnih parametara koji određuju preživljavanje nakon VSZ. U ovoj studiji prevladavaju nešokabilni ritmovi. Podaci iz literature se razlikuju. Novije studije pokazuju da je procenat šokabilnih ritmova kod VSZ u padu poslednjih decenija [26], dok se u drugim istraživanjima uglavnom javljaju šokabilni ritmovi [27]. Šokabilni ritmovi pokazuju veći procenat uspostavljanja ROSC-a u odnosu na nešokabilne [26,27]. Procenat uspostavljenog ROSC-a do prijema u bolnicu se poslednjih godina kreće od oko 12% do skoro 40% u domaćim istraživanjima [10,15,19]. U odnosu na njih, rezultati ove studije se svrstavaju u grupu većeg procenta dobijenog ROSC-a. Dispečeri kao karika koja povezuje unesrećenog i ekipu SHMP, u ovom radu su prepoznali 75% VSZ, što je više u odnosu na novije rezultate domaćeg istraživanja, u kojima je procenat prepoznavanja oko 52% [10]. Procena dispečera se vrši na osnovu podataka od pozivaoca, zatim znanja i iskustva. U SHMP Pančevo ne postoji jedinstveni protokol primanja poziva i njihove klasifikacije po redovima hitnosti, što može objasniti 25% neprepoznatih VSZ. Takođe, pozivaoci često ne umeju da objasne situaciju na terenu, pa se dešava da se stanja prvog reda hitnosti ne

with more comorbidities. Compared to similar studies, the results obtained also indicate to older population, with an average age over 65 years [10,17,20]. Data from the world literature agree with the results of this study, showing that the residence is convincingly in the first place in terms of the location where the OHCA [17,21] occurred. This has considerable significance. First of all, it entails the issue of performing the BLS in the given conditions, since in most cases bystanders at this location are laypeople, mostly family members or acquaintances. Then it points to the importance of training citizens in general, especially those who are not healthcare workers, since they in more than 75% of cases witnessed the OHCA [22]. In this study, laypeople were also the most common witnesses (77.8%). BLS measures are mainly applied to a small number of afflicted [15,20,23]; results range from 3.7% to about 17%, which coincides with these results (13.9%). When observing the distribution by month, peaks are present in October, then March and April. Data from the literature are with a similar distribution, the autumn and winter months are generally in the first place [16,23]. Circadian rhythm indicates peaks in two time periods 15:00-15:59h and 19:00-19:59h (4 OHCA) and the period 08:00h-08:59h and 12:00h-12:59h. Other studies confirm that OHCA occurs mainly during the day, with fewer casualties during the night [24]. This can be explained by the more frequent occurrence of arrhythmia during the day compared to the night, as the most common cause of OHCA among cardiac etiology, but also a meagre number of calls relating to OHCA during the night, usually due to the absence of bystanders to report it [25]. The initial rhythm is one of the significant parameters that determine survival after OHCA. In this study, non-shockable rhythms predominate. Data from the literature differs. Recent studies show that the percentage of shockable rhythms in OHCA has been declining in recent decades [26], while in other studies there are mostly shockable rhythms [27]. Shockable rhythms show a higher percentage of established ROSC than non-shockable [26,27]. The percentage of established ROSC to hospital admission in recent years has ranged from about 12% to nearly 40% in domestic research [10,15,19]. According to that, the results of this study are classified as a higher percentage of ROSC established. The dispatcher is the link that connects the afflicted person and the EMS team, who in this study recognized 75% of OHCA, which is more than the recent results in domestic research, in which the percentage of recognition is about 52% [10]. The assessment of the dispatcher is carried out based on data from the caller, also knowledge and experience. In EMS Pančevo there is not a unique protocol for receiv-

prepoznaju. Podaci iz SAD govore u prilog većeg procenta uspostavljenog ROSC-a u grupi pacijenata kod kojih su dispečeri koristili protokol [28].

ZAKLJUČAK

Uzimajući u obzir analizirane parametre, vidi se da su najčešća mesta zadesa VSZ prebivalište, a najčešći svedoci laici, koji u malom procentu započnu mere KPR do dolaska ekipe SHMP. Zato je pored periodične obuke stanovništva neophodna sistematska i učestalija obuka za BLS. Sa druge strane, beleži se četvrtina neprepoznatih VSZ od strane dispečera. Razlog leži u nepostojanju jedinstvenih dispečerskih protokola za sve SHMP na državnom nivou. Povećanjem broja edukacija zdravstvenih radnika i uvođenjem jedinstvenog protokola i upitnika za dispečere kojima bi lakše i brže donosili odluke o stepenu hitnosti i prepoznali VSZ, kao i edukacijama šire populacije za BLS, dovelo bi do porasta uspostavljanja ROSC-a, a samim tim i preživljavanja pacijenata sa VSZ.

SPISAK SKRAĆENICA

ASZ- akutni srčani zastoj
KPR- kardiopulmonalna reanimacija
VSZ- vanbolnički srčani zastoj
KVS- kardiovaskularni
ROSC- return of spontaneous circulation
SHMP- Služba za hitnu medicinsku pomoć
KP- kućna poseta
PP- protokol poziva
OBPVO- Opšta bolnica Pančevo
BLS- basic life support

Sukob interesa: Nije prijavljen.

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ing calls and their classification by order of urgency, which can explain 25% of unrecognized OHCA. Also, callers often do not know how to explain the situation on the site, so it happens that urgent conditions are not recognized. Data from the U.S. show a higher percentage of established ROSC in the group of patients in whom dispatchers used the protocol [28].

CONCLUSION

Taking into account the analyzed parameters, it can be seen that the most common places of accidents are residences, and the most common bystanders are laypeople, who in a small percentage start CPR measures until the arrival of the EMS team. Therefore, in addition to periodic training of the population, systematic and frequent training for the BLS is necessary. On the other hand, it was recorded a quarter of unrecognized OHCA by dispatchers. The reason lies in the non-existent unique dispatch protocols for all EMS on the state level. Educating health care workers, and introducing a unique protocol and questionnaire for dispatchers that would more easily and quickly make decisions about the degree of urgency and recognize OHCA, as well as education of the wider population for BLS would lead to an increase in the establishment of ROSC, and thus the survival of patients with OHCA.

LIST OF ABBREVIATIONS

ACA- acute cardiac arrest
CPR- cardiopulmonary resuscitation
CVS- cardiovascular
ROSC- the return of spontaneous circulation
EMS- Emergency Medical Service
HV- home visit
CP- call protocol
GHP - General Hospital Pančevo
BLS - Basic Life Support

Conflict of interest: None declared.

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UTICAJ PERIOPERATIVNIH FAKTORA NA ISHOD KOD PACIJENATA SA RUPTURIRANOM ANEURIZMOM ABDOMINALNE AORTE

ORIGINALNI RAD

ORIGINAL ARTICLE

THE IMPACT OF PERIOPERATIVE FACTORS ON THE OUTCOME IN PATIENTS WITH RUPTURED ABDOMINAL AORTIC ANEURYSM

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SAŽETAK

Uvod: Aneurizma je permanentno, lokalizovano proširenje dijametra arterije za minimum 50% u odnosu na njen fiziološki promer. Njena najčešća lokalizacija je na abdominalnoj aorti. Ruptura, kao najčešća komplikacija aneurizme, klinički je značajna jer je odlikuje visok stepen smrtnosti. Pacijenti sa rupturom aneurizme abdominalne aorte podvrgavaju se hitnom operativnom tretmanu gde su, uprkos naporima hirurga i ekspanzivnom napretku medicine i tehnologije, intraoperativni i postoperativni mortalitet i dalje zastupljeni u visokom procentu.

Cilj rada: Ispitati na koji način različiti perioperativni faktori utiču na ishod kod pacijenata sa rupturom aneurizme abdominalne aorte.

Materijal i metode: Retrospektivna studija zasnovana na medicinskoj dokumentaciji za dvogodišnji period, u okviru koje su deskriptivnim statističkim metodama obrađeni i analizirani perioperativni klinički parametri i njihov uticaj na ishod kod 57 pacijenata operisanih zbog rupture aneurizme abdominalne aorte.

Rezultati: Preoperativne vrednosti hemoglobina i komponenti hemostaznog sistema, intraoperativna nadoknada krvi i intraoperativni pH, kao i postoperativne vrednosti kalijuma, laktata i količina diureze u prva 24 sata nakon operacije, pokazali su statistički značajan uticaj na ishod kod pacijenata operisanih u Kliničkom centru Vojvodine zbog rupture aneurizme abdominalne aorte.

Zaključak: Operativni ishod kod rAAA je, uprkos dugogodišnjim istraživanjima perioperativnih faktora i pokušajem nalaženja idealnog skoring-sistema, i dalje nepredvidiv.

Ključne reči: aneurizma, ruptura, abdominalna aorta

ABSTRACT

Introduction: An aneurysm is a permanent, localized extension of an artery diameter by at least 50% relative to its physiological diameter. Its most common localization is on the abdominal aorta. Rupture, the most common complication of an aneurysm, is clinically significant because of the high mortality rate. Patients with ruptured aneurysm of the abdominal aorta undergo urgent surgical treatment, where despite the efforts of surgeons and expansive progress in both medicine and technology, intraoperative and postoperative mortality is still present in a high percentage.

Aim: To examine how different perioperative factors affect the outcome in patients with ruptured aneurysms of the abdominal aorta.

Material and methods: A retrospective study based on medical records for a two-year period, in which descriptive statistical methods processed and analyzed perioperative clinical parameters and their impact on outcome in 57 patients operated on for rupture of abdominal aortic aneurysm.

Results: Preoperative values of hemoglobin and components of the hemostasis system, intraoperative blood replenishment and intraoperative pH, and postoperative values of potassium, lactate, and the amount of diuresis in the first 24 hours after surgery showed a statistically significant effect on the outcome in patients operated at the Clinical Center of Vojvodina due to rupture of abdominal aortic aneurysm.

Conclusion: The operative outcome in rAAA is still unpredictable despite many years of research into perioperative factors and attempts to find an ideal scoring system.

Keywords: aneurysm, rupture, abdominal aorta

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Primljeno • *Received*: October 24, 2023; **Revidirano • *Revised*:** October 31, 2023; **Prihvaćeno • *Accepted*:** December 22, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47314

UVOD

Aneurizma predstavlja trajnu lokalizovanu dilataciju dijametra arterije za bar 50% u odnosu na normalni promer za datu lokalizaciju [1]. Može da se formira na bilo kom arterijskom krvnom sudu, ali je najčešća lokalizacija abdominalna aorta, i to njen infrarenalni segment. Aneurizme se mogu iskomplikovati rupturom, trombozom, i distalnim embolizacijama, a klinički najbitnija i potencijalno fatalna komplikacija jeste ruptura [2]. Na infrarenalnoj lokalizaciji najznačajnija komplikacija je ruptura. U čak 50% slučajeva, ruptura je prva manifestacija aneurizme [3]. Rizik rupture je povezan sa apsolutnom veličinom aneurizme, polom (češće se javlja kod žena), oblikom aneurizme i prisustvom parijetalnih trombotičnih masa. Pušenje i hronična opstruktivna bolest pluća su takođe nezavisni prediktori rupture aneurizme abdominalne aorte [2]. Ruptura aneurizme abdominalne aorte (u daljem tekstu rAAA) se može manifestovati u vidu retroperitonealnog krvarenja, intraperitonealnog krvarenja, hronične rupture, aorto-enterične fistule i aorto-kavalne fistule. Najčešće su rupture u retroperitonealnom i intraperitonealnom prostoru. Dijagnoza rAAA se postavlja klinički, ultrazvučno ili CT angiografijom [1]. Ovo stanje zahteva hitan hirurški tretman u cilju spašavanja života. Tretman može biti otvoreni hirurški ili endovaskularni. Otvoreni hirurški pristup se sastoji od ksifopubične laparotomije, evisceracije creva, proksimalne i distalne vaskularne kontrole i rekonstrukcije aneurizmatski izmenjene aorte, uz ili bez evakuacije hematoma.

Ruptura aneurizme je odgovorna za približno 1,5% smrti kod muškaraca preko 55 godina starosti i trinaesti je uzrok smrti po učestalosti u zapadnom svetu. Autopsione studije ukazuju na ukupan mortalitet ovih bolesnika od 90%, ukoliko se uzmu u obzir pacijenti koji ne stignu živi do bolnice. Intrahospitalno preživljavanje preostalih bolesnika, prema podacima objavljenim u literaturi, kreće se u širokom rasponu od 25 do 70% [2].

Preživljavanje ovih pacijenata zavisi od vrste rupture, vremena koje je proteklo od inicijalnih simptoma do ukazivanja prve medicinske pomoći, kao i stizanja u odgovarajuću hiruršku ustanovu koja se bavi aortnom hirurgijom. Smrt u prvih 30 dana nakon operacije uglavnom nastaje zbog disfunkcije nekog vitalnog organa, izolovanog organskog sistema ili, veoma često, zbog multiorganske sistemske disfunkcije [2].

Višedecenijskim analiziranjem velikog broja perioperativnih faktora i pridruženih komorbiditeta, proučavanjem njihove kako pojedinačne, tako i međusobno zavisne povezanosti sa ishodom operacionog tretmana pacijenata sa rAAA, oformljeni su standardizovani skoring-sistemi za procenu perioperativnog rizika. U upotrebi je nekoliko skoring sistema, od kojih se u lite-

INTRODUCTION

An aneurysm is a permanent localized dilation of an artery diameter of at least 50% compared to the normal diameter for a given localization [1]. It can be formed on any arterial blood vessel, but the most common localization is the abdominal aorta, namely its infrarenal segment. Aneurysms can be complicated by rupture, thrombosis, and distal embolization, and the most clinically important and potentially fatal complication is rupture [2]. At infrarenal localization, the most significant complication is rupture. In even 50% of cases, rupture is the first manifestation of an aneurysm [3]. The risk of rupture is related to the size of the aneurysm, gender (it occurs more often in women), the form of the aneurysm, and the presence of parietal thrombotic masses. Smoking and chronic obstructive pulmonary disease are also independent predictors of abdominal aortic aneurysm rupture [2]. Rupture of abdominal aortic aneurysm (hereinafter referred to as rAAA) can manifest itself in the form of retroperitoneal bleeding, intraperitoneal hemorrhage, chronic rupture, aorto-enteric fistula, and aorto-caval fistula. The most common are ruptures into the retroperitoneal and intraperitoneal space. Diagnosis of rAAA is made clinically, with ultrasound or CT angiography [1]. This condition requires urgent surgical treatment to save lives. Treatment can be open surgical or endovascular. The open surgical approach consists of xenophobic laparotomy, intestinal evisceration, proximal and distal vascular control, and reconstruction of the aneurysmatically altered aorta, with or without evacuation of the hematoma.

Aneurysm rupture is responsible for approximately 1.5% of deaths in men over the age of 55 and is the thirteenth leading cause of death in the Western world. Autopsy studies indicate a total mortality rate of 90% if patients who do not make it to the hospital alive are taken into account. Intrahospital survival of the remaining patients, according to data published in the literature, ranges from 25 to 70% [2].

The survival of these patients depends on the type of rupture, the time that elapsed from the initial symptoms to the first medical treatment, as well as, the arrival at the appropriate surgical institution dealing with aortic surgery. Death in the first 30 days after surgery is mainly due to dysfunction of a vital organ, an isolated organ system, or very often, due to multiorgan systemic dysfunction [2].

Decades of analyzing a large number of perioperative factors and associated comorbidities, and studying their individual and interdependent relationships with the outcome of operational treatment of patients with rAAA, standardized scoring systems for perioperative risk assessment have been established. Several

raturi najčešće navode *Vascular-Physiological and Operative Severity score for emUmeration of Mortality and Morbidity (V-POSSUM)*, *Ruptured Abdominal Aortic Aneurysm RAAA-POSSUM* [4], *Hardman index* [4], *Glasgow Aneurysm score* [5], *Dutch aneurysm score* [6], i u novije doba – *Edinburg Ruptured Aneurysm score* [7] i *Vancouver Scoring System* [7]. Svaki od ovih skoring sistema koristi se različitom kombinacijom hemodinamskih, biohemijskih i kliničkih varijabli. Cilj ovih skoring sistema jeste da se pokuša kvantifikovati rizik za svakog pacijenta sa rAAA.

CILJ RADA

Cilj ovog rada jeste da se ispita da li su pojedini perioperativni (preoperativni, intraoperativni, i postoperativni) klinički parametri uticali na ishod hirurškog tretmana pacijenata sa rupturiranom aneurizmom abdominalne aorte.

MATERIJAL I METODE

Sprovedena je retrospektivna studija na osnovu prikupljene medicinske dokumentacije iz arhive Klinike za vaskularnu i transplantacionu hirurgiju i arhive Urgentnog centra Kliničkog centra Vojvodine. Ispitivanje je obuhvatilo dvogodišnji period (01.01.2016.-31.12.2017.). Analizirali smo podatke za sve pacijente koji su zbog rAAA operisani u operativnom bloku Urgentnog centra Kliničkog centra Vojvodine. Kriterijumi za uključivanje u studiju podrazumevali su sledeće: lokalizaciju aneurizme na abdominalnoj aorti i intraoperativno preživljavanje pacijenta, a kriterijumi za isključivanje iz studije su bili lokalizacija aneurizme na torakoabdominalnoj aorti i intraoperativni mortalitet. U posmatranom periodu ukupno je operisano 82 pacijenta sa rAAA. Od toga, za 21 pacijenta, uvidom u njihovu medicinsku dokumentaciju, nisu bili pronađeni adekvatni klinički parametri koji bi odgovarali studiji, te su ovi pacijenti bili izostavljeni iz istraživanja. Od preostalog 61 pacijenta, 4 su preminula intraoperativno što je, uvidom u kriterijume za uključivanje i isključivanje i sledstvenim izuzimanjem ovih pacijenata iz dalje studije, svelo broj uzorka na 57.

Na osnovu praćenja ishoda operacije u prvih 30 postoperativnih dana, sve pacijente podelili smo u dve grupe:

1. pacijenti koji su preživeli 30 dana od operacije
2. pacijenti koji su preminuli u roku od 30 dana od operacije.

Kod pacijenata smo pratili ukupno 22 perioperativna parametra: 9 preoperativnih, 4 intraoperativna i 9 postoperativnih parametara (Tabela 1).

scoring systems are in use, the most commonly cited in the literature *are the Vascular-Physiological and Operative Severity score for emUmeration of Mortality and Morbidity (V)-POSSUM*, *Ruptured Abdominal Aortic Aneurysm RAAA-POSSUM* [4], *Hardman index* [4], *Glasgow Aneurysm score* [5], *Dutch aneurysm score* [6], and more recently – *Edinburgh Ruptured Aneurysm score* [7] and *Vancouver Scoring System* [7]. Each of these scoring systems is used by a different combination of hemodynamic, biochemical, and clinical variables. The goal of these scoring systems is to try to quantify the risk for each patient with rAAA.

THE AIM OF THE WORK

This study aims to examine whether certain perioperative (preoperative, intraoperative, and postoperative) clinical parameters affected the outcome of surgical treatment of patients with ruptured abdominal aortic aneurysm.

MATERIAL AND METHODS

A retrospective study was conducted based on the collected medical records from the archives of the Clinic for Vascular and Transplant Surgery and the archives of the Emergency Center of the Clinical Center of Vojvodina. The study included a two-year period (01.01.2016.-31.12.2017). We analyzed the data for all patients who were due to rAAA operated in the operational block of the Emergency Center of the Clinical Center of Vojvodina. The inclusion criteria in the study involved the following: localization of aneurysms on the abdominal aorta and intraoperative survival of the patient, and the criteria for exclusion from the study were the localization of the aneurysm on the thoracoabdominal aorta and intraoperative mortality. During the study, a total of 82 patients with rAAA were operated on. Of these, for 21 patients, adequate clinical parameters corresponding to the study were not found by examining their medical records, and these patients were omitted from the research. Of the remaining 61 patients, 4 died intraoperatively, which, by examining the inclusion and exclusion criteria, and consequently excluding these patients from further study, reduced the sample to 57.

Based on the monitoring of the outcome of surgery in the first 30 postoperative days, we divided all patients into two groups:

1. Patients who survived 30 days of surgery
2. Patients who died within 30 days of surgery.

In patients, we monitored a total of 22 perioperative parameters: 9 preoperative, 4 intraoperative, and 9 postoperative parameters (Table 1).

Kod svakog pacijenta kod kojeg je na osnovu anamnestičkih i/ili heteroanamnestičkih podataka i kliničkog pregleda i eventualnih dodatnih dijagnostičkih procedura (ultrazvuk, CT angiografija) u sklopu prijemnog odeljenja Urgentnog centra Kliničkog centra Vojvodine postavljena dijagnoza rAAA, hitno su sprovođeni laboratorijski nalazi, te je indikovana hitna hirurška procedura od strane dežurnog vaskularnog hirurga. Ti nalazi obavezno su podrazumevali sledeće kliničke parametre koje smo i obuhvatili našom studijom: hemoglobin (Hgb), hematokrit (Hct), broj trombocita (Tr), serumska urea (Ur), serumski kreatinin (Kr), aktivirano parcijalno tromboplastinsko vreme (APTT), protrombinsko vreme (PT), kalijum (K) i broj eritrocita (Er). Istovremeno je vršeno otvaranje istorije bolesti, obezbeđivanje disajnog puta po potrebi, rezervacija krvi i krvnih derivata, postavljanje periferne i centralne venske linije, arterijske linije, urinarnog katetera, zatim brz transport u operacionu salu.

Indikovana hitna aneurizmektomija je sprovođena od strane vaskularnih hirurga Klinike za vaskularnu i transplantacionu hirurgiju Kliničkog centra Vojvodine, uz saradnju i asistenciju odgovarajućeg medicinskog osoblja. Tokom ove operacione procedure praćene su različite intraoperativne kliničke varijable koje su kumulativno sadržane i evidentirane u protokolu anestezije. Neke od njih koristili smo za potrebe studije, a to su: izmereni intraoperativni gubitak krvi, nadoknada krvi (resuspendovani eritrociti, sveža smrznuta plazma i autologno vraćena krv iz *Cell saver*-a), diureza i intraoperativni pH. Postoperativno, pacijenti su smeštani u jedinice intenzivne terapije Urgentnog centra Kliničkog centra Vojvodine, gde su im tokom boravka svakodnevno, i u više navrata, mereni postoperativni parametri čije smo vrednosti koristili za istraživanje: dvadesetčetvoročasovna diureza, dvadesetčetvoročasovni unos tečnosti, serumska urea (Ur), serumski kreatinin (Kr), kao i sledeće varijable gasnih analiza: pH, kalijum (K), laktati, parcijalni pritisak kiseonika (pO2) i saturacija kiseonikom (sO2). Parametri sa definisanim referentnim vrednostima, kao i klinički promenljive varijable, tabelarno su prikazani (Tabela 1). Referentne vrednosti primenjene u studiji uzete su iz laboratorije Urgentnog centra Kliničkog centra Vojvodine, gde se koriste u svakodnevnoj kliničkoj praksi kao zvanične referentne vrednosti. Koristili smo se podacima koji su obuhvatili prva 24 sata nakon operacije. Preživeli pacijenti bili su premešteni na odeljenje Klinike za vaskularnu i transplantacionu hirurgiju Kliničkog centra Vojvodine. Nakon otpusta pacijenata sa odeljenja, procena o daljem preživljavanju donosila se na osnovu obavezne prve ambulantne kontrole na Specijalističkoj poliklinici Klinike za vaskularnu i transplantacionu hirurgiju Kliničkog centra Vojvodine.

Each patient diagnosed with rAAA, based on anamnestic and/or heteroanamnestic data and clinical examination, and possible additional diagnostic procedures (ultrasound, CT angiography) within the reception department of the Emergency Center of the Clinical Center of Vojvodina, rAAA was diagnosed, had laboratory findings urgently carried out, and urgent surgical procedure was indicated by the on-call vascular surgeon. These findings necessarily implied the following clinical parameters that we included in our study: hemoglobin (Hgb), hematocrit (Hct), platelet count (Tr), serum urea (Ur), serum creatinine (Kr), activated partial thromboplastin time (APTT), prothrombin time (PT), potassium (K), and erythrocyte count (Er). At the same time, the opening of the medical history, provision of the airway as needed, provision of blood and blood derivatives, placement of peripheral and central venous lines, arterial line, urinary catheter, and rapid transport to the operating room were performed.

The indicated emergency aneurysmectomy was performed by vascular surgeons of the Clinic for Vascular and Transplant Surgery of the Clinical Center of Vojvodina, with the cooperation and assistance of appropriate medical staff. During this operational procedure, various intraoperative clinical variables were monitored, which are cumulatively contained and recorded in the anesthesia protocol. Some of them were used for the study, namely: measured intraoperative blood loss, blood compensation (resuspended erythrocytes, fresh frozen plasma, and autologously restored blood from *Cell saver*), diuresis, and intraoperative pH. Postoperatively, patients were placed in intensive care units of the Emergency Center of the Clinical Center of Vojvodina, where postoperative parameters were measured daily and on several occasions whose values we used for research: twenty-four-hour diuresis, twenty-four-hour fluid intake, serum urea (Ur), serum creatinine (Kr), as well as the following variables of gas analysis: pH, potassium (K), lactates, partial oxygen pressure (pO2), and oxygen saturation (sO2). Parameters with defined reference values as well as clinically changeable variables are tabularly presented (Table 1). The reference values applied in the study were taken from the laboratory of the Emergency Center of the Clinical Center of Vojvodina, where they are used in everyday clinical practice as official reference values. We used data that covered the first 24 hours after surgery. The surviving patients were transferred to the Department of the Clinic for Vascular and Transplant Surgery of the Clinical Centre of Vojvodina. After the discharge of patients from the department, the court on further survival was made on the basis of the mandatory first outpatient control at the specialist polyclinic of the Clinic for Vas-

Tabela 1. Klasifikacija posmatranih parametara sa definisanim referentnim vrednostima i varijabli koje su individualno zavisne

Table 1. Classification of observed parameters with defined reference values and variables that are individually dependent

Parametar / *Parameter*	**Referentna vrednost / *Reference value***
Preoperativni / *Preoperative*	
Hemoglobin (g/L) / *Hemoglobin (g/L*	120-160
Hematokrit (L/L) / *Hematocrit (L/L)*	0.37-0.5
Broj trombocita (10X9/l) / *Platelet count (10X9/l)*	140-400
APTT	< 1.3
PT	< 1.3
Serumska urea (mmol/L) / *Serum urea (mmol/L)*	2.2-7.1
Serumski kreatinin (nmol/l) / *Serum creatinine (nmol/l)*	49-115
Kalijum (mmol/L) / *Potassium(mmol/L)*	3.5-5.5
Broj eritrocita(10x12/L) / *Number of erythrocytes(10x12/L)*	3.9-6.0
Intraoperativni / *Intraoperative*	
pH	7.34-7.45
Postoperativni / *Postoperative*	
Diureza (ml) / *Diuresis (ml)*	500-2000
Serumska urea (mmol/L) / *Serum urea (mmol/L)*	2.2-7.1
Serumski kreatinin (nmol/l) / *Serum creatinine (nmol/l)*	49-115
pH	7.34-7.45
Kalijum (mmol/L) / *Potassium (mmol/L)*	3.5-5.5
Laktati / *Elbows*	0.5-1
pO2 (mmHg)	66-100
Saturacija kiseonikom (%) / *Oxygen saturation (%)*	>96%
Intraoperativne varijable / *Intraoperative variables*	
Gubitak krvi (ml) / *Blood loss (ml)*	
Nadoknada krvi (ml) / *Blood compensation (ml)*	
Diureza(ml) / *Diuresis(ml)*	
Postoperativne varijable / *Postoperative variables*	
Unos tečnosti (ml) / *Fluid intake (ml)*	

U sklopu statističke obrade podataka koristili smo se deskriptivnom statistikom kako za obe grupe zajedno, tako i za svaku posebno, te na kraju komparativnom statistikom jedne grupe u odnosu na drugu. Analiza podataka bila je zasnovana na rezultatima testova statističke značajnosti (t-test i ANOVA), korelacija i χ^2 testa i na merama centralne tendencije (aritmetička sredina, medijana i raspon minimalnih i maksimalnih vrednosti). Deskriptivna i komparativna statistika odrađene su u programu Microsoft Office Excel 2007.

cular and Transplant Surgery of the Clinical Center of Vojvodina.

As part of the statistical data processing, we used descriptive statistics for both groups together and for each separately, and finally comparative statistics of one group with the other. The analysis of the data was based on the results of statistical significance tests (t-test and ANOVA), correlations and $\chi 2$ tests, and measures of central tendency (arithmetic mean, median, and range of minimum and maximum values). Descriptive and comparative statistics were done in Microsoft Office Excel 2007.

The research was approved by the Ethics Committee of the Clinical Centre of Vojvodina.

RESULTS

In a total sample of 57, the number of men was 50 (87.72%), while the number of women was 7 (12.28%). Within the age structure where the average age was 69.9 years, the youngest person was 54 years old, while the oldest person was 85. The group of survivors counted 30 patients – 4 women and 26 men, while in the second group, there were 27 patients – 3 women and 24 men (Table 2). By group, the median age was 68.6 for survivors (range 55-85) and deceased 71.3 (range 54-85). The descriptive statistics for both of these groups are presented in a tabular manner (Table 3).

Tabela 2. Demografski podaci ispitivanog uzorka

Table 2. Demographic data of the sample examined

Pol/Grupa	**Broj preživelih**	**Broj preminulih**	**Ukupno**
Muškarci	26	24	50
Žene	4	3	7
Ukupno	30	27	57

Based on the data, it follows that in most patients with rAAA (regardless of their subsequent outcome), just before surgery, hemoglobin, hematocrit, and erythrocyte counts were reduced, while serum urea and creatinine were elevated. It was also found that in patients prothrombin time was prolonged. During the operation, most of the patients were in acidosis. In the first 24 hours after surgery, regardless of the subsequent outcome, urea and creatinine, as well as preoperatively were elevated in most cases. Lactate values were also postoperatively elevated in patients of both study groups. In the conducted research within the preoperative parameters, we obtained the following results (Table 4).

Tabela 3. Deskriptivna statistika za sve pacijente

Table 3. Descriptive statistics for all patients

Varijabla / *Variable*	Srednja vrednost / *Mean*	Medijana / *Median*	Minimum / *Minimum*	Maksimum / *Maximum*
Hgb(g/L)	105.6	105	44	171
HCT(L/L)	0.36	0.318	0.148	0.396
Tr(10x9/L)	186	171	13.7	398
APTT	1.13	1.05	0.76	2.42
PT	1.42	1.27	0.98	3.93
Ur(mmol/L) / *your(mmol/L)*	9.23	8.1	3.9	18.1
Kr(nmol/L)	144.7	133	59	574
K(mmol/l)	4.31	4.3	1.02	6.80
Er(10x12/L)	3.57	3.8	1.63	6.02
Gubitak krvi(ml) / *Blood loss(ml)*	1914.6	1700	300	5500
Nadoknada krvi(ml) / *Blood compensation(ml)*	2006	1980	765	4500
Diureza(ml) / *Diuresis(ml)*	563	420	0	4125
pH	7.21	7.24	6.8	7.44
Diureza(ml) / *Diuresis(ml)*	1551	1700	0	3370
Unos tečnosti(ml) / *Fluid intake(ml)*	6012	5840	0	14665
Ur(mmol/l) / *your(mmol/l)*	9.07	8.4	3.9	19.2
Kr(nmol/l)	154	128	49	569
pH	7.2	7.3	6.84	7.43
K(mmol/l)	4.89	4.75	2.4	7.14
Laktati / *Elbows*	3.95	2.09	21.32	21.32
pO2(mmHg)	116	107.1	247.7	247.7
sO2(%)	92.4	96.5	47.3	100

Istraživanje je bilo odobreno od strane Etičkog odbora Kliničkog centra Vojvodine.

REZULTATI

U ukupnom uzorku od 57, broj muškaraca iznosio je 50 (87,72%), dok je broj žena bio 7 (12,28%). U okviru starosne strukture gde je prosečna starost iznosila 69,9

The mean hemoglobin and hematocrit values in both groups were lower than the reference values, but in the group of deceased, these deviations were more pronounced. Platelet counts in both study groups ranged at reference intervals. The APTT in both groups was in the range of reference values, while the PT in the group of deceased was extended. Serum urea was

Tabela 4. Preoperativni parametri za obe grupe

Table 4. Preoperative parameters for both groups

	Preživeli / *Survived*			Preminuli / *Deceased*		
Parametar / *Parameter*	**Srednja vrednost / *Mean***	**Medijana / *Median***	**Opseg / *Range***	**Srednja vrednost / *Mean***	**Medijana / *Median***	**Opseg / *Range***
Hgb	115.5	116.5	65-155	94.5	88	44-171
HCT	0.34	0.36	0.15-0.46	0.26	0.30	0.14-0.56
Tr	196.95	188	13.7-387	173.92	163	22-398
APTT	1.02	0.98	0.78-1.84	1.26	1.22	0.76-2.42
PT	1.25	1.23	0.98-1.97	1.61	1.40	1.02-3.93
Ur	8.45	7.75	3.9-18.1	10.1	8.7	4.9-17.5
Kr	127.56	113.5	59-333	163.77	143	69-574
K	4.13	4.2	2.4-5.3	4.52	4.6	1.02-6.8
Er	3.76	3.8	2.44-5.04	3.37	3.36	1.63-6.02

godina, najmlađa osoba je imala 54 godine, dok je najstarija osoba imala 85 godina. Grupa preživelih brojala je 30 pacijenata – 4 žene i 26 muškaraca, dok je u drugoj grupi bilo 27 pacijenata – 3 žene i 24 muškarca (Tabela 2). Gledano po grupama, srednja vrednost godina iznosila je 68,6 za preživele (opseg 55-85), a za preminule 71,3 (opseg 54-85). Deskriptivna statistika za obe navedene grupe prikazana je tabelarno (Tabela 3).

Na osnovu podataka proizilazi da su kod većine pacijenata sa rAAA (nezavisno od njihovog kasnijeg ishoda) neposredno pred operaciju vrednosti hemoglobina, hematokrita i broja eritrocita bile snižene, dok su serumska urea i kreatinin bili povišeni. Takođe, ustanovljeno je da je kod pacijenata protrombinsko vreme bilo produženo. Tokom same operacije većina pacijenata bila je u acidozi. U prva 24 časa nakon operacije, nezavisno od kasnijeg ishoda, urea i kreatinin su, kao i preoperativno, bili povišeni u većini slučajeva. Takođe, vrednosti laktata postoperativno su bile povišene kod pacijenata obe studijske grupe. U sprovedenom istraživanju u okviru preoperativnih parametara dobili smo sledeće rezultate (Tabela 4).

Srednja vrednost hemoglobina i hematokrita u obe posmatrane grupe bile su nižih vrednosti u odnosu na referentne vrednosti, s tim da su u grupi preminulih ova odstupanja bila izraženija. Broj trombocita se u obe studijske grupe kretao u referentnim intervalima. APTT je u obe posmatrane grupe bilo u opsegu referentnih vrednosti, dok je PT u grupi preminulih bilo produženo. Serumska urea je bila viša u odnosu na referentne vrednosti u obe grupe, s tim da je u grupi preživelih imala neznatnije odstupanje u odnosu na grupu preminulih. Serumski kreatinin je u grupi preminulih bio znatnije povišen nego kod preživelih pacijenata. Preoperativno izmereni kalijum se u obe studijske grupe pokazao kao parametar koji nije odstupao od fizioloških vrednosti. Broj eritrocita je u obe posmatrane grupe bio snižen, s tim da je u grupi pacijenata sa boljim ishodom bio bliži granici referentnih vrednosti u odnosu na grupu sa letalnim ishodom. Sumarno, svi preoperativni para-

higher than the reference values in both groups, but in the group of survivors, it had a slight deviation from the group of deceased. Serum creatinine was significantly elevated in the group of deceased than in surviving patients. Preoperatively measured potassium in both study groups proved to be a parameter that did not deviate from physiological values. The number of erythrocytes in both groups was lowered, but in the group of patients with better outcomes, it was closer to the benchmark limit compared to the group with lethal outcomes. In sum, all preoperative parameters that deviated from the reference range had a more pronounced deviation in the group with a subsequent lethal outcome.

The collected intraoperative variables for the given patient groups are presented in a tabular manner (Table 5).

Intraoperative blood loss was higher in patients with lethal outcomes, as was blood compensation. Diuresis during the operation had slightly more value in the survivors than in the deceased but without any major differences in these two groups. The intraoperatively measured pH proved to be a parameter that was lowered in both groups, with a greater deviation in later deceased patients.

The collected and statistically processed data for postoperative parameters and variables for both study groups are presented in a tabular manner (Table 6).

The values of diuresis measured in the first 24 hours after surgery in both groups were within physiological values, but with values lower in patients who subsequently died. Fluid intake in both study groups was without any major differences in quantity. Serum urea, as well as serum creatinine in both groups, were above the upper limits of their reference values, with a slightly higher deviation in the group of deceased. The mean postoperatively measured potassium in both groups showed no deviation from the reference values. Lactates were elevated in both groups, with higher values predominant in the group of deceased.

Tabela 5. Intraoperativne vrednosti različitih paramatera i varijabli za obe grupe

Table 5. Intraoperative values of different pairs of amateurs and variables for both groups

	Preživeli / *Survived*			**Preminuli / *Deceased***		
Parametar / *Parameter*	**Srednja vrednost / *Mean***	**Medijana / *Median***	**Opseg / *Range***	**Srednja vrednost / *Mean***	**Medijana / *Median***	**Opseg / *Range***
Gubitak krvi(ml) / *Blood loss(ml)*	1706	1425	300-3800	2147	1700	500-5500
Nadoknada krvi(ml) / *Blood compensation(ml)*	1728	1665	765-4125	2315	2183	900-3880
Diureza(ml) / *Diuresis(ml)*	575	510	0-2800	549	350	0-4500
pH	7.29	7.32	6.94-7.44	7.13	7.15	6.8-7.42

Tabela 6. Postoperativne vrednosti kliničkih parametara i varijabli za obe grupe

Table 6. Postoperative values of clinical parameters and variables for both groups

Parametar / *Parameter*	Preživeli / *Survived*			Preminuli / *Deceased*		
	Srednja vrednost / *Mean*	Medijana / *Median*	Opseg / *Range*	Srednja vrednost / *Mean*	Medijana / *Median*	Opseg / *Range*
Diureza(ml) / *Diuresis(ml)*	1980	1925	150-3370	1074	1150	0-3050
Unos tečnosti (ml) / *Fluid intake (ml)*	5735	5452	0-14665	6319	6775	0-13650
Ur(mmol/L) / *your(mmol/L)*	8.58	7.9	4.0-17	9.62	9.0	3.9-19.2
Kreatinin(nmol/L) / *Creatinine(nmol/L)*	134.36	129	59-303	175.85	128	49-569
pH	7.3	7.34	7.2-7.49	7.08	7.18	6.84-7.32
Kalijum(mmol/L) / *Potassium(mmol/L)*	4.45	4.4	2.4-6.52	5.39	5.5	3.29-7.14
Laktati / *Elbows*	1.62	1.27	0.6-5.56	6.55	4.39	1.7-21.32
pO2(mmHg)	110.27	113.6	32.3-203	122.5	97.3	31.4-247.7
sO2(%)	93.08	96.6	57.8-100	91.8	96	47.3-99.2

metri koji su odstupali od referentnog opsega imali su izraženije odstupanje u grupi sa naknadnim letalnim ishodom.

Prikupljene intraoperativne varijable za date grupe pacijenata prikazane su tabelarno (Tabela 5).

Intraoperativni gubitak krvi bio je veći kod pacijenata sa letalnim ishodom, kao i nadoknada krvi. Diureza u toku operacije je kod preživelih imala nešto više vrednosti nego kod preminulih, ali bez nekih većih razlika u ove dve grupe. Intraoperativno izmereni pH pokazao se kao parametar koji je u obe grupe bio snižen, s tim da je veće odstupanje bilo kod kasnije preminulih pacijenata.

Prikupljeni i statistički obrađeni podaci za postoperativne parametre i varijable za obe studijske grupe prikazane su tabelarno (Tabela 6).

Vrednosti diureze izmerene u prva 24 sata nakon operacije su u obe grupe bile u okviru fizioloških vrednosti, s tim da su ove vrednosti bile niže kod pacijenata koji su naknadno preminuli. Unos tečnosti je u obe studijske grupe bio bez nekih većih međusobnih razlika u količini. Serumska urea, kao i serumski kreatinin su u obe grupe bili iznad gornjih granica svojih referentnih vrednosti, s nešto većim odstupanjem u grupi preminulih. Srednje vrednosti postoperativno izmerenog kalijuma u obe grupe nisu pokazale nikakvo odstupanje od referentnih vrednosti. Laktati su bili povišeni u obe grupe, s predominacijom viših vrednosti u grupi preminulih. Srednje vrednosti pO2 su bile povišene u obe grupe, dok je saturacija bila snižena u obe grupe.

Na osnovu primenjenih statističkih metoda, došlo se do zaključka da su se kao statistički značajni za ishod kod pacijenata sa rAAA pokazali sledeći parametri: hemoglobin, APTT, PT pre operacije; zapremina intraoperativno nadoknađene krvi i vrednost pH tokom operacije; zatim vrednosti kalijuma, laktata i količina diureze nakon operacije.

Mean pO2 levels were elevated in both groups, while saturation was lowered in both groups.

Based on the applied statistical methods, it was concluded that the following parameters were shown as statistically significant for the outcome in patients with rAAA: hemoglobin, APTT, PT before surgery; the volume of intraoperatively compensated blood and the pH value during surgery; and the values of potassium, lactate, and the amount of diuresis after surgery.

DISCUSSION

Treatment of patients with rupture aneurysm is still one of the greatest challenges for both vascular surgeons and anesthesiologists because it is a life-threatening condition, where most of them are elderly patients, with one or more associated comorbidities associate (which, in our region, are often inadequately treated or even before rupture of the aneurysm and admission to a health institution unknown to the patient himself) [2].

The median age of all patients in our study was 69.9, which is slightly lower than in other studies that analyzed age as an outcome prediction factor in patients with rAAA, while male predominance in our study followed the representation of men in other studies of this type. In the study from the Netherlands, the average age was 76 for Amsterdam, and 73 years for Gröningen and Rotterdam, with male predominance by more than 80% for all three cities observed [8]. The average age closer to ours was recorded in Padua, where in a seventeen-year study it was 71.1 years [9]. In a 2004 paper published by Markovic and co-authors, which covered a ten-year period, the average age was 67 years, and the male representation was 83% [10], which is relatively close to our percentage of 87.7% for male patients. In our country, the average age of sur-

DISKUSIJA

Tretman bolesnika sa rupturiranom aneurizmom i dalje je jedan od najvećih izazova, kako za vaskularne hirurge, tako i za anesteziologe iz razloga što se radi o životno ugrožavajućem stanju gde se većinom radi o pacijentima starijeg životnog doba, sa pridruženim jednim ili više komorbiditeta (koji su u našim krajevima često neadekvatno lečeni, ili čak pre rupture aneurizme i prijema u zdravstvenu ustanovu nepoznati samom pacijentu) [2].

Srednja vrednost godina svih pacijenata u našoj studiji iznosila je 69,9, što je za nijansu niže nego u drugim studijama koje su godine starosti analizirale kao faktor predikcije ishoda kod pacijenata sa rAAA, dok je predominacija muškog pola u našoj studiji ispratila zastupljenost muškaraca u drugim studijama ovog tipa. U studiji iz Holandije, prosečna starost iznosila je 76 godina za Amsterdam i 73 godine za Groningen i Roterdam, s predominacijom muškog pola za više od 80% za sva tri posmatrana grada [8]. Prosečna starost bliža našoj zabeležena je u Padovi, gde je u sedamnaestogodišnjoj studiji ona iznosila 71,1 godina [9]. U radu iz 2004., koji su objavili Marković i saradnici, a koja je obuhvatila desetogodišnji period, zabeležena prosečna starost iznosila je 67 godina i zastupljenost muškog pola od 83% [10], što je relativno blizu našem procentu od 87,7% za pacijente muškog pola. Kod nas, prosečna starost preživelih bila je 68,6, a u grupi preminulih iznosila je 71,3. Naučnici iz Finske izneli su podatke koji takođe ne odstupaju mnogo od naših; 70 godina je bila srednja vrednost godina kod preživelih, a 74 kod preminulih [11]. U našoj studiji, starost se nije dokazala kao statistički značajna za ishod.

Nilson (Neilson) i saradnici su za potrebe svoje studije *The Rapid Ruptured Abdominal Aortic Aneurysm score* pratili smrtnost u 30 dana nakon operacije. Kod njih je taj procenat iznosio 32,9% [12]. U već navedenoj holandskoj studiji, smrtnost u prvih 30 dana posle operacije kretala se u rasponu od 26-36%, u zavisnosti od posmatranog grada [8]. Obe ove studije u obzir su uzimale kako pacijente operisane klasičnom aneurizmektomijom, tako i pacijente operisane endovaskularnim tretmanom.

S druge strane, u studiji sprovedenoj u Švajcarskoj koja se bavila isključivo pacijentima operisanim otvorenim hirurškim tretmanom, smrtnost u prvih 30 dana bila je 30% [13]. U devetogodišnjoj studiji koju su sproveli Hili (Healey) i saradnici, smrtnost u prvih 30 dana od operacije iznosila je 33,4%, takođe za otvorenu aneurizmektomiju [14]. Za razliku od studija sprovedenih u zemljama Zapada, studija sličnog karaktera sprovedena u Beogradu (u kojoj su, kao i u našoj studiji, pacijenti bili operisani otvorenom hirurškom tehnikom) imala vivors was 68.6, and in the group of deceased, it was 71.3. Scientists from Finland have presented data that also do not deviate much from ours; the age of 70 was the mean of the years in survivors, and 74 in the deceased [11]. In our study, age did not prove to be statistically significant for the outcome.

Neilson and co-authors, for the purpose of their study on *The Rapid Ruptured Abdominal Aortic Aneurysm score*, tracked mortality for 30 days after surgery. This percentage was 32.9% [12]. In the Dutch study, mortality in the first 30 days after surgery ranged from 26-36%, depending on the city observed [8]. Both of these studies took into account both patients operated on for classical aneurysmurectomy, as well as patients operated on endovascular treatment.

On the other hand, in a study conducted in Switzerland, which looked exclusively at patients with open-label surgical treatment, mortality in the first 30 days was 30% [13]. In a nine-year study conducted by Healey and co-authors mortality in the first 30 days of surgery was 33.4%, also for open aneurysmatomy [14]. Unlike studies conducted in Western countries, a study of a similar character was conducted in Belgrade (in which, as in our study, patients were operated on with an open surgical technique) had a mortality rate similar to ours [15]. In their case, this number was 48.3% while in our study it was 47.3%. Since scientists in countries with higher standards of living have proven that it is not impossible to reduce mortality to below 40% unrelated to the method of surgical approach, and the outcome in our patients is similar to that of the Belgrade study, we can conclude that the quality of health care and health services has a major impact on outcomes in patients with rAAA. More modern technology and a more modern operational approach contribute to a better outcome.

Hemoglobin, which is shown as statistically significant in our study, is a parameter most commonly used in studies of a similar character to assess its correlation with the outcome after surgery. The mean hemoglobin values in our study were 115.5 for survivors, and 94.5 for deceased patients. Davidović and his co-authors proved it as statistically significant for the outcome, in whose work the values in survivors were 111.4, and in the deceased 99.4 [15]. The study was conducted in Switzerland, which had the same number of subjects as ours, for the mean hemoglobin values in survivors were 122.7, and 91.8 in the group of deceased, and was also proven to be statistically significant [13].

The components of the hemostasis system in the preoperative period (APTT, PT) in our study proved to be statistically significant for the outcome. Kawatani and co-authors in their study studied the effect of the

je procenat smrtnosti sličan našem [15]. Kod njih je taj broj iznosio 48,3%, dok je u našoj studiji bio 47,3%. Pošto su naučnici u zemljama sa višim životnim standardom dokazali da nije nemoguće smrtnost svesti na ispod 40% nevezano za način hirurškog pristupa, a ishod kod naših pacijenata je sličan kao u beogradskoj studiji, možemo doći do zaključka da kvalitet zdravstvene zaštite i zdravstvenih usluga ima veliki uticaj na ishod kod pacijenata sa rAAA. Savremenija tehnologija i savremeniji operativni pristup doprinose i boljem ishodu.

Hemoglobin, koji se pokazao kao statistički značajan u okviru našeg ispitivanja, jeste parametar koji se najčešće koristi u studijama sličnog karaktera za procenu njegove korelacije sa ishodom nakon operacije. Srednje vrednosti hemoglobina u našoj studiji iznose 115,5 za preživele, i 94,5 za preminule pacijente. Kao statistički značajnog za ishod dokazali su ga i Davidović i saradnici, u čijem su radu vrednosti kod preživelih iznosile 111,4, a kod preminulih 99,4 [15]. Studija koja je imala isti broj ispitanika kao i naša, a sprovedena u Švajcarskoj, kao srednju vrednost hemoglobina imala je 122,7 kod preživelih i 91,8 u grupi preminulih, i takođe je bila dokazana kao statistički značajna [13].

Komponente hemostaznog sistema u preoperativnom periodu (APTT, PT) su se u našoj studiji pokazale kao statistički značajne za ishod. Kavatani (Kawatani) i saradnici u sklopu svoje studije proučavali su uticaj istih ovih parametara na pacijente operisane endovaskularnom metodom, gde se ovi parametri nisu dokazali kao statistički značajni za ishod [16].

Količina intraoperativno nadoknađene krvi u većini radova je opisana kroz jedinice, to jest kao minimalni broj jedinica transfundovane krvi. U našoj studiji napravljena je mala metodološka razlika. Intraoperativna nadoknada krvi koja se dokazala kao značajna u našoj studiji, bila je izražena u mililitrima, podrazumevajući kako zapreminu jedinice resuspendovanih eritrocita i sveže smrznute plazme, tako i zapreminu autologno vraćene krvi *Cell saver*-om.

Intraoperativno izmerene vrednosti pH u obe naše studijske grupe najvećim delom su se kretale oko 7,29 kod preživelih, i 7,13 kod preminulih. Postoperativno smo mogli primetiti sličnu situaciju – pH je kod najvećeg broja preživelih bio bliži referentnim vrednostima u odnosu na pH preminulih pacijenata.

Brojni radovi se više bave vrednostima uree i kreatinina postoperativno, nego što se baziraju na postoperativnu diurezu. Svakako, na osnovu prikupljenih podataka u okviru naše studije, koji su diurezu nakon operacije pokazali kao statistički značajnu za ishod, možemo reći da su u našem radu pacijenti sa boljim ishodom postoperativno imali više vrednosti diureze u

same parameters on patients operated on endovascular methods, where these parameters were not proven to be statistically significant for the outcome [16].

The amount of intraoperatively compensated blood in most papers is described through units, or the minimum number of units of transfused blood. In our study, a small methodological difference was made. Intraoperative blood compensation, which proved to be significant in our study, was expressed in milliliters, implying both the volume of a unit of resuspended erythrocytes and fresh frozen plasma, as well as the volume of autologously returned blood by Cell saver.

Intraoperatively measured pH values in both of our study groups were largely around 7.29 in survivors, and 7.13 in the deceased. Postoperatively, we were able to observe a similar situation – the pH of most survivors was closer to the reference values compared to the pH of deceased patients.

Several papers deal more with the values of urea and creatinine postoperatively, than they are based on postoperative diuresis. Certainly, based on the collected data within our study, which showed diuresis after surgery as statistically significant for the outcome, we can say that in our work patients with a better outcome postoperatively had higher values of diuresis compared to those with a later lethal outcome. The difference in mean values for both observed groups was over 900ml. The maximum values were also higher in the group of survivors, while in the group of deceased, there was even anuria.

Postoperatively measured lactates in our study proved to be statistically significant for the outcome. In a study conducted by Singhal and associates [17], lactates were also statistically significant, with mean values of 1.9 for survivors, and 7 for the deceased. In our country, these values were 1.62 for survivors, and 6.55 in the group of deceased patients. However, they used the first lactate values measured after surgery for the study, while we used values obtained between 20 and 24 hours after surgery. Lieberg and colleagues pointed out that perioperatively elevated lactate values proved to be determinants of mortality after surgery in patients with rAAA [18].

Combining different clinical, biochemical, and laboratory parameters, numerous studies have been carried out around the world for decades to find the ideal scoring system for assessing outcomes in patients with rAAA. Some of the scores that have previously been applied extensively are *POSSUM, Hardman index,* and *Glasgow Aneurysm score*, with the *Glasgow Aneurysm score* proven to be reliable in predicting outcomes but in elective operations rAAA [19]. *The POSSUM* score consists of two components; physiological variables

odnosu na one sa kasnijim letalnim ishodom. Razlika u srednjim vrednostima za obe posmatrane grupe iznosila je preko 900ml. Maksimalne vrednosti su takođe bile više u grupi preživelih, dok je u grupi preminulih bila prisutna čak i anurija.

Postoperativno izmereni laktati su se u našoj studiji pokazali kao statistički značajni za ishod. U studiji koju su sproveli Singal (Singhal) i saradnici [17] laktati su takođe bili statistički značajni, sa srednjim vrednostima od 1,9 za preživele, i 7 za preminule. Kod nas su te vrednosti iznosile 1,62 za preživele i 6,55 u grupi preminulih pacijenata. Međutim, oni su za studiju koristili prve vrednosti laktata izmerene nakon operacije, dok smo se mi koristili vrednostima dobijenim između 20. i 24. časa nakon operacije. Liberg (Lieberg) i saradnici istakli su da su se perioperativno povišene vrednosti laktata pokazale kao determinante mortaliteta nakon operacije pacijenata sa rAAA [18].

Kombinujući različite kliničke, biohemijske i laboratorijske parametre, u svetu se već decenijama unazad vrše brojna istraživanja u cilju pronalaženja idealnog skoring-sistema za procenu ishoda kod pacijenata sa rAAA. Neki od skorova koji su ranije primenjivani intenzivno jesu *POSSUM, Hardman index* i *Glasgow Aneurysm score*, pri čemu je *Glasgow Aneurysm score* dokazan kao pouzdan u predikciji ishoda samo kod elektivnih operacija rAAA [19]. *POSSUM* skor sastoji se od dve komponente: fizioloških varijabli (godine, prisustvo kardiomiopatije i/ili respiratornih oboljenja, krvni pritisak, puls, *Glasgow coma score*, količina hemoglobina, broj leukocita, urea, natrijum, kalijum, EKG) i 6 operativnih parametara. *Hardman index* sadrži pet parametara – godine, vrednost hemoglobina, koncentraciju serumskog kreatinina, ishemične promene na EKG i prisutnost gubitka svesti [20].

U novije doba pokušava se dobiti skor koji bi imao minimalni broj varijabli koje su brzo i lako dostupne. Skoring-sistem takvog tipa je *Vancouver score* koji se računa na osnovu samo tri podatka – prosečne starosti pacijenta, da li je prisutan gubitak svesti i da li je došlo do zastoja srca. Sličan je i *Edinburgh Ruptured Aneurysm score* čija se vrednost dobija na osnovu procene stanja svesti, vrednosti sistolnog pritiska i hemoglobina preoperativno [7]. U skoring-sisteme novije generacije, sa redukovanim brojem parametara dodaje se i *Dutch Aneurysm score* za čije je računanje bitno razmatrati godine pacijenta, sistolni krvni pritisak, koncentracije hemoglobina, i da li je kod navedenog bolesnika bila potrebna kardiopulmonalna resuscitacija [6].

U poslednjih nekoliko godina rade se i studije na temu upoređivanja različitih skoring-sistema u cilju pronalaženja najboljeg. Iako se ovi skoring-sistemi primenjuju u kliničkoj praksi, ipak nijedan od njih se

(age, presence of cardiomyopathy and/or respiratory diseases, blood pressure, pulse, *Glasgow coma score*, hemoglobin amount, leukocyte count, urea, sodium, potassium, ECG), and 6 operating parameters. *The Hardman index* contains five parameters – years, hemoglobin value, serum creatinine concentration, ischemic changes in ECG, and the presence of loss of consciousness [20].

In recent times, an attempt has been made to obtain a score that would have a minimum number of variables, which are quickly and easily accessible. The scoring system of this type is *the Vancouver score*, which is calculated based on only three data – the average age of the patient, whether there is a loss of consciousness, and whether there was a cardiac arrest. Similar is *the Edinburgh Ruptured Aneurysm score*, whose value is obtained from the assessment of the state of consciousness, and the values of systolic pressure and hemoglobin preoperatively [7]. In scoring systems of the new generation, with a reduced number of parameters, the *Dutch Aneurysm score* is added, for which it is important to consider the patient's age, systolic blood pressure, hemoglobin concentrations, and whether cardiopulmonary resuscitation was required in this patient [6].

In recent years, studies have been done on the topic of comparing different scoring systems, in order to find the best. Although these scoring systems are applied in clinical practice, none of them can be used independently as the only criterion for decisions about whether or not to operate on a patient, as well as what the subsequent outcome will be. Certainly, it would not be ethical to treat patients solely based on a scoring system. Our study does not contain data that would fully correspond to any of the above scoring systems (state of consciousness, systolic blood pressure, comorbidities, leukocyte count, sodium concentration, and cardiological parameters – cardiac arrest, ECG record, and cardiopulmonary resuscitation data), because we could not find data relevant to each of the above parameters in the medical records. The only one of the observed parameters contained in both the scoring systems and our study, that had statistical significance in our study, was hemoglobin. Serum creatinine concentration preoperatively used in the *Hardman index* is not statistically significant. Also, the study did not prove a significant impact of preoperative values of potassium and urea, which are used in calculating the value *of the POSSUM score.*

CONCLUSION

Based on the applied statistical methods, it was concluded that the following parameters were shown as

ne može koristiti samostalno, tj. kao jedini kriterijum za odluke o tome da li pacijenta operisati ili ne, kao i kakav će kasniji ishod biti. Svakako, ne bi bilo ni etički pacijente tretirati samo na osnovu skoring-sistema. Naša studija ne sadrži podatke koji bi u potpunosti odgovarali nekom od navedenih skoring-sistema (stanje svesti, sistolni krvni pritisak, komorbiditeti, broj leukocita, koncentracija natrijuma i kardiološki paramteri – zastoj srca, EKG zapis, i podatak o kardiopulmonalnoj resuscitaciji) iz razloga što u medicinskoj dokumentaciji nismo mogli pronaći podatke relevantne za svaki od navedenih parametara. Jedini od posmatranih parametara sadržan i u skoring-sistemima i u našoj studiji, a koji je imao statistički značaj u našoj studiji bio je hemoglobin. Koncentracija serumskog kreatinina preoperativno, koja se koristi u sklopu *Hardman index*-a, kod nas nije zabeležena kao statistički značajna. Takođe, studijom nismo dokazali značajan uticaj preoperativnih vrednosti kalijuma i uree koji se koriste u računanju vrednosti *POSSUM score*.

ZAKLJUČAK

Na osnovu primenjenih statističkih metoda došlo se do zaključka da su se, kao statistički značajni za ishod kod pacijenata sa rAAA, pokazali sledeći parametri: hemoglobin, APTT, PT pre operacije; zapremina intraoperativno nadoknađene krvi i vrednost pH tokom operacije; kao i vrednosti kalijuma, laktata i količina diureze nakon operacije.

Sukob interesa: Nije prijavljen.

statistically significant for the outcome in patients with rAAA: hemoglobin, APTT, PT before surgery; the volume of intraoperatively compensated blood and the pH value during surgery; and the values of potassium, lactate, and the amount of diuresis after surgery.

Conflict of interest: None declared.

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INTRAOPERATIVNI ULTRAZVUK U LOKALIZOVANJU NEPALPABILNIH LEZIJA DOJKE

SERIJA SLUČAJEVA

CASE SERIES

INTRAOPERATIVE ULTRASOUND IN LOCALIZING NONPALPABLE BREAST LESIONS

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SAŽETAK

Uvod: Intraoperativni ultrazvuk u hirurgiji tumora dojke je relativno novi pristup u lokalizovanju nepalpabilnih tumora. Brojne su prednosti ove tehnike u odnosu na mamografsku preoperativnu lokalizaciju žičanom iglom (*wire needle localisation - WNL),* koja predstavlja standardni pristup u lokalizovanju nepalpabilnih lezija dojke. Pokazalo se da operacije tumora dojke vođene ultrazvukom daju manji procenat pozitivnih ivica resekcije, uz manji volumen ekscidiranog zdravog tkiva dojke oko tumora.

Cilj: Cilj ovog rada je procena uspešnosti ekscizije nepalpabilnih lezija u dojci lokalizovanjem tih lezija intraoperativnim ultrazvukom.

Materijal i metode: Analiza je retrospektivna, obuhvata pacijente operisane na Odeljenju onkološke hirurgije KBC „Bežanijska kosa" u periodu od januara 2013. do decembra 2017. godine. Inkluzioni kriterijum je nepalpabilna lezija kod koje je intraoperativni ultrazvuk bio jedino sredstvo lokalizovanja. Procena uspešnosti identifikovanja i ekscizije nepalpabilnih lezija izražena je u procentima (namera/uspešna realizacija).

Rezultati: Od 2627 pacijentkinja operisanih u ovom periodu, 317 pacijentkinja (11,9%) je imalo nepalpabilne lezije, od kojih su 173 lokalizovane *WNL*, a 144 intraoperativnim ultrazvukom (IOUZ).

Od 144 pacijentkinje kod kojih su lezije lokalizovane IOUZ, 61 je imalo karcinom dojke, a 83 benigne lezije. Na osnovu operativnih nalaza sve nepalpabilne lezije u dojkama su uspešno lokalizovane intraoperativnim ultrazvukom i ekscidirane (144/144 – 100%).

Zaključak: Intraoperativni ultrazvuk predstavlja optimalno sredstvo lokalizovanja ultrazvukom vidljivih nepalpabilnih lezija u dojci kod kojih je indikovana hirurška ekscizija.

Ključne reči: Intraoperativni ultrazvuk, dojka, nepalpabilna lezija

ABSTRACT

Introduction: Intraoperative ultrasound in breast tumor surgery is a relatively new technique used for localizing nonpalpable breast lesions. This procedure has multiple advantages over wire needle localization (WNL), which is a standard approach to localizing nonpalpable breast lesions. It has been shown that intraoperative application of ultrasound is presented with a decrease in tumor-infiltrated resection margins, and with less excised healthy tissue around the tumor.

Aim: The purpose of this article is to evaluate the success rate of nonpalpable breast lesion excisions by localizing them with intraoperative ultrasound.

Material and methods: This is a retrospective study, which involves patients from the Department of surgical oncology at "Bežanijska kosa" treated in the period between January 2013 and December 2017. Medical records of the patients who were not operated on for nonpalpable breast lesions using intraoperative ultrasound were isolated. Success rate of identifying and excising nonpalpable lesions is presented in percentages, so this finding can be compared to other published studies.

Results: Of the 2627 patients operated on during this period, 317 (11.9%) patients had nonpalpable lesions, of which 173 were localized by WNL, and 144 were localized by intraoperative ultrasound (IOUS).

Of 144 patients whose lesions were localized by IOUS, 61 patients had breast cancer, while 83 patients had benign lesions. Based on the medical records, all non-palpable lesions were successfully located and excised with intraoperative ultrasound (144/144- 100%).

Conclusion: Intraoperative ultrasound represents an optimal technique for localizing nonpalpable breast lesions that are visible on ultrasound and are an indication for surgical removal.

Keywords: Intra-operative ultrasound, breast, nonpalpable lesion

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Primljeno • *Received*: October 23, 2023; **Revidirano • *Revised*:** November 20, 2023; **Prihvaćeno • *Accepted*:** November 22, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47287

UVOD

Primena intraoperativnog ultrazvuka u hirurgiji tumora dojke je relativno nov pristup u ovoj oblasti onkološke hirurgije, sa još uvek nedovoljno precizno definisanim principima tehnike izvođenja. U kliničku praksu je uveden kao tehnika lokalizovanja nepalpabilnih tumora [1-12], i u svim publikovanim studijama pokazao je značajnu efikasnost, uključujući i nedavno obavljene studije [13-15]. Takodje je pokazao i značajne komparativne prednosti u odnosu na *WNL*, koja je još uvek standardni pristup u lokalizovanju nepalpabilnih lezija dojke [3-6,10,12,16,17].

Pored ovih prednosti, pokazalo se i da operacije tumora dojke vođene ultrazvukom imaju manji procenat pozitivnih ivica resekcije, uz manji volumen ekscidiranog zdravog tkiva dojke oko tumora. Ove činjenice dovele su do toga da se poslednjih godina intraoperativni ultrazvuk primenjuje i u hirurgiji palpabilnih tumora [14,18-24], u cilju optimizacije resekcione procedure i prevazilaženja nedostataka klasične palpacijom vođene hirurgije. Palpacijom vođena hirurgija je subjektivna tehnika koja daje i do 41% pozitivnih ivica resekcije [24], a sa druge strane nepotrebno veliki volumen ekscidiranog tkiva. Krekel i saradnici su pokazali u *COBALT trial-u* [24] da intraoperativno korišćenje ultrazvuka kod palpabilnih tumora daje za 15% manje pozitivnih ivica resekcije nego palpacijom vođena hirurgija, uz značajno manji volumen preparata (*specimen*), a što bi trebalo da utiče na bolji estetski rezultat operacije i bolji kvalitet života.

U opisima tehnike primene intraoperativnog ultrazvuka većina autora se oslanja na markiranje projekcije tumora na koži dojke pre početka operacije, a kada je operacija u toku proverava se odnos tumora i okolnog tkiva uvlačenjem sonde u ranu. Po završetku ekscizije ultrazvukom se pregleda preparat *ex vivo*, uz naknadne ekscizije zidova lože tumora, ukoliko je neka od ivica resekcije isuviše blizu ivici tumora.

Hirurški tim KBC „Bežanijska kosa" razvio je originalnu tehniku dodatnog intraoperativnog markiranja nepalpabilnih lezija dojke specijalno konstruisanim iglama [25,26], koje se u leziju uvode intraoperativno pod kontrolom ultrazvuka, i predstavljaju stabilni marker nepalpabilne lezije. Ovim se prevazilaze neke neprecizности i nedostaci standardne tehnike upotrebe intraoperativnog ultrazvuka.

Cilj ovog rada je procena uspešnosti ekscizije nepalpabilnih lezija u dojci lokalizovanjem tih lezija intraoperativnim ultrazvukom.

MATERIJAL I METODE

Analiza je retrospektivna i obuhvata pacijente operisane na Odeljenju onkološke hirurgije KBC „Bežanijska

INTRODUCTION

The use of intraoperative ultrasound in breast tumor surgery is a relatively new approach in this field of surgical oncology, and the principles pertaining to the surgical technique are insufficiently defined. It was introduced into clinical practice as a localization technique for nonpalpable tumors [1-12], and in all published studies, including recently conducted ones, it showed significant efficacy [13-15]. It also appeared to have significant advantages over *WNL,* which is still a standard approach to localizing nonpalpable breast lesions [3-6,10,12,16,17].

Apart from these advantages, ultrasound-guided breast surgery has presented with a decreased rate of positive surgical margins and less excised healthy breast tissue around the tumor. In recent years, this has led to the use of intraoperative ultrasound in surgical management of palpable breast tumors as well [14,18-24], with the aim of optimizing the resection procedure and overcoming the imperfections of classic palpation-guided surgery. Palpation-guided surgery is a subjective technique with up to 41% of positive surgical margins [24], and an unnecessarily large volume of excised tissue. Krekel and colleagues showed in the *COBALT trial* [24] that the use of intraoperative ultrasound in palpable tumors resulted in a 15%-decrease in positive surgical margins compared to palpation-guided surgery, as well as a significantly lower volume of the preparation (*specimen*), which should bring about a better esthetic result and better quality of life.

When describing the intraoperative ultrasound technique, most authors rely on projection-marking on the skin of the breast prior to surgery, and during surgery the relationship between the tumor and the surrounding healthy tissue is checked by inserting a probe in the wound. Upon excision, the specimen is examined *ex vivo* using ultrasound, followed by re-excisions of the walls of tumor bed if any surgical margin is too close to the tumor margin.

The surgical team of the University Hospital Medical Centre "Bežanijska kosa" have developed an original technique of additional intraoperative marking of nonpalpable lesions with specially designed needles [25,26], which are intraoperatively inserted into the lesion under the control of ultrasound being stable markers of a nonpalpable lesion. This is how some inaccuracies and shortcomings of intraoperative ultrasound are overcome.

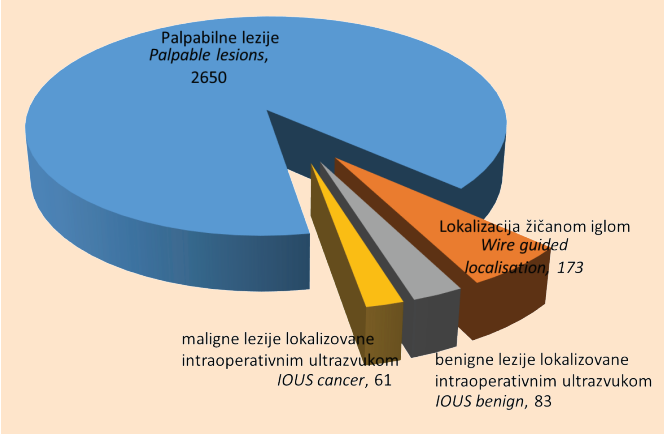
The aim of this paper is to evaluate the success rate of nonpalpable breast lesion excisions by localizing them with intraoperative ultrasound.

kosa“ u periodu od januara 2013. do decembra 2017. godine. Inkluzioni kriterijum je nepalpabilna lezija kod koje je intraoperativni ultrazvuk bio jedino sredstvo lokalizovanja. Procena uspešnosti identifikovanja i ekscizije nepalpabilnih lezija izražena je u procentima (namera/uspešna realizacija).

REZULTATI

U navedenom periodu operisano je 2627 pacijentkinja sa malignim i benignim tumorima dojke. Od toga 317 (11,9%) pacijentkinja je imalo nepalpabilne lezije, od kojih je 173 lokalizovano *WNL („wire needle localisation“)* preoperativnom lokalizacijom na mamografu (većinom su u pitanju mikrokalcifikati, koji se ultrazvukom teško vizualizuju), a 144 intraoperativnim ultrazvukom.

Od 144 pacijentkinje kod kojih su lezije lokalizovane intraoperativnim ultrazvukom 61 je imala karcinom dojke, a 83 benigne lezije. Imajući u vidu da je 6 pacijentkinja imalo dve nepalpabilne lezije, jedna pacijentkinja tri, i jedna četiri nepalpabilne lezije (sve multiple lezije su bile benigne – fibroadenomi), ukupan broj benignih nepalpabilnih lezija je 94 kod 83 pacijentkinje (Prilog I).



Slika 1. Odnos palpabilnih i nepalpabilnih lezija

Figure 1. Ratio of palpable and non-palpable lesions

Na osnovu operativnih nalaza sve nepalpabilne lezije u dojkama su uspešno lokalizovane intraoperativnim ultrazvukom i ekscidirane (144/144 – 100%).

Najmanja lezija bila je promera 4mm (fibroadenom), a najveća 12mm (karcinom – nepalpabilan zbog volumena dojke).

DISKUSIJA

Jedan od najvažnijih pomaka u dijagnostici i lečenju karcinoma dojke poslednjih decenija predstavlja uvođenje skrining programa, koji je u razvijenim zemljama sveta sa visokom incidencom karcinoma dojke iniciran krajem osamdesetih godina XX veka. Efekat skrininga

MATERIAL AND METHODS

A retrospective analysis included patients who were surgically treated at the Department of surgical oncology of the University Hospital Medical Centre “Bežanijska kosa“ in the period between January 2013 and December 2017. The inclusion criterion was a nonpalpable lesion localized only by means of intraoperative ultrasound. The evaluation of successful identification and excisions of nonpalpable lesions is expressed in percentages (intention/successful realization).

RESULTS

During the above-mentioned period, 2627 patients were operated on for malignant and benign breast tumors. A total of 317 (11.9%) patients had nonpalpable lesions out of which 173 were localized with *WNL* (wire needle localization) pre-operatively with the help of mammography (those were mostly microcalcifications that were difficult to visualize with ultrasound), and 144 were localized with intraoperative ultrasound.

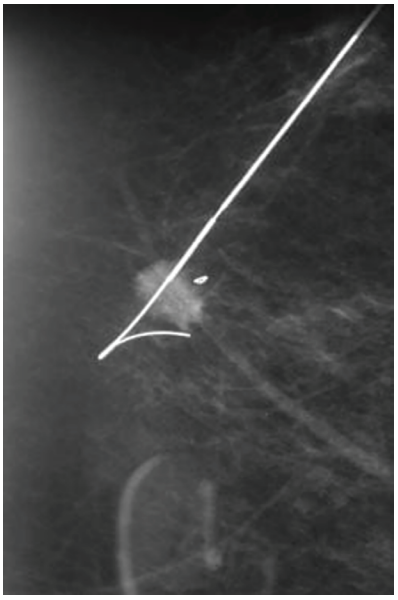
Of the total number of 144 patients whose lesions were localized using intraoperative ultrasound, 61 patients had breast cancer, whereas 83 patients had benign lesions. Considering that there were six patients with two nonpalpable lesions, one patient with three lesions, and one patient with four nonpalpable lesions (all multiple lesions were benign – fibroadenomas), there was a total of 94 benign nonpalpable lesions in 83 patients (Appendix I).

Based on operative findings, all nonpalpable breast lesions were successfully localized using intraoperative ultrasound and then excised (144/144 – 100%).

The smallest lesion was 4mm in diameter (a fibroadenoma), whereas the largest one was 12mm in diameter (nonpalpable carcinoma due to the volume of the breast).

DISCUSSION

The introduction of screening programs, as one of the most important recent achievements, was initiated in developed countries with high cancer incidence at the end of 1980s. The effect of screening on disease control is based on the detection and treatment of a tumor in its early stages, and it is stronger than the effect of any other therapeutic tool developed in the 20th century; breast cancer mortality has been reduced by around 30% in countries with screening programs. Apart from reduced mortality, the detection of tumors in early stages enables surgical treatment with fewer functional and esthetic consequences compared to classical therapeutic procedures, but at the same time it imposes the need to modify classical surgical techniques due

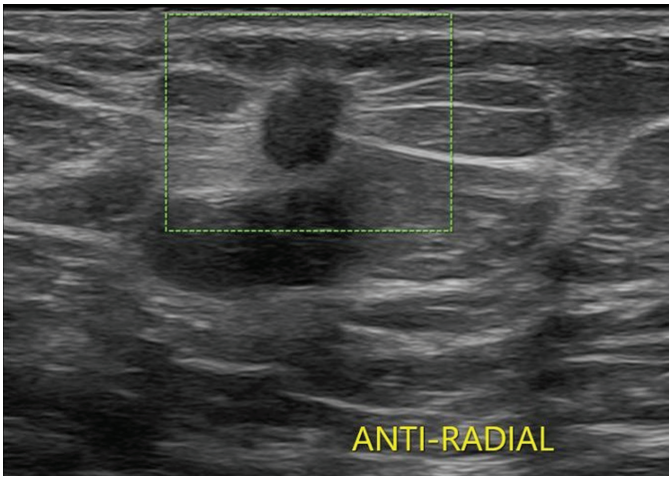


Slika 2. Mamografsko lokalizovanje nepalpabilne lezije žičanom iglom

Figure 2. Mammographic localization of a non-palpable lesion with a wire needle

na kontrolu bolesti je zasnovan na otkrivanju i lečenju tumora u ranijim fazama bolesti, a jači je od bilo kog drugog terapijskog sredstva razvijenog tokom XX veka; za oko 30% je smanjena smrtnost od ove bolesti u zemljama sa skrining programima. Pored smanjene smrtnosti, otkrivanje tumora u ranijim fazama omogućava hirurško lečenje sa manje funkcionalnih i estetskih posledica u odnosu na klasične terapijske procedure, ali u isto vreme nameće potrebu za modifikacijom klasičnih hirurških tehnika zbog otkrivanja proporcionalno većeg broja lezija u dojci koje se zbog malih dimenzija ne palpiraju. Osnovno sredstvo u lokalizovanju i izvodjenju ekscizije lezija dojke u klasičnoj hirurgiji je palpacija.

Hirurgija nepalpabilnih tumora dojke predstavlja novo poglavlje u oblasti hirurgije tumora dojke jer podrazumeva vizualizacionu podršku koju klasična hirurgija ne poznaje. Vizualizacione tehnike koje se koriste u tu svrhu su iste one kojima se tumori dojke dijagnostikuju: mamografija i ultrazvuk. Mamografsko lokalizovanje nepalpabilnih lezija dojke je dominantan pristup, sprovodi se preoperativnim uvodjenjem žičane igle ili radioaktivnog obeleživača u leziju pod kontrolom mamografa, a ti markeri služe hirurgu kao orijentacija u pogledu mestu lezije tokom operacije. Intraoperativni ultrazvuk je mnogo ređe korišćeno sredstvo u lokalizovanju nepalpabilnih lezija u dojci, ali ima značajne komparativne prednosti u odnosu na mamografsko lokalizovanje jer prevazilazi probleme i nedostatke mamografskog (preoperativnog) lokalizovanja: stres pacijentkinje, organizaciono uskladjivanje rada mamografskog kabineta i operacione sale, mogućnost pomeranja markera od trenutka obeležavanja



Slika 3. Ultrazvukom viđen i lokalizovan nepalpabilni tumor dojke

Figure 3. A non-palpable breast tumor seen and localized by ultrasound

to detecting proportionally larger number of breast lesions which are nonpalpable because of small dimensions. Palpation is the basic means of localizing and performing breast lesion excisions in classical surgery.

Nonpalpable breast tumor surgery is a new chapter in the field of breast tumor surgery as it involves visualization support unknown to classical surgery. Visualization techniques used for this purpose are the same techniques that are used for diagnosing breast cancer: mammography and ultrasound. Mammographic localization of nonpalpable breast lesions is a dominant approach, it is carried out by preoperatively introducing a wire needle or a radiographic marker into the lesion during mammography, and surgeons use these markers as orientation regarding the location of the lesion during surgery. Intraoperative ultrasound is less frequently used for localizing nonpalpable breast lesions, but it has significant advantages over mammographic localization as it overcomes the problems and imperfections of mammographic (preoperative) localization: in-hospital stress, coordinating the activities in the mammography room and the ones in the operating theatre, the possibility of marker-migration from the moment of marking to the moment of surgery. The only limitations regarding the application of ultrasound are associated with the surgeon's knowledge and the availability of an ultrasound in the operating theatre, as well as lesions that are not ultrasound-visible.

In this study, we analyzed the use of intraoperative ultrasound in localizing nonpalpable breast lesions over the five-year period in a medical center where intraoperative ultrasound is used routinely. Our aim was to determine the success rate in detecting and adequately removing nonpalpable lesions.

All 155 (100%) preoperatively diagnosed ultrasound-visible nonpalpable lesions in 144 patients (61

do operacije. Jedina ograničenja u primeni ultrazvuka se odnose na edukovanost hirurga i opremljenost hirurške sale ultrazvučnim aparatom, kao i na lezije koje se ne vizualizuju ultrazvukom.

U našem radu analizirali smo upotrebu intraoperativnog ultrazvuka u lokalizovanju nepalpabilnih lezija u dojci u petogodišnjem periodu u medicinskom centru u kome se intraoperativni ultrazvuk rutinski koristi. Naš cilj je bio da utvrdimo procenat uspešnosti nalaženja i adekvatnog uklanjanja nepalpabilnih lezija.

Od 155 preoperativno dijagnostikovanih ultrazvukom vidljivih nepalpabilnih lezija kod 144 pacijentkinje (61 maligna, 94 benigne), koje su operisane pomoću IOUZ lokalizovanja, svih 155 je uspešno identifikovano i hirurški uklonjeno (100%). Ovo je rezultat koji je u skladu sa rezultatima većine publikovanih studija [1-15], gde je procenat uspešnosti lokalizovanja nepalpabilnih lezija intraoperativnim ultrazvukom 100% ili 99%. Ovaj procenat uspešnosti je bolji u odnosu na preoperativno mamografsko lokalizovanje, koje je na osnovu podataka iz literature neuspešno u 2% – 10% slučajeva [3,8].

ZAKLJUČAK

Alternativni modaliteti vizualizacionog lokalizovanja nepalpabilnih lezija u dojci podrazumevaju preoperativno lokalizovanje i obeležavanje mesta lezije plasiranjem obeleživača (žičana igla, radioaktivni obeleživač) ili obeležavanjem mesta projekcije lezije na koži dojke, pod kontrolom ultrazvuka ili mamografije.

Intraoperativno ultrazvučno lokalizovanje nepalpabilnih lezija ima višestruke prednosti nad preoperativnim obeležavanjem: 1) vizualizacija u realnom vremenu, dok traje hirurška procedura; 2) neograničena mogućnost ponavljanja i provere tačnosti lokalizacije nepalpabilne lezije u dojci; 3) nepostojanje rizika migracije markera u vremenu od preoperativnog obeležavanja do izvođenja hirurškog zahvata; 4) nepostojanje rizika nepreciznosti preoperativnog obeležavanja, zbog, na primer, delimično drugačijeg položaja pacijenta tokom preoperativnog obeležavanja u odnosu na položaj pacijenta na operacionom stolu.

Čak i neznatno remećenje pozicije preoperativnog obeležavanja ne može se popraviti nikakvom naknadnom intervencijom na hirurškom stolu, a može voditi neadekvatnoj operaciji, tj. propustu da se iz dojke ukloni nepalpabilna lezija koja je bila cilj operacije.

Ograničenost korišćenja intraoperativnog ultrazvuka u hirurgiji nepalpabilnih lezija u dojci odnosi se na lezije koje se zbog svojih morfoloških karakteristika teško vizualizuju ultrazvukom, pre svega mikrokalcifikati (DCIS). U ovim slučajevima neophodno je preoperativno lokalizovanje takvih lezija mamografom, kao dija-

malignant and 94 benign) who were operated on using intraoperative ultrasound were successfully identified and surgically removed. This result is consistent with the results of most published studies [1-15], where the success rate of localizing nonpalpable lesions using intraoperative ultrasound was 100% or 99%. This success rate is better than in preoperative mammographic localization, which is, according to literature, unsuccessful in 2%-10% of cases [3,8].

CONCLUSION

Alternative modalities of image-guided localization of nonpalpable breast lesions include preoperative localization and marking the site of the lesion by inserting a marker (a wire needle or a radiographic marker), or projection-marking on the skin of the breast under the control of ultrasound or mammography.

Intraoperative ultrasound localization of nonpalpable lesions has multiple advantages over preoperative marking: 1) real-time vizualization, during the surgical procedure; 2) unlimited possibility of repeating and checking the accuracy of the localization of a nonpalpable breast lesion; 3) the absence of the marker-migration risk in the period of time between preoperative marking and the surgical procedure; 4) the absence of the risk of inaccurate preoperative marking due to, for example, a partially different position of the patient during preoperative marking compared to the position of the patient on the operative table.

Even a slight disturbance of the preoperative marking position cannot be corrected by any subsequent intervention on the operative table, and it could lead to inadequate surgery, i.e., a failed attempt to remove the nonpalpable lesion from the breast, which was the initial aim of the surgery.

A limitation in using intraoperative ultrasound in surgical management of nonpalpable breast lesions refers to the lesions that are difficult to visualize with ultrasound due to their morphological characteristics (primarily microcalcifications – DCIS). In these cases, it is necessary to preoperatively localize such lesions using mammography as a diagnostic technique that visualizes such changes well, marking the lesion location with a wire needle.

The optimal quality of nonpalpable breast lesion surgery is achieved by an adequate choice of a localizing technique, whereby intraoperative ultrasound has absolute advantages over preoperative ultrasound localization, except in the case of a lesion that is not ultrasound-visible and is detected by mammography when preoperative marking with the help of mammography should be applied.

Conflict of interest: None declared.

gnostičkom tehnikom koja ove promene dobro vizualizuje, uz obeležavanje lokacije lezija žičanom iglom.

Optimalni kvalitet hirurgije nepalpabilnih lezija u dojci postiže se adekvatnim izborom tehnike lokalizovanja, pri čemu intraoperativni ultrazvuk ima apsolutne prednosti nad preoperativnim ultrazvučnim lokalizovanjem, dok u slučaju ultrazvukom nevidljivih a mamografski detektabilnih lezija treba primeniti preoperativno obeležavanje uz pomoć mamografa.

Sukob interesa: Nije prijavljen.

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FUNKCIONALNI REZULTATI LEČENJA PACIJENATA SA POVREDOM MEKIH TKIVA VOLARNE STRANE RUČNOG ZGLOBA

SERIJA SLUČAJEVA

CASE SERIES

FUNCTIONAL RESULTS IN THE TREATMENT OF PATIENTS WITH SOFT TISSUE INJURIES TO THE VOLAR ASPECT OF THE WRIST

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SAŽETAK

Uvod: Šaka je izuzetno važan deo tela kompleksne anatomije. U njoj se nalaze važni neurovaskularni elementi. Mnoge površinske povrede šake, naizgled trivijalne, često su povezane sa povredama tetiva, nerava i krvnih sudova. Istraživanje se odnosi na povrede mekih tkiva, dok su povrede kostiju isključene iz studije.

Cilj rada: Cilj rada je da se prikaže funkcionalni rezultat lečenja pacijenata sa povredom mekih tkiva volarne strane ručnog zgloba.

Metode: Izvršena je retrospektivna analiza 20 pacijenata lečenih na Odeljenju mikrohirurgije Urgentnog centra u Beogradu. Ispitivali smo: grubu motornu snagu šake (GMS), opseg pokreta, test diskriminacije dve tačke (engl. *two-point discrimination test – 2PD*), a pacijenti su popunjavali Upitnik za procenu invaliditeta ruku, šaka i ramena (*the Disabilities of the Arm, Shoulder and Hand – DASH questionnaire*).

Rezultati: U našoj studiji, GMS povređene ruke bila je 80,9 % snage nepovređene ruke. Srednji opseg pokreta ručnog zgloba, kao i *DIP*, *PIP* i *MCP* zglobova, bio je u rasponu od 77,45 % do 91,6 %, u odnosu na nepovređenu ruku. Senzorni oporavak nivoa S3+ dostiglo je 10 % pacijenata. Prosečni *DASH* skor je bio 19,78.

Zaključak: Naše istraživanje pokazuje da je pravilno i blagovremeno lečenje neophodno za dobar funkcionalni rezultat lečenja ovih povreda.

Ključne reči: gruba motorna snaga, srednji opseg pokreta, senzorni oporavak

ABSTRACT

Introduction: The hand is a very important body part with complex anatomy. Important neurovascular structures are located in the hand. Many superficial injuries of the hand, which may at first glance appear harmless, are often associated with injuries to tendons, nerves, and blood vessels. This paper describes soft tissue injuries, while injuries to the bone have been excluded from the study.

Aim: The aim of this study is to present the functional outcome of the treatment of patients with soft tissue wounds to the volar aspect of the wrist.

Methods: A retrospective analysis of 20 patients treated at the Microsurgery Department of the Emergency Center in Belgrade was performed. We observed the following: gross grip strength (GGS) of the hand, range of motion, the two-point discrimination test (2PD), while the patients filled out the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire.

Results: In our study, the GGS of the injured hand was 80.9% of the strength of the uninjured hand. The mean range of motion of the wrist, as well as of the DIP, PIP, and MCP joints, ranged from 77.45% to 91.6%, as compared to the uninjured hand. An S3+ level of sensory recovery was achieved by 10% of patients. The average DASH score was 19.78.

Conclusion: Our study shows that proper and timely treatment is necessary for a good functional result in the treatment of these injuries.

Keywords: gross grip strength, mean range of motion, sensory recovery

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Primljeno • *Received*: October 20, 2023; **Revidirano • *Revised*:** October 30, 2023; **Prihvaćeno • *Accepted*:** November 8, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47238

UVOD

Anatomski, predeo ručja (*carpus*) čini osam malih kostiju povezanih ligamentima i zglobnim kapsulama. Kosti su poređane u dva reda: gornji red čine *os scaphoideum*, *os lunatum*, *os triquetrum* i *os pisiforme*, dok donji red sačinjavaju *os trapezium*, *os trapezoideum*, *os capitatum* i *os hamatum*. Na prednjoj strani se nalazi vertikalni žleb ručja (*sulcus carpi*) kojeg bočno ograničavaju dva uzvišenja – spoljašnje i unutrašnje. Ova dva ispupčenja povezuje poprečna veza (*retinaculum flexorum s. lig. carpi transversum*). Poprečna veza sa žlebom ručja obrazuje osteofibrozni kanal (lat. *canalis carpi*) kojim prolaze tetive pregibača prstiju kao i *n. medianus* [1]. Devet fleksornih tetiva prolazi kroz karpalni tunel i ulazi u dlan. Tetiva površinskog pregibača se deli blizu metakarpofalangealnih zglobova (lat. *articulationes metacarpophalangeae – MCP*) na dva kraka, između kojih prolazi tetiva dubokog fleksora. Površinski fleksor se pripaja na palmarnoj strani medijalne falange, a duboki fleksor nastavlja put kroz fleksorni kanal do pripoja na palmarnoj strani distalne falange. Fleksorne tetive prolaze kroz fibroosealne kanale [1]. Inervacija potiče od *n. medianus*-a i *n. ulnaris-a* koji prolaze dubokom stranom tetive *m. flexor carpi ulnaris*-a i ulaze u Gijonov kanal. *N. medianus* prolazi ispod i između *m. flexor carpi radialis*-a i *m. palmaris longus*-a i ulazi u karpalni kanal. *Nervus ulnaris* daje senzitivnu inervaciju petog prsta, medijalne polovine četvrtog prsta i njima pripadajućeg dela dlana. U šaci, duboka grana ulnarnog nerva inerviše mišiće hipotenara *(m. opponens digiti minimi, m. abductor digiti minimi, m. flexor digiti minimi brevis*), treći i četvrti lumbrikalni mišić, dorzalne i palmarne interosealne mišiće, *m. adductor pollicis* i duboku granu *m. flexor pollicis brevis*-a, dok superficijalna grana inerviše *m. palmaris brevis*. U šaci, *n. medianus* daje rekurentnu granu za mišiće tenara (*m. opponens pollicis, m. abductor pollicis brevis* i površinski deo *m. flexor pollicis brevis*-a), zajedničke i posebne palmarne grane za prste, koje senzorno inervišu prva tri prsta i radijalnu stranu četvrtog prsta. Arterijsku mrežu krvnih sudova šake formiraju *a. radialis* i *a. ulnaris*. Obe ove arterije se u visini ručja granaju formirajući *arcus palmaris superficialis*. Površinski arkus se nalazi neposredno ispod palmarne fascije, a čine ga površinska grana *a. radialis* (*ramus palmaris superficialis art. radialis*) i *a. ulnaris*. *Ramus palmaris superficialis* daje četiri *aa. digitales palmares communes*, koje se u visini *MCP* zglobova granaju dajući *aa. digitales palmares propriae*. U nivou distalne falange formiraju *rete arteriosum* [2]. Arterija radialis, pre nego što da granu za površinski arkus, daje granu za palac (*a. princeps pollicis*), koja se račva na dve arterije u visini glavice prve metakarpalne kosti. Duboki palmarni arkus obrazuju *a. radialis* i *ramus profundus a. ulnaris*, u

INTRODUCTION

Anatomically, the region of the wrist (Lat. *carpus*) consists of eight small bones connected by ligaments and joint capsules. The bones are arranged in two rows: the upper row consists of the scaphoid bone (Lat. *os scaphoideum*), the lunate bone (Lat. *os lunate*), the *triquetral* bone (Lat. os triquetrum), and the pisiform bone (Lat. *os pisiforme*), while the lower row consists of the trapezium bone (Lat. *os trapezium*), the trapezoid bone (Lat. *os trapezoideum*), the capitate bone (Lat. *os capitatum*), and the hamate bone (Lat. *os hamatum*). On the anterior aspect, there is a vertical carpal groove (Lat. *sulcus carpi*), which is laterally limited by two elevations – external and internal. These two protrusions are connected by a transverse ligament (Lat. *retinaculum flexorum s. lig. carpi transversum*). The transverse connection with the carpal groove forms an osteofibrous canal (Lat. *canalis carpi*) through which the tendons of the flexors of the fingers, as well as the median nerve (Lat. *n. medianus*) pass [1]. Nine flexor tendons pass through the carpal tunnel and enter the palm. The superficial flexor tendon divides near the metacarpophalangeal joints (Lat. *articulationes metacarpophalangeae*; MCP) into two branches. The deep flexor tendon passes between these two branches. The superficial flexor attaches on the palmar side of the medial phalanx, while the deep flexor continues through the flexor canal to its attachment on the palmar side of the distal phalanx. Flexor tendons pass through fibro-osseous canals [1]. Innervation comes from the median nerve and the ulnar nerve (Lat. *n. ulnaris*), which pass along the deep side of the tendon of the *m. flexor carpi ulnaris* and enters the Guyon canal. The median nerve passes underneath and between the *m. flexor carpi radialis* and the *m. palmaris longus* and enters the carpal tunnel. The ulnar nerve provides sensory innervation of the fifth finger, the medial half of the fourth finger, and the corresponding part of the palm. In the hand, the deep branch of the ulnar nerve innervates the hypothenar muscles (*m. opponens digiti minimi, m. abductor digiti minimi, m. flexor digiti minimi brevis*), the third and fourth lumbrical muscles, the dorsal and palmar interosseous muscles, the *m. adductor pollicis*, and the deep branch of the *m. flexor pollicis brevis*, while the superficial branch of the ulnar nerve innervates the *m. palmaris brevis*. In the hand, the median nerve gives off a recurrent branch for the thenar muscles (*m. opponens pollicis*, *m. abductor pollicis brevis*, and the superficial part of the *m. flexor pollicis brevis*), as well as common and individual palmar branches for the fingers, which provide sensory innervation the first three fingers and the radial aspect of the fourth finger. The arterial network of blood vessels of the hand is formed by the ra-

visini baza kostiju područja. Duboki palmarni arkus daje završne grane za mišiće i zglobove [3].

Povrede mekih tkiva, zglobova i kostiju podlaktice su veoma česte na odeljenjima za hitne slučajeve. Postoje velike varijacije u ozbiljnosti povreda, od malih lacerација, koje uključuju samo kožu, do ekstenzivnih povreda, čak i gubitka ekstremiteta. I najtrivijalnije rane mogu biti povezane sa oštećenjem tetive ili nerva, što, ukoliko se propusti, može imati trajne funkcionalne posledice po pacijenta. Iako se istraživanje odnosi na meka tkiva, a ne na povrede kostiju, nije ih moguće u potpunosti odvojiti. U nekim slučajevima, komponenta mekih tkiva je mnogo važnija od preloma, a propust u dijagnostici ima za posledicu loš ishod [4]. Cilj ovog istraživanja je da se prikaže funkcionalni rezultat pacijenata sa povredom mekih tkiva volarne strane ručnog zgloba.

MATERIJALI I METODE

Ovo je retrospektivna studija koja je obuhvatila 20 pacijenata, od kojih 16 muškog a četiri ženskog pola, prosečne starosti 48,25 godina (u rasponu od 35 do 68 godina), lečenih na Odeljenju mikrohirurgije Urgentnog centra, u periodu od 01. 10. 2014. godine do 01.10.2016. godine. Sledeće varijable su analizirane u ovoj grupi pacijenata: pol, godine života, zanimanje, mehanizam povrede, dominantnost ruke i koja je ruka povređivana.

Operisani pacijenti su lečeni unutar 48 sati, u opštoj ili regionalnoj anesteziji. Nakon obrade rane, rađena je sutura tetiva neresorptivnim koncem 2/0, i arterija i nerava koncem 8/0, uz upotrebu mikroskopa. Postoperativno, plasirana je nadlakatna gips šina sa prstima u fleksiji u trajanju od četiri nedelje. Svi pacijenti su primali antibiotsku terapiju, antitetanusnu zaštitu, OHB 12 i niskomolekularni heparin. Posle skidanja imobilizacije pacijenti su upućeni na fizikalnu terapiju.

Procenu smo vršili nakon minimum šest meseci od povređivanja. Merili smo: grubu motornu snagu šake (GMS), opseg pokreta, test diskriminacije dve tačke (engl. *two-point discrimination test – 2PD*), a pacijenti su popunjavali Upitnik za procenu invaliditeta ruku, šaka i ramena (*the Disabilities of the Arm, Shoulder and Hand – DASH questionnaire*). GMS smo testirali dinamometrom. Testirane su povređena i zdrava ruka, a rezultati su izraženi u procentima, u odnosu na nepovređenu ruku. Goniometrom je određivan opseg pokreta u ručnom zglobu, interfalangealnom zglobu (lat. *articulatio interphalangealis – IP*) palca, te distalnom interfalangealnom zglobu (lat. *articulatio interphalangealis distalis – DIP*), proksimalnom interfalangealnom zglobu (lat. *articulatio interphalangealis proximalis – PIP*) i metakarpofalangealnom zglobu (lat. *articulatio metacarpophalangealis – MCP*) ostalih prstiju.

dial artery and the ulnar artery (Lat. *a. radialis* and *a. ulnaris*). Both of these arteries branch off at the level of the palm forming the superficial palmar arch (Lat. *arcus palmaris superficialis*), which is located directly below the palmar fascia, and is made up of the superficial branch of the radial artery (Lat. *ramus palmaris superficialis art. radialis*) and the ulnar artery. The superficial branch of the radial artery gives off four common palmar digital arteries (Lat. *aa. digitales palmares communes*), which branch off at the level of the MCP joints, into the proper palmar digital arteries (Lat. *aa. digitales palmares propriae*). At the level of the distal phalanx, they form the *rete arteriosum* [2]. The radial artery, before giving off a branch for the superficial arch, gives off a branch for the thumb (*a. princeps pollicis*), which branches into two arteries at the level of the head of the first metacarpal bone. The deep palmar arch is formed by the radial artery and the deep palmar branch of the ulnar artery (Lat. *ramus profundus a. ulnaris*), at the level of the bases of the metacarpal bones. The deep palmar arch provides terminal branches for muscles and joints [3].

Injuries to the soft tissues, joints, and bones of the forearm are very common in emergency departments. There is great variation in the severity of the injuries, ranging from small lacerations involving only the skin, to extensive injuries, or even loss of a limb. Even the most trivial wounds can be associated with tendon or nerve damage, which, if missed, can have permanent functional consequences for the patient. Although the present study deals with soft tissue injuries rather than injuries to the bone, it is not possible to completely separate them. In some cases, the soft tissue component of an injury is much more important than the fracture, and failure to diagnose this results in a poor outcome [4]. The aim of this study is to present the functional result of patients with soft tissue injury of the volar side of the wrist.

MATERIALS AND METHODS

This is a retrospective study which included 20 patients, of whom 16 male and four female, with the average age of 48.25 years (ranging from 35 to 68 years), treated at the Microsurgery Department of the Emergency Center, in the period between October 1, 2014 and October 1, 2016. The following variables were analyzed in this group of patients: sex, age, occupation, mechanism of injury, hand dominance, as well as which hand was injured.

The surgically treated patients were operated on within 48 hours, under general or regional anesthesia. After the wound was treated, tendons were sutured with non-absorbable 2/0 thread, while the arteries and

Kako bismo opisali dobijene rezultate, poredili smo ih sa rezultatima za zdravu ruku i predstavili pomoću *total active motion (TAM)* skale, koju je ustanovilo Američko udruženje za hirurgiju šake (engl. American Association for Hand Surgery). Prema ovoj skali, zbir aktivnog opsega pokreta za *MCP*, *PIP*, *DIP* zglobove se poredi sa *TAM* skorom kontralateralne strane ili normom od 260°. Ova skala opisuje četiri kategorije oporavka opsega pokreta: odlično (oporavak 100%), dobro (>75%), srednje dobro (>50%) i loše (<50%). Za praćenje oporavka senzibiliteta koristili smo *MRC* skalu (engl. *Medical Research Council (MRC) Scale for Sensory Recovery Following Peripheral Nerve Injury*) koja uzima u obzir: taktilni senzibilitet, vrednost *2PD*, bolni senzibilitet i prisustvo ili odsustvo hiperestezija. *2PD* test pokazuje najmanje rastojanje u milimetrima koje pacijent još uvek prepoznaje kao dve odvojene tačke. Dobijeni rezultati na *MRC* skali su se kretali od ocene S0, koja je označavala potpuni gubitak osećaja, do S4 koja je podrazumevala kompletan oporavak (diskriminacija dve tačke na rastojanju od 4 mm – 6 mm). Kroz *DASH* upitnik pacijenti su opisivali mogućnost obavljanja svakodnevnih aktivnosti. Rezultati se kreću od 0 – 100, gde je 0 najbolji, a 100 najslabiji rezultat.

REZULTATI

Kada je u pitanju način povređivanja, 12 pacijenata je zadobilo povrede staklom, 6 pacijenata se povredilo brusilicom, dok se dvoje povredilo nožem. Po zanimanju su pacijenti bili sledeće strukture: četiri penzionera, 6 nezaposlenih i 10 fizičkih radnika. Dvanaest pacijenata je povredilo dominantnu ruku. Gruba motorna snaga povređene ruke bila je 80,9 % snage nepovređene ruke (u rasponu od 65,7 % do 97,8%). Srednji opseg pokreta u poređenju sa nepovređenom rukom bio je 116,2° (91,6%) za ručni zglob, dok je za *DIP*, *PIP* i *MCP* zglobove opseg pokreta bio 222,5° (77,45%) za drugi prst, 227,5° (83,05%) za treći prst, 230° (91,2%) za četvrti prst i 218,7° (84,9%) za peti prst. Kod dva pacijenta je postojala i povreda tetive *musculus flexor pollicis* longus-a. U *IP* zglobu palca izmeren je obim pokreta od 90° koliki je bio i na nepovređenoj ruci. Deset pacijenata je imalo povredu *nervus*-a *ulnaris*-a, pet pacijenata je povredilo *nervus medianus*, dok je pet imalo povređena oba nerva. Pet slučajeva od deset tretiranih povreda *nervus*-a *ulnaris*-a je pokazalo senzorni oporavak nivoa S1, četiri su dostigla nivo S2, dok je jedan imao nivo S3+. Među pacijentima sa povredom *n. medianus*-a, četiri su dostigla nivo S3 a jedan je imao nivo S2. Kod pacijenata sa povredom oba nerva, dva su dostigla S3 nivo, dva S2 nivo, a jedan je imao S3+ nivo. Od svih slučajeva, S3+ nivo je dostiglo 10% pacijenata. Prosečan *DASH* skor je bio 19,78 (u rasponu od 51,66 do 0).

nerves were sutured with 8/0 thread, with the use of a microscope. Postoperatively, an above-the-elbow plaster splint was placed, with the fingers in flexion, for four weeks. All patients received antibiotic therapy, protection from tetanus, hydroxocobalamin, and low molecular heparin. After the casts were removed, the patients were referred for physical therapy.

We performed an assessment after a minimum of six months from the injury. We measured the following: gross grip strength (GGS) of the hand, range of motion, the two-point discrimination test (2PD), while the patients filled out the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire. We tested the GGS with a dynamometer. Both the injured hand and the healthy hand were tested, and the results were expressed in percentages, as compared to the uninjured hand. A goniometer was used to determine the range of motion in the wrist, the interphalangeal joint (IP), (Lat. *articulatio interphalangealis*) of the thumb, as well as the distal interphalangeal joint (DIP), (Lat. *articulatio interphalangealis distalis*), the proximal interphalangeal joint (PIP), (Lat. *articulatio interphalangealis proximalis*), and the metacarpophalangeal joint (MCP), (Lat. *articulatio metacarpophalangealis*) of the other fingers.

In order to describe the results that were obtained, we compared them with the results for the healthy hand and presented them using the total active motion (TAM) scale, established by the American Association for Hand Surgery. According to this scale, the sum of the active range of motion for the MCP, PIP, DIP joints is compared with the TAM score of the contralateral side or the 260° norm. This scale defines four categories of range of motion recovery: excellent (100% recovery), good (>75%), fair (>50%), and poor (<50%). To monitor sensory recovery, we used the MRC scale (the Medical Research Council Scale for Sensory Recovery Following Peripheral Nerve Injury), which takes into account: tactile sensitivity, the 2PD value, pain sensitivity, and the presence or absence of hyperesthesia. The 2PD test shows the smallest distance in millimeters that the patient still recognizes as two distinct points. The results on the MRC scale ranged from S0, which indicated complete loss of sensation, to S4, which implied complete recovery (discrimination distance recognition of 4 mm – 6 mm). In the DASH questionnaire, patients described their ability to perform daily activities. The score range is from 0 – 100, with 0 being the best and 100 being the worst score.

RESULTS

Regarding the mechanism of injury, 12 patients were injured by glass, 6 patients were injured by a grinder, while two were injured by a knife. As to the patients'

DISKUSIJA

Povrede volarne strane ručnog zgloba mogu da dovedu do značajnih oštećenja mekih struktura, uglavnom zbog površinske lokalizacije i velikog broja tetiva, živaca i arterija u tom području [5]. Funkcionalni integritet šake zahteva intaktne neurovaskularne strukture i zglobove [6]. Blizina struktura predstavlja veliki izazov u njihovoj identifikaciji. Lečenje je posebno zahtevno u kombinovanim nervno-tetivnim povredama. Postoperativno, međustrukturne adhezije predstavljaju glavni problem. Produžena neaktivnost postoperativno povećava sklonost ka adhezijama, dok rana pokretljivost otežava zarastanje nerava [7]. Naše istraživanje je pokazalo da su se muškarci češće povređivali od žena. Naša studija takođe pokazuje da je češće povređivana dominantna ruka, što je u skladu sa studijom Ogemdija i saradnika [8]. Ova studija pokazuje da je najčešći mehanizam povređivanja bio nožem i staklom, što je pokazalo i naše istraživanje. Takođe, u ovom istraživanju je pokazano da su najčešće povređivani bili državni službenici, dok su u našoj studiji to bili fizički radnici. U našem radu je pokazano da srednji opseg pokreta, za sve opisane zglobove prema *TAM* skali, spada u kategoriju dobro (oporavak >75%), kao što pokazuje i studija Striklanda i saradnika [9]. GMS povređene ruke je u našoj studiji bila 80,9%, što je slično rezultatima Stefaničevog rada u kojem je GMS iznosila 79% [10]. U Časardovom radu, senzorni oporavak nivoa S3+ i više za *n. ulnaris* dostiglo je 26,5% pacijenata, a za *n. medianus* 31% pacijenata, dok naš rad takav oporavak pokazuje kod 10% pacijenata za oba nerva [11]. Prosečan *DASH* skor u ovoj studiji je bio 19,78, koji je u skladu sa rezultatima drugih studija [12,13]. U poređenju sa svetskim radovima (Strikland, Časard, Stefanič i drugi radovi), naši rezultati lečenja su slični ili identični.

ZAKLJUČAK

Povrede volarne strane ručnog zgloba su veoma teške za lečenje zbog velikog broja važnih neurovaskularnih elemenata koji se nalaze u toj regiji. Lezije *n. ulnaris*-a i *n. medianus*-a daju veliki procenat invalidnosti kod pacijenata. Ovo je važno, jer se radi o pacijentima prosečne starosti 48 godina, dakle radno aktivnih, zbog čega je važno pravilno lečiti i dobiti što je moguće bolji funkcionalni rezultat. Korist od toga ima i sam pacijent, ali i država zbog manjih troškova lečenja i mogućnosti pacijenta da nastavi rad u svojoj struci. Pravilno i blagovremeno hirurško lečenje je imperativ za dobar rezultat ovih povreda.

Sukob interesa: Nije prijavljen.

occupation, the group structure was as follows: four pensioners, 6 unemployed persons, and 10 manual workers. Twelve patients injured their dominant hand. The gross grip strength of the injured hand was 80.9% of the GGS of the uninjured hand (ranging from 65.7% to 97.8%). The mean range of motion compared to the uninjured hand was 116.2° (91.6%) for the wrist, while for the DIP, PIP, and MCP joints the range of motion was 222.5° (77.45%) for the second finger, 227, 5° (83.05%) for the third finger, 230° (91.2%) for the fourth finger, and 218.7° (84.9%) for the fifth finger. In two patients, there was an injury to the tendon of the *flexor pollicis longus*. In the IP joint of the thumb, a 90° range of motion was measured, which was the same as in the uninjured hand. Ten patients had an injury to the ulnar nerve, five patients had an injury to the median nerve, while five had injuries to both nerves. Five out of ten cases of treated ulnar nerve injuries showed S1 level sensory recovery, four patients achieved S2 level of recovery, while one had an S3+ level. Among the patients with median nerve injury, four achieved S3 level of recovery, while one had S2 level of recovery. In patients with injury to both nerves, two achieved S3 level, two achieved S2 level, while one achieved S3+ level of recovery. Out of all cases, S3+ level of recovery was achieved by 10% of patients. The mean DASH score was 19.78 (range: 51.66 – 0).

DISCUSSION

Injuries to the volar aspect of the wrist can lead to significant damage to soft-tissue structures, mainly due to the superficial localization and the large number of tendons, nerves and arteries in that area [5]. Functional integrity of the hand requires intact neurovascular structures and joints [6]. The closeness of the structures presents a major challenge in their identification. Treatment is particularly challenging in combined nerve-tendon injuries. Postoperatively, interstructural adhesions are a major problem. Prolonged inactivity postoperatively increases the tendency towards adhesions, while early mobility hinders nerve healing [7]. Our study has shown that men injured themselves more often than women. Our study also shows that the dominant hand is more often injured, which is in keeping with the study by Ogemdi et al. [8]. This study showed that the most common mechanisms of injury were knife and glass injuries, which our study has also shown. Additionally, this study showed that civil servants were injured most frequently, while in our study it was manual workers being injured the most. In our study, the average range of motion, for all the described joints, according to the TAM scale, fell into the category of good (recovery >75%), as also shown by the study

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by Strickland et al. [9]. The GGS of the injured hand in our study was 80.9%, which is similar to the results obtained in the study by Stefanich et al., where the GGS was 79% [10]. In the study by Chassard et al., sensory S3+ level recovery and higher for the ulnar nerve was achieved by 26.5% of patients, and by 31% of patients for the median nerve, while our study has shown such recovery in 10% of patients for both nerves [11]. The average DASH score in the present study was 19.78, which is consistent with the results of other studies [12,13]. When compared to other international studies (Strickland, Chassard, Stefanich, and other studies), our treatment results are similar or identical.

CONCLUSION

Injuries to the volar aspect of the wrist are very difficult to treat because of the large number of important neurovascular elements located in that region. Lesions to the ulnar nerve and the median nerve cause a high percentage of disability in patients. This is important, because these are patients with an average age of 48 years, i.e. working individuals, which is why it is important to treat them properly and get the best possible functional result. Both the patient and the state benefit from this, due to lower treatment costs and the patient's ability to continue working in his/her profession. Proper and timely surgical treatment is imperative for a good outcome in these injuries.

Conflict of interest: None declared.

SITUS INVERSUS TOTALIS: POGLED NA SLIKU U OGLEDALU

PRIKAZ SLUČAJA

CASE REPORT

SITUS INVERSUS TOTALIS: AN OVERVIEW OF THE MIRROR IMAGE

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SAŽETAK

Uvod: Situs inversus totalis (SIT) je redak fenomen i incidenca ovog stanja se kreće od 1:10,000 do 1:20,000 osoba. Radi se o stanju u kome je raspored unutrašnjih organa slika u ogledalu normalne anatomije. Može se javiti samostalno ili kao deo sindroma sa drugim nepravilnostima. Urođene srčane mane su prisutne kod oko 5-10% ovakvih osoba. Osnovni uzrok i genetika situs inversusa su složeni.

Prikaz slučaja: Pacijentkinja starosti 69 godina, upućena je u maju 2023. godine na Odeljenje opšte hirurgije radi operacije ventralne kile. Ovo je njena treća hospitalizacija na istom odeljenju; tokom 1998. godine imala je operaciju slepog creva, a u 2018. godini pacijentkinji je zbog kalkuloze žučne kese urađena holecistektomija.

Nakon prijema pacijentkinja je upućena na CT toraksa i abdomena, kako bi se potvrdila tačna anatomija, s obzirom da je od ranije bila upoznata sa svojim stanjem i postojanjem situs insversusa. Prilikom CT pregleda potvrđen je raspored trbušnih organa kao slika u ogledalu normalne anatomije i srce na desnoj strani grudnog koša.

Zaključak: Većina osoba sa SIT vodi potpuno normalan život. Očekivani životni vek i rizik od dobijanja stečenih bolesti su slični kao kod osoba iz opšte populacije. U određenom broju slučajeva postoji povezanost sa pojedinim patološkim entitetima. Kod pacijenata sa prisustvom SIT uobičajeni uzroci akutnog abdominalnog bola često dovode do pogrešnih zaključaka, a lokalizacija uzroka bola u stomaku je izuzetno komplikovana i teška. Identifikovanje osoba sa SIT omogućava da se smanje rizici tokom hirurških zahvata i interventnih procedura.

Ključne reči: situs inversus, dextrocardia, slika u ogledalu

ABSTRACT

Introduction: Situs inversus totalis (SIT) is a rare phenomenon and the incidence of this condition ranges from 1:10.000 to 1:20.000 people. It is a condition in which the arrangement of internal organs is a mirror image of normal anatomy. It can occur independently or as part of a syndrome with other abnormalities. Congenital heart defects are present in about 5-10% of such individuals. The underlying cause and genetics of situs inversus are complex.

Case report: A 69-year-old female patient was referred to the Department of General Surgery in May 2023 for ventral hernia surgery. This was her third admission to the same department; in 1998, she had appendectomy, and in 2018, the patient underwent a cholecystectomy due to gallbladder calculus.

Upon admission, the patient was referred for a CT scan of the thorax and the abdomen, in order to confirm the correct anatomy, given that she was already familiar with her condition and the existence of situs inversus. During the CT examination, the arrangement of the abdominal organs was confirmed as a mirror image of normal anatomy with the heart on the right side of the chest.

Conclusion: Most people with SIT live completely normal lives. Life expectancy and risk of acquired diseases are similar to those of the general population. In a certain number of cases, there is a connection with certain pathological entities. In patients with SIT, common causes of acute abdominal pain often lead to wrong conclusions, and the localization of the cause of abdominal pain is extremely complicated and difficult. Identifying people with SIT makes it possible to reduce risks during surgical procedures and interventional procedures.

Keywords: situs inversus, dextrocardia, mirror image

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Primljeno • *Received*: November 22, 2023; **Revidirano • *Revised*:** December 3, 2023; **Prihvaćeno • *Accepted*:** December 12, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47845

UVOD

Terminološki izraz „situs" u medicinskoj literaturi podrazumeva položaj srca, odnosno pretkomora srca i unutrašnjih organa u telu [1].

Ovaj koncept se odnosi i na konfiguraciju asimetrične anatomske strukture kod pojedinca, a postoje tri moguća oblika: situs solitus (normalna anatomija), situs inversus (raspored unutrašnjih organa poput slike u ogledalu uobičajene, normalne anatomije) i situs ambiguous. U situs solitusu, desno plućno krilo ima tri režnja i bronh iznad plućne arterije, dok levo plućno krilo ima dva režnja sa bronhom ispod plućne arterije. Veći režanj jetre se nalazi sa desne strane, a želudac i slezina sa leve strane abdomena. Morfološka leva pretkomora je levo od morfološke desne pretkomore. Kod postojanja situs inversusa levo plućno krilo ima tri režnja, a desno dva režnja; veći režanj jetre je na levoj strani, želudac i slezina su na desnoj strani tela, a morfološka leva pretkomora je desno od morfološke desne pretkomore [2].

Između ova dva entiteta, situs solitusa (normalnog anatomskog rasporeda) i situs inversus totalisa (obrnutog rasporeda unutrašnjih organa, slike normalne anatomije u ogledalu), leži spektar situs ambiguousa (nedeterminisanog rasporeda), koji se karakteriše izomerijom, heterotaksijom i višestrukim malformacijama u jednom ili više torakalnih ili trbušnih organa [3].

Situs inversus je kategorisan kao heterotaksijski sindrom, koji je rezultat neuspešnog uspostavljanja normalne levo-desne asimetrije tokom embrionalnog razvoja i povezan je sa nizom srčanih i ekstrakardijalnih urođenih anomalija. Rotacija za 270 stepeni u smeru kazaljke na satu umesto normalnih 270 stepeni suprotno od kazaljke na satu prilikom razvoja torako-abdominalnih organa embriona rezultuje njihovim pozicioniranjem u toraksu i abdomenu nalik slici u ogledalu [4].

Raspored unutrašnjih organa kod situs inversusa je slika u ogledalu normalne anatomije. Može se javiti samostalno (izolovano, bez drugih abnormalnosti ili stanja) ili kao deo sindroma sa raznim drugim nepravilnostima. Urođene srčane mane su prisutne kod oko 5-10% ovakvih osoba. Osnovni uzrok i genetika situs inversusa su složeni, a u literaruri su opisani i porodični slučajevi [5].

Reč je o izuzetno retkom fenomenu i incidenca ovog stanja se prema podacima iz literature kreće od 1:10,000 do 1:20,000 osoba [6], bez razlike u učestalosti kod žena i muškaraca i među pripadnicima različitih rasa [7,8].

Između ostalih gena, u nastanak ovog fenomena uključen je i gen na dugačkom kraku hromozoma 14, koji se prenosi autozomno recesivno sa nepotpunom penetracijom [9].

INTRODUCTION

In medical literature, the term situs implies the position of the heart, i.e. its atria and the internal organs of the human body [1].

This concept also refers to the configuration of an asymmetrical anatomical structure in an individual, and there are three possible forms: situs solitus (normal anatomy), situs inversus (the arrangement of the internal organs is a mirror image of the usual, normal anatomy), and situs ambiguous. In situs solitus, the right lung has three lobes and a bronchus above the pulmonary artery, whereas the left lung has two lobes and a bronchus below the pulmonary artery. The larger lobe of the liver is on the right, and the stomach and spleen are located on the left side of the abdomen. The morphological left atrium is to the left of the morphological right atrium. In situs inversus, the left lung has three lobes, and the right lung has two lobes; the larger lobe of the liver is on the left, and the stomach and the spleen are located on the right side of the body; the morphological left atrium is to the right of the morphological right atrium [2].

Between these two entities, situs solitus (the normal anatomical arrangement) and situs inversus totalis (reversed internal organs, a mirror image of the normal anatomy), there lies the spectrum of situs ambiguous (indeterminate anatomical arrangement), which is characterzed by isomerism, heterotaxy and multiple malformations in one or more thoracic or abdominal organs [3].

Situs inversus is categorized as heterotaxy syndrome, which results from a failure to form normal asymmetry along the left-right axis during the embryonic development and it is associated with a number of cardiac and extracardiac congenital anomalies. The 270-degree clockwise rotation instead of the normal 270-degree counterclockwise rotation during the development of the thoraco-abdominal organs of the embryo results in their mirror-image positioning in the thorax and the abdomen [4].

The arrangement of the internal organs in situs inversus is a mirror-image of normal anatomy. It can occur independently (isolated, without any other anomalies or conditions), or as part of a syndrome with various other abnormalities. Congenital heart defects are present in about 5-10% of such individuals. The underlying cause and genetics of situs inversus is complex, and some familial cases have been described in literature as well [5].

It is an extremely rare phenomenon and, according to literature data, the incidence of this condition ranges from 1:10.000 to 1:20.000 individuals [6], with no difference in frequency in males and females and in members of different races [7,8].

Trenutni stav među istraživačima je da su rotacija organa i njihova migracija tokom embrionalnog razvoja rezultat lanca signala. Sekrecija proteina pod nazivom „Sonic hedgehog" (Shh) utiče na ekspresiju dva transformišuća faktora rasta, koji se nazivaju Nodal i Lefti. Kada se ovi proteini luče na levoj strani embriona, srce se okreće udesno, što rezultuje situs solitusom. Ako se Shh protein luči na desnoj strani, srce se okreće ulevo, što dovodi do situs inversusa. Ako se ovaj protein luči sa obe strane, signal je nejasan; 50% takvih slučajeva će rezultovati situs solitusom, a kod 50% slučajeva će nastati situs inversus. Međutim, ostaje neizvesno šta uzrokuje proizvodnju Shh proteina. Nedavno je identifikovan gen pod nazivom Pitk2, koji kontroliše lučenje proteina Shh i Nodal [10].

Da je nasledna komponenta svakako prisutna i da postoje porodični slučajevi, potvrđuju Herera Ortiz i saradnici, koji opisuju 46-godišnju pacijentkinju sa SIT i akutnom upalom žučne kese, čijoj je sestri takođe dijagnostikovano ovo stanje [11].

SIT takođe može da bude povezan sa drugim entitetima kao što su prekid vene kave, Kartagener sindrom, Ivemark sindrom i Yoshikawa sindrom. Procenjuje se da blizu 25% pacijenata sa SIT-om i dekstrokardijom ima i Kartagener sindrom [11].

Primarnu cilijarnu diskineziju (PCD), poznatu i kao Kartagenerov sindrom, karakteriše sledeća trilogija: dekstrokardija, rekurentni sinusitis i bronhiektazije; pacijenti muškog pola su skoro infertilni zbog slabije pokretljivosti spermatozoida. Incidenca ovog autozomnog recesivnog sindroma je oko 1/30.000 živorođenih [12].

Kod primarne cilijarne diskinezije postoje mutacije koje remete pokretljivost cilija, organela sličnih dlakama, koje sa površine ćelije uranjaju u vanćelijski prostor. One se viđaju u različitim tkivima uključujući respiratorni epitel, a poremećaj njihove pokretljivosti može izazvati simptome kao što su hronični bronhitis, inflamirani ili inficirani sinus [13].

Pacijenti sa ovim sindromom često tokom godine imaju više epizoda infekcija respiratornog trakta i egzacerbacije bronhiektazija usled lošeg mukocilijarnog klirensa, a kod pojedinih muških pacijenata javlja se i sterilitet zbog diskinezije spermatozoida [14].

Ivemarkov sindrom je retko urođeno stanje koje se odražava na više sistema organa u telu. Klasifikovan je kao heterotaksijski poremećaj ili poremećaj lateralnosti. Ovi termini se odnose na neuspeh unutrašnjih organa grudnog koša i abdomena da budu raspoređeni na odgovarajuće mesto u telu. Karakteriše ga potpuno odsustvo (asplenija) ili nerazvijenost (hipoplazija) slezine, srčane malformacije i abnormalni raspored unutrašnjih organa grudnog koša i abdomena [15].

Among other genes, a gene on the long arm of chromosome 14, which is inherited as autosomal recessive with incomplete penetration, is involved in the origin of this phenomenon [9].

Researchers currently believe that the rotation of organs and their migration during embryonic development are the result of a chain of signals. The secretion of a protein called "Sonic hedgehog" (Shh) affects the expression of two transforming growth factors, Nodal and Lefty. When these proteins are secreted on the left side of the embryo, the heart turns to the right, resulting in situs solitus. If Shh protein is secreted on the right side, the heart turns to the left, bringing about situs inversus. When this protein is secreted on both sides, the signal is unclear; 50% of such cases will result in situs solitus, and 50% of cases will result in situs inversus. However, it remains unclear what causes Shh to be produced. A gene called PITX2, which controls the secretion of Shh and Nodal proteins, has been identified recently [10].

Herrera Ortiz and colleagues confirmed the presence of a hereditary component and the existence of familial cases; they described a 46-year-old patient with SIT and acute inflammation of the gallbladder whose sister had also been diagnosed with this condition [11].

SIT can also be associated with other entities such as vena caval interruption, Kartagener's syndrome, Ivemark syndrome, and Joshikawa syndrome. It is estimated that approximately 25% of patients with SIT and dextrocardia also have Kartagener's syndrome [11].

Primary ciliary dyskinesia (PCD), also known as Kartagener's syndrome, is characterized by the following conditions: dextrocardia, recurrent sinusitis and bronchiectasis; male patients are almost infertile due to lower sperm motility. The incidence of this autosomal recessive syndrome is around 1/30.000 live births [12].

In primary ciliary dyskinesia there are mutations that disrupt the motility of cilia, hair-like organelles, which plunge from the cell surface to the extracellular space. They are found in a variety of tissues including the respiratory epithelium, and disruption of their motility can cause symptoms such as chronic bronchitis, inflamed or infected sinuses [13].

Patients with this syndrome often have several episodes of respiratory tract infections and exacerbation of bronchiectasis due to poor mucociliary clearance during the year, and some male patients also experience infertility due to sperm dyskinesia [14].

Ivemark syndrome is a rare congenital condition that affects multiple organ systems in the body. It is classified as heterotaxy syndrome or laterality disorder.

Yoshikawa's sindrom karakteriše prisustvo SIT-a, postojanje bilateralne renalne displazije, pankreatičnih fibroza i mekonijalnog ileusa [16].

Situs inversus totalis može da bude povezan i sa drugim brojnim pridruženim kongenitalnim anomalijama kao što su duodenalna atrezija, asplenizam, postojanje multiplih slezina, ektopični i potkovičasti bubrezi, te druge plućne i vaskularne abnormalnosti [1].

PRIKAZ PACIJENTA

Pacijentkinja starosti 69 godina, dobrog opšteg stanja, upućena je na Odeljenje opšte hirurgije radi operacije postoperativne incizione ventralne kile.

Ovo je njena treća hospitalizacija na istom odeljenju; anamnestički je dobijen podatak da je tokom 1998. godine zbog akutnog bola u stomaku imala operaciju slepog creva. O ovoj najranijoj hospitalizaciji pacijentkinja ne poseduje medicinsku dokumentaciju.

Tokom svoje druge hospitalizacije u 2018. godini, pacijentkinja je nakon epizode bolova u epigastrijumu usled kalkulozne žučne kese i posle ultrazvučnog pregleda abdomena informisana o postojanju SIT i reverzne anatomije. U tom trenutku je njena starost iznosila 64 godine. Operacija žučne kese je planirana i započeta laparoskopski, ali je tokom operativnog zahvata radi bolje vizualizacije i orijentacije doneta odluka da se uradi medio-medijalna laparotomija i konverzija zahvata u klasičnu, "otvorenu" holecistektomiju. Postoperativni tok je protekao uz blagu potkožnu infekciju, a nakon tri nedelje je otpuštena sa odeljenja oporavljena.

U maju 2023. godine je hospitalizovana po treći put na Odeljenju opšte hirurgije radi hirurškog lečenja postoperativne, neukleštene i negangrenozne postoperativne incizione hernije na prednjem trbušnom zidu, a na mestu operativnog reza od prethodne operacije. Laboratorijska evaluacija je pokazala da su kod pacijentkinje hematološki i biohemijski parametri unutar opsega normalnih vrednosti. Na preoperativnom CT grudnog koša prikazana je dekstrokardija, bez prisustva bronhiektazija. Inače je pacijentkinja anamnestički negirala hronični kašalj, nazalnu kongestiju i česte upale sinusa, čime je isključena povezanost sa Kartagenerovim sindromom.

Istovremeno je urađen i CT abdomena kako bi se potvrdila tačna anatomija, s obzirom na to da je pacijentkinja nakon prethodne hospitalizacije na ovom odeljenju bila upoznata sa svojim stanjem i postojanjem situs insversusa. Prilikom CT pregleda potvrđen je raspored trbušnih organa kao slika u ogledalu normalne anatomije, sa jetrom na levoj strani i slezinom na desnoj strani hipohondrijuma (Slika 1 i 2). Nije uočena nijedna druga kongeniitalna anomalija, kao ni postojanje neke vaskularne abnormalnosti.

These terms refer to the failure of the internal organs of the thorax and the abdomen to be arranged in their appropriate positions in the body. This syndrome is characterized by complete absence (asplenia) or underdevelopment (hypoplasia) of the spleen, cardiac malformations, and abnormal arrangement of the internal organs of the thorax and the abdomen [15].

Yoshikawa's syndrome is characterized by the presence of SIT, bilateral renal dysplasia, pancreatic fibrosis, and meconium ileus [16].

Situs inversus totalis may be linked to a number of other associated congenital anomalies such as duodenal atresia, asplenia, multiple spleens, ectopic and horseshoe kidneys, and other pulmonary and vascular abnormalities [1].

CASE REPORT

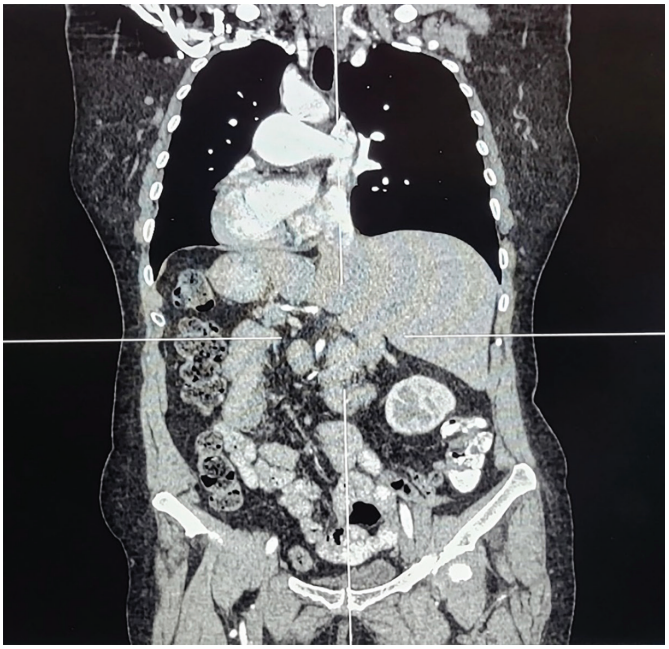
A 69-year-old female patient, in good general condition, has been referred to the Department of General Surgery for postoperative incisional ventral hernia surgery.

She was admitted for the third time to the same ward; through history taking it was found out that she had had appendectomy in 1998 due to acute pain. The patient had no medical documentation about the first admission.

During her second stay at the department in 2018, the patient was informed of the existence of SIT and the reverse anatomy after she had experienced epigastric pain due to gallbladder calculus and undergone ultrasound examination of the abdomen. She was 64 years old then. Gallbladder surgery was planned and started as a laparoscopic procedure, but for better visualization and orientation, a decision was made to perform a midline laparotomy and turn the procedure into classical, "open" cholecystectomy. The postoperative course was accompanied by mild subcutaneous infection, and three weeks later she was discharged fully recovered.

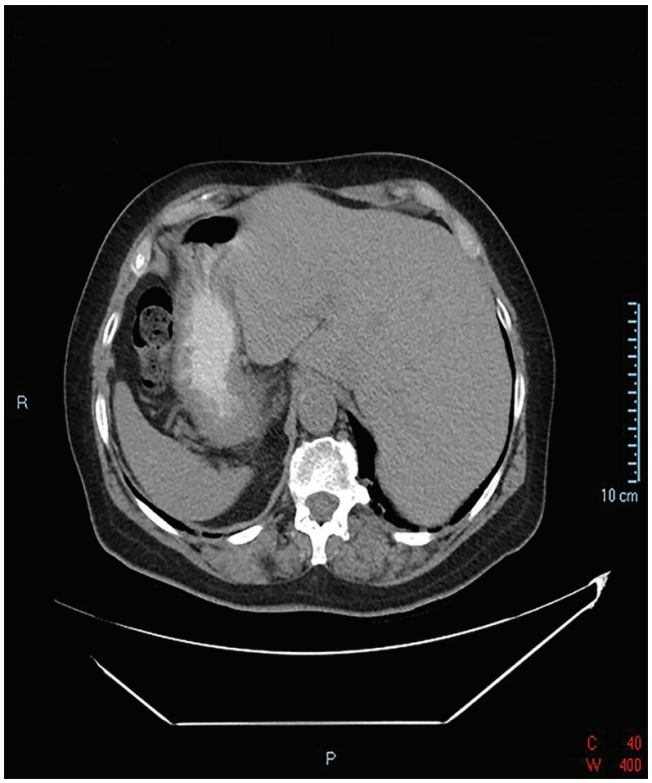
In May 2023 she was admitted to the Department of General Surgery for the third time, for surgical treatment of non-strangulated, non-gangrenous postoperative incisional hernia on the anterior abdominal wall, at the site of the surgical incision from the previous surgery. Laboratory tests showed that the patient's hematological and biochemical parameters were within reference ranges. A preoperative chest CT showed dextrocardia, with no bronchiestasis. The patient denied chronic cough, nasal congestion and frequent sinus infections, which rulled out the presence of Kartagener's syndrome.

At the same time, a CT scan of the abdomen was performed in order to determine the correct anatomy



Slika 1. CT abdomena, frontalni presek

Figure 1. CT of the abdomen, frontal section



Slika 2. CT abdomena, horizontalni presek

Figure 2. CT of the abdomen, horizontal section

Od pacijentkinje je dobijena pismena saglasnost za sprovođenje planirane procedure i detaljno su joj objašnjeni rizici od potencijalnih komplikacija. Herniotomija i rekonstrukcja zida abdomena urađeni su sa prolenskom mrežicom po metodi Rives-Stoppa, „sublay" tehnikom, u opštoj anesteziji uz predhodno informisanje svih članova hirurškog i anesteziološkog tima o specifičnom stanju pacijentkinje. Prisustvo samog SIT nije imalo neposrednog uticaja na tok anestezije, organizaciju operativnog zahvata, kao ni na odabir operativne tehnike.

Postoperativno je pacijentkinja lečena infuzionom, analgetskom, antibiotskom i antiagregacionom terapijom. Nakon deset dana hospitalizacije otpuštena je na kućno lečenje potpuno oporavljena i u dobrom opštem stanju.

DISKUSIJA

Osobe koje imaju situs inversus sa dekstrokardijom, bez drugih propratnih urođenih anomalija imaju normalan očekivani životni vek i sličan rizik od dobijanja stečenih bolesti kao i druge osobe koje su iste starosne dobi i pola. U retkim slučajevima kod osoba kod kojih postoje i srčane anomalije, očekivano trajanje života se smanjuje, u zavisnosti od težine defekta [17].

Pojedinac može biti rođen sa SIT koji nije povezan ni sa jednim propratnim sindromom, te može ostati neprimećen, dugo vremena bez ikakvih simptoma, slučajno otkriven i dijagnostikovan tek prilikom radioloških pretraga usled neke bolesti ili patološkog stanja [18].

as the patient had been aware of her condition and the presence of situs inversus totalis since her previous hospital stay. During the CT scan, the arrangement of the internal organs was confirmed, being a mirror image of normal anatomy, with the liver on the left and the spleen on the right side of the hypochondrium (Image 1 and Image 2). No other congenital anomaly was observed, nor was there any vascular abnormality.

An informed consent was obtained from the patient for the planned surgical procedure and the risk of potential complications was explained to her in detail. Herniotomy and reconctruction of the abdominal wall were performed using a Prolene mesh following the Rives-Stoppa, "sublay", technique under general anesthesia having previously informed all the members of the surgical and anesthesiological team of the patient's specific condition. The established SIT did not have a direct impact on the process of anesthesia, the organization of the surgical procedure, and the selection of the surgical technique.

Postoperatively, the patient was treated with infusion, analgesics, antibiotics, and antiplatelet therapy. Having spent ten days in hospital, the patient was discharged home fully recovered and in good general condition.

U svom radu Laksman i saradnici opisuju osobu ženskog pola, kojoj je situs inversus totalis dijagnostikovan tek u kasnoj životnoj dobi (84 godine), potpuno slučajno, u sklopu kliničke i radiološke dijagnostike zbog karcinoma mokraćne bešike [19].

Takođe, Lohman i saradnici prikazuju pacijentkinju bez predhodnih saznanja o postojanju situsa, kojoj je ovo stanje dijagnostikovano tek u 75. godini, prilikom hospitalizacije usled akutne upale žučne kese i bolova u levom hipohondrijumu [20].

Pacijentkinja iz našeg prikaza je takođe za svoje stanje saznala u starijem životnom dobu, u svojoj 64. godini. Pre ove planirane i zakazane hospitalizacije radi operacije ventralne kile, lečena je i dva puta operisana na istom odeljenju prema urgentnom scenariju sa bolovima u stomaku usled apendicitisa i kalkuloze žučne kese.

SIT može predstavljati pravi dijagnostički izazov kod bolesti gde je lokacija organa ključna, kao što su akutni holecistitis ili apendicitis [21].

Uobičajeni uzroci akutnog abdominalnog bola kod pacijenta sa SIT mogu lako dovesti do pogrešne dijagnoze. Na primer, u slučaju apendicitisa kod ovih osoba, bol se može lokalizovati u levoj ilijačnoj jami, pa postoji mogućnost da se pogrešno dijagnostikuje kao akutni divertikulitis. Kod holecistitisa, bol se kod prisustva SIT može naći u levom gornjem kvadrantu i lako može da se pogrešno dijagnostikuje kao gastritis. Stoga, lekar mora uvek da zadrži određenu dozu kliničke sumnje, da razmišlja o eventualnom postojanju SIT i da na osnovu fizičkog pregleda naknadno izvrši odgovarajuće radiološke dijagnostičke procedure [11].

Takođe, zanimljivo je da samo 50% pacijenata sa levostranim slepim crevom oseća bol na levoj strani abdomena. Ova komplikovana klinička prezentacija može da se objasni činjenicom da su u konstelaciji situs inversusa transponovani trbušni organi, ali ne i komponente perifernog nervnog sistema, tako da pacijenti u ovim slučajevima često doživljavaju potpuno zbunjujući i difuzni bol u stomaku [11].

Samim tim dijagnoza akutnog apendicitisa nije uvek jednostavna, a mortalitet i morbiditet ovog stanja mogu se povećati ukoliko se hirurško lečenje odlaže. Veća je verovatnoća da će se uspostaviti pogrešna dijagnoza kada pacijent ima atipične simptome kao što je bol na neočekivanoj lokaciji. Ovakav scenario se može desiti jer slepo crevo i inače može imati različit anatomski položaj: retrocekalni, subcekalni, preilealni, postilealni, karlični, subhepatični, mezocelijačni, levostrani, a postoji i projekcija desnostranog dugog slepog creva u oblast levog donjeg kvadranta [12]. Ovi autori u svom sistematskom pregledu literature analiziraju 70 do sada objavljenih radova sa ukupno 73 pacijenta sa akutnim apendicitisom i SIT ili malrotacijom creva.

DISCUSSION

People who have situs inversus with dextrocardia and with no accompanying congenital anomalies, have normal life expectancy and a similar risk of acquired diseases like other people of the same age and sex. In rare cases, in people who have additional cardiac anomalies, life expectancy is decreased depending on the severity of the defect [17].

An individual may be born with SIT which is not associated with any accompanying syndrome, so it may remain unnoticed for a long time, with no symptoms whatsoever, and then be accidentally discovered and diagnosed during radiological examination due to a disease or a patological condition [18].

Lakshman and colleagues described a female person who had been diagnosed with situs inversus totalis only in her old age (when she was 84 years old), completely accidentally, as part of clinical and radiological diagnostics for bladder cancer [19].

Additionally, Lochman and colleagues presented a female patient who had no prior knowledge of the existence of situs inversus and who had been diagnosed with this condition as late as the age of 75, when she was admitted to hospital due to acute cholecystitis and pain in the left hypochondrium [20].

The patient from our case report also found out about her condition accidentally, in later life, at the age of 64. Before this planned and scheduled admission for ventral hernia surgery, she had been treated and operated on twice at the same department as an emergency case suffering from abdominal pain due to appendicitis and gallbladder calculus.

SIT can be a real diagnostic challenge in diseases where organ location is crucial, such as acute cholecystitis or appendicitis [21].

Common causes of acute abdominal pain in a patient with SIT can lead to a misdiagnosis. For example, if such a person suffers from appendicitis, pain may be localized in the left iliac fossa, so the condition may be misdiagnosed as acute diverticulitis. In cholecystitis, in individuals with SIT pain can be located in the left upper quadrant and it can be easily misdiagnosed as gastritis. Therefore, the doctor must remain suspicious to a certain extent, think about the possible presence of SIT, and perform subsequent radiological diagnostic procedures based on physical examnation [11].

It is also interesting that only 50% of all patients with left-sided appendicitis feel pain on the left side of the abdomen. This complicated clinical presentation can be explained by the fact that in the constellation of situs inversus the abdominal organs are transposed, but the components of the peripheral nervous system are not, so patients in such cases experience confusing and diffuse abdominal pain [11].

Zbog atipične anatomije „slike u ogledalu" i dijagnoza kamena u žučnoj kesi kod pacijenata sa situs inversusom je izuzetno teška, posebno kod onih sa nepoznatom istorijom ovog stanja. Usled neuobičajene anatomije žučne kese, klinička slika ovih pacijenata obično uključuje bol u levom gornjem kvadrantu dok će 30% pacijenata razviti i bol u epigastriju. Otprilike 10% ovih pacijenta se žali na bol u desnom gornjem kvadrantu, što je klasična prezentacija bola kod pacijenata sa normalnom anatomijom i dodatno komplikuje prepoznavanje etiologije i lokalizacije bola [22].

Uprkos niskoj incidenci i činjenici da se radi o retkoj pojavi, u toku prelaparoskopske ere u literaturi je objavljeno nešto manje od 40 prikaza slučajeva „otvorenih" holecistektomija kod pacijenata sa situs inversusom (20), a u svom radu iz 2019. godine AlKilejli i saradnici sistematizuju ukupno 92 do tada urađene laparoskopske holecistektomije i objavljene prikaze slučajeva pacijenata sa prisustvom situs inversusa [16].

U osnovi, principi lečenja holelitijaze su isti kod osoba sa SIT kao i kod pojedinca sa uobičajenom anatomijom. Laparoskopska holecistektomija nije kontraindikovana kod pacijenata sa situs inversusom i holelitijazom, samo postoji potreba za veoma pažljivim preoperativnim i intraoperativnim planiranjem operativnog zahvata kada se ovi pacijenti upućuju na laparoskopsku holecistektomiju. Operativna postavka laparoskopskog monitora, položaj operatora i asistenata i plasiranje porta su presudni u postizanju bezbednog i uspešnog završetka laparoskopske holecistektomije [23].

Konfiguracija i organizacija operacione sale kao slike u ogledalu prilikom laparoskopske holecistektomije postiže se postavljanjem hirurga i medicinske sestre na desnu, a asistenta na levu stranu pacijenta. Najteži deo disekcije u uslovima postojanja situs inversusa je to što su levoruki ili ambidekstralni hirurzi u ovakvim situacijama u prednosti. Kada je reč o desnorukom hirurgu, njegove motoričke sposobnosti u levoj ruci mogu biti nedovoljne za preciznu disekciju i procenu bezbednosti. Najkritičnija tačka operacije u ovakvoj konstelaciji je postavljanje klipsi, što zahteva od operatora i preciznost i snagu u istom trenutku [24].

U literaturi su pored operacija apendektomije i holecistektomije opisani i mnogi drugi hirurški zahvati iz oblasti abdominalne hirurgije kod pacijenata sa SIT, uključujući sleeve gastrektomiju kod morbidne gojaznosti, proksimalnu resekciju želuca, distalnu resekciju želuca, totalnu gastrektomiju zbog maligniteta, laparoskopsku pankreato-duodenektomiju, nefrektomiju, komplikovanu cistu holedoha, različite kolorektalne operacije, resekciju sigmoidnog creva, resekciju rektuma, itd. Nakon početne dezorijentisanosti, iskusni hirurzi mogu uspešno i bezbedno da obave sve ove procedure [25].

Therefore, the diagnosis of acute appendicitis is not always simple, and mortality and morbidity of this condition can increase if surgical treatment is delayed. A misdiagnosis is more likely if the patient has atypical symptoms such as pain in an unexpected location. This is a realistic scenario because the appendix has diverse anatomical positions: retrocecal, subcecal, preileal, postileal, pelvic, subhepatic, mesoceliac, left-sided, and there is also right-sided long appendix projecting into the left lower quadrant area [12]. In their systematic literature review, these authors have analiyzed 70 published papers including a total of 73 patients with acute appendicitis and SIT or bowel malrotation.

Because of the atypical "mirror image" anatomy, the diagnosis of gallbladder calculus in patients with situs inversus is extremely difficult, especially in those who have not been aware of this condition. Due to the unusual anatomy of the gallbladder, the clinical presentation of these patients usually includes the left upper quadrant pain, while 30% of patients will develop epigastric pain. Approximately 10% of such patients complain of feeling pain in the right upper quadrant, which is a classic presentation of pain in patients with normal anatomy, and it further complicates the recognition of etiology and localization of pain [22].

Despite low incidence and the fact that it occurs rarely, during the pre-laparoscopic era there were below 40 published cases of "open" cholecystectomies in patients with situs inversus (20), and in their paper from 2019, AlKhlaiwy and colleagues systematized a total of 92 laparoscopic cholecystectomies and the published case reports of patients with situs inversus [16].

Basically, the principles of treating cholelithiasis are the same in individuals with SIT and those with normal anatomy. Laparoscopic cholecystectomy is not contraindicated in patients with situs inversus and cholelithiasis, only there is a need for very careful preoperative and intraoperative planning of the surgical procedure when these patients are referred for laparoscopic cholecystectomy. The monitor positioning, the position of the operator and the assistants, as well as port placing are crucial for a safe and successful completion of laparoscopic cholecystectomy [23].

The configuration and the organization of the operating theatre as a mirror image during laparoscopic cholecystectomy is achieved by positioning the surgeon and the nurse to the right and the assistant to the left of the patient. When it comes to the most difficult part of dissection in the presence of situs inversus, left-handed or ambidextrous surgeons have an advantage over right-handed surgeons in such situations. A right-handed surgeon's motor skills in the left hand can be insufficient for precise dissection and safety as-

Medicinska primena savremenih dijagnostičkih metoda iz oblasti radiologije (ultrazvuka, CT i MR) je od velike pomoći u utvrđivanju osnovne anatomije, a naročito pre bilo kakvih hirurških intervencija kod osoba sa situsom inversusom kako bi se izbegle potencijalne nezgode i obezbedio dobar klinički tok [26].

ZAKLJUČAK

Situs inversus totalis je retka anatomska varijacija, čija se prevalenca u literaturi kreće od 1:10,000 – 1:20,000. Smatra se da je većina ovih slučajeva posledica sporadične genetske mutacije, ali su opisani i pojedini obrasci nasleđivanja (autozomno-dominanto, autozomno-recesivno i recesivni tip nasleđivanja vezan za X hromozom).

Većina osoba sa ovim stanjem vodi potpuno normalan život bez ikakvih zdravstvenih tegoba i sazna za svoju anatomsku varijaciju sasvim slučajno, kada se zbog bolesti ili nekog patološkog stanja podvrgne radiološkoj dijagnostici. Očekivani životni vek i rizik od dobijanja stečenih bolesti su slični kao i kod osoba iz opšte populacije koje su iste starosne dobi i pola. U određenom broju slučajeva SIT može da bude povezan sa pojedinim patološkim entitetima, stanjima i sindromima. Procenjuje se da oko 1 od 20 ovih pacijenata može da ima neki vid srčanih anomalija, a oko 1 od 5 pacijenata može imati koegzistirajući Kartagenerov sindrom.

Kod pacijenata sa prisustvom SIT uobičajeni uzroci akutnog abdominalnog bola mogu lako dovesti do pogrešnih zaključaka. Zbog neuobičajene anatomije, prepoznavanje upale slepog creva, bola usled želudačne patologije ili kamena u žučnoj kesi kod pacijenata sa situs inversusom je izuzetno komplikovano i teško, posebno ukoliko istorija ovog stanja nije poznata pacijentu.

Blagovremeno identifikovanje osoba sa SIT može pomoći da se smanje rizici i spreče greške tokom hirurških zahvata i interventnih procedura, pre svega kod urgentnih stanja u oblasti abdominalne hirurgije, endoskopije i interventne radiologije. Prisustvo dekstrokardije na rutinskom rendgenskom snimku grudnog koša treba odmah da pobudi sumnju na postojanje ovakve anatomije.

Pojava „slike u ogledalu“ je svakako nesvakidašnji prizor u medicini i veliki izazov, sa kojim se čak i lekari sa mnogo godina iskustva susreću eventualno samo jednom tokom svog radnog veka. Operativni zahvati kod ovih pacijenata su potpuno izvodljivi i mogući uz pažljivo planiranje svakog narednog koraka i visok stepen fleksibilnosti celokupnog hirurškog tima.

Sukob interesa: Nije prijavljen.

sessment. The most critical point of surgery in such a constellation is the placemet of clips, which requires the surgeon to be precise and strong at the same time [24].

In addition to appendectomy and cholecystectomy surgeries, many other surgical interventions in the field of abdominal surgery in patients with SIT have been described in literature, including sleeve gastrectomy in morbid obesity, proximal gastrectomy, distal gastrectomy, total gastrestomy due to malignancy, laparoscopic pancreaticoduodenectomy, nephrectomy, complicated choledochal cyst, various colorectal surgeries, sigmoid colectomy, rectal resection, etc. After the initial disorientation, experienced surgeons can perform all these procedures successfully and safely [25].

Medical application of modern diagnostic methods in the field of radiology (ultrasound, CT, MRI) is of great help in determining the basic anatomy, especially before any surgical interventions in individuals with situs inversus in order to avoid potential accidents and ensure a good clinical course[26].

CONCLUSION

Situs inversus totalis is a rare anatomical variation, whose prevalence in literature ranges from 1:10.000 to 1:20.000. It is believed that most of these cases are the result of a sporadic genetic mutation, but certain inheritance patterns have also been described (autosomal dominant, autosomal recessive, and X-linked recessive inheritance).

Most people with this condition live completely normal lives without any health problems and find out about their anatomical variation by accident when they undergo radiological diagnostics due to a disease or a patological condition. Life expectancy and the risk of acquired diseases are similar to those of general population of the same age and sex. In some cases, SIT can be associated with certain patological entities, conditions, and syndromes. It is estimated that around 1 in 20 patients can have some type of cardiac anomaly, whereas 1 in 5 patients may have coexisting Kartagener's syndrome.

In patients with SIT, common causes of acute abdominal pain can easily lead to misconclusions. Due to the unusual anatomy, recognition of appendicitis, pain due to a gastric pathology or gallstones in patients with situs inversus is extremely complicated and difficult, especially if the history of this condition is unknown to the patient.

Timely identification of indivisuals with SIT can help reduce risks and prevent errors during surgical procedures and interventional procedures, especially in emergency situations in the field of abdominal surgery,

endoscopy, and interventional radiology. The presence of dextrocardia in a routine chest X-ray should immediately arouse suspicion of unusual anatomy.

"Mirror image" is certainly an unusual sight in medicine and a great challenge as well, which even very experienced doctors may encounter only once during their entire career. Surgical interventions are completely feasible and possible with careful planning of every single step and a high level of flexibility of the entire surgical team.

We, undersigned, declare under full criminal accountability and liability that this paper has not been published in any medical journal and that it has not been simultaneously submitted for publication in another journal, that the manuscript has been read and approved by all authors who meet the authorship criteria, that the contact information are correct for all authors, as well as that the corresponding author, on behalf of other authors, signs the Copyright Agreement, by means of which all authors transfer their copyright to the publisher of this journal.

Conflict of interest: None declared.

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GIGANTSKI FILODNI TUMOR: PRIKAZ SLUČAJA I PREGLED LITERATURE

PRIKAZ SLUČAJA

CASE REPORT

A GIANT PHYLLODES TUMOR: A CASE REPORT AND LITERATURE OVERVIEW

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SAŽETAK

Uvod: Filodni tumori dojke su veoma retki u Srbiji i svetu. Ovi tumori često predstavljaju dilemu u dijagnostici i lečenju.

Prikaz slučaja: Predstavljamo 60-godišnju ženu sa masivnim tumorom u levoj dojci koji je imala 15 godina. Prema histopatološkoj dijagnozi, u pitanju je granični (*borderline*) filodni tumor retke veličine 18x17x7 cm i težine 4,6 kg.

Zaključak: Tačna preoperativna dijagnoza i pravilan tretman omogućavaju adekvatnu operaciju i izbegavanje ponovne operacije. Ovo je ključno za ovakve filodne tumore zbog njihove sklonosti ka recidivu i malignog potencijala koji imaju neki od ovih tumora.

Ključne reči: filodni, cistosarkom, klasifikacija, lokalni recidiv

ABSTRACT

Introduction: Phyllodes tumors of the breast are extremely uncommon, both in Serbia and worldwide. Identifying and treating these tumors can be challenging and they often represent a dilemma in diagnosis and treatment.

Case report: We are presenting the case of a 60-year-old female with a large breast tumor that she had had for 15 years. According to the histopathologic diagnosis, it is a borderline phyllodes tumor measuring 18x17x7 cm and weighing 4.6 kg.

Conclusion: An accurate preoperative diagnosis and proper management of borderline phyllodes tumors are crucial for successful surgery and for avoiding any further surgeries. This secondary prevention is critical because phyllodes tumors often recur and have malignant potential.

Keywords: phyllodes, cystosarcoma, classification, local recurrence

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Primljeno • *Received*: October 15, 2023; **Revidirano • *Revised*:** October 17, 2023; **Prihvaćeno • *Accepted*:** October 20, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47147

UVOD

Filodni tumor (FT), poznat i kao *cistosarcoma phillodes*, čini <1% svih tumora dojke, a ima incidencu od oko 2,1 na milion slučajeva [1,2,3].

Ovi tumori se sastoje i od stromalnih i od epitelnih elemenata, i tradicionalno se svrstavaju u benigne, granične (borderline) i maligne na osnovu grupe histoloških parametara. Na osnovu histoloških parametara utvrđuje se priroda tumorskih granica uključujući stepen celularnosti strome i atipiju, broj mitoza, i prekomerni rast strome [4,5]. Svi oblici filodnih tumora imaju maligni potencijal. Filodni tumori su uglavnom dobro ograničeni i mogu pritiskati okolno tkivo.

Većina malignih filodih tumora češće ima odlike liposarkoma ili rabdomiosarkoma nego fibrosarkoma. Procena broja mitoza može biti od pomoći pri dijagnostikovanju malignog tumora [6]. Operacija je jedini raspoloživi vid lečenja kod ovakvih pacijenata, pa je veoma važno odabrati adekvatnan vid hirurškog lečenja.

PRIKAZ SLUČAJA

Ovde je prikazan redak slučaj. Pacijentkinja je 60-godišnja žena sa masivnim tumorom u levoj dojci od kojeg je prethodno bolovala 15 godina. Imala je bolove u levoj dojci. Tokom poslednje tri godine, tumor je počeo drastično da se povećava (Slika 1).

Pacijentkinja se javila na Institut za onkologiju i radiologiju Srbije gde je urađena dijagnostika, uključujući mamografiju i ultrazvuk. Mamografija je pokazala izuzetno obimnu levu dojku. Intenzivna senka je zauzela celu dojku. Uprkos očiglednoj promeni, parenhim leve dojke nije bio vidljiv.

Urađena je simpleks mastektomija bez disekcije aksilarnih limfnih čvorova (Slike 2,3,4). Histopatološki pregled nakon operacije pokazao je da je reč o granič-

INTRODUCTION

Breast tumors that belong to the category of phyllodes tumors (PT), and are also referred to as *cystosarcoma phyllodes*, account for less than 1% of all breast tumors. Their incidence is about 2.1 per one million [1,2,3].

Traditionally, phyllodes tumors containing both stromal and epithelial elements are graded into benign, borderline, and malignant categories based on histological parameters. A set of histologic features determines the nature of tumor borders, including the degree of stromal cellularity and atypia, mitotic count, and stromal overgrowth [4,5]. All forms of phyllodes tumors are regarded as having malignant potential. Phyllodes tumors are usually well-demarcated and may compress the surrounding tissue.

Most malignant phyllodes tumors contain liposarcomatous or rhabdomyosarcomatous elements rather than a fibrosarcomatous component. Counting the number of mitoses can aid in identifying a malignant tumor [6]. Surgery is the only treatment for these patients, so it is crucial to select the appropriate surgical option.

CASE REPORT

A rare case is presented by this case report. The patient was a 60-year-old female who presented with a massive tumor in her left breast, which she had suffered from for 15 years prior to surgery. She had pain in her left breast. Over the final three years, the size of the tumor increased drastically (Figure 1).

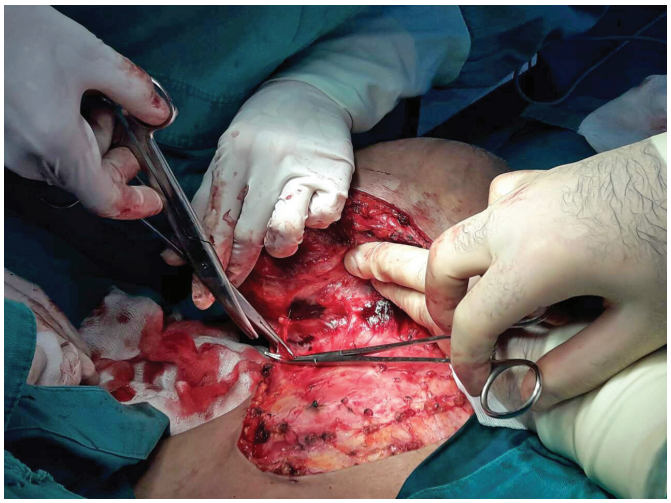
She reported to the Institute of Oncology and Radiology of Serbia, where the diagnostic process was performed, including mammography and ultrasonography. The mammography showed an extremely voluminous left breast. The tumor's intense shadow oc-

Slika 1. Pacijentkinja - 60-godišnja žena sa masivnim tumorom u levoj dojci

Figure 1. The patient was a 60-year-old female who presented with a massive tumor in her left breast

Slika 2. Izvedena je simpleks mastektomija

Figure 2. A simplex mastectomy was performed



Slika 3. Fotografija sa operacije

Figure 3. A picture taken during surgery

Slika 4. Fotografisano prvog dana nakon operacije

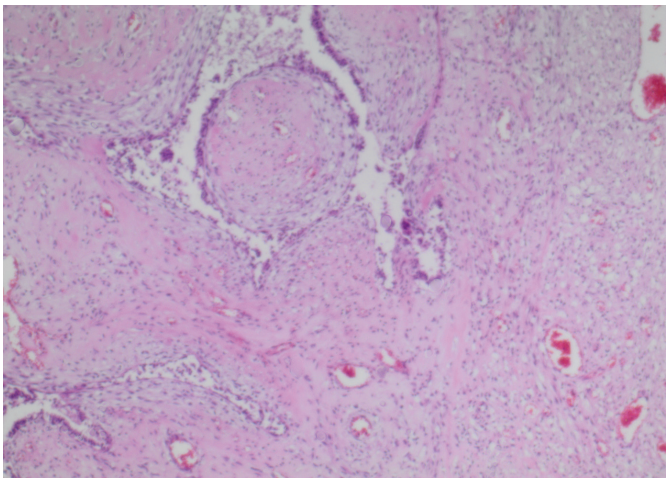
Figure 4. A picture taken on the first day upon surgery

nom (borderline) filodnom tumoru dojke. Na poprečnom preseku, videlo se da je tumor veličine 18x17x7 cm infiltrirao skoro celo tkivo dojke. Posmatranjem tumorskog preseka utvrđeno je da tumor sadrži brojne centralne šupljine koje su bile nekrotične.

Stroma tumora je bila umereno celularna. Utvrđeno je da poseduje blagi pleomorfizam i nizak mitotički indeks, koji je delimično modifikovan hijalinom. Takođe je utvrđeno da je epitelna komponenta delimično atrofična, delom skvamozna metaplazija, i fokalna atipična hiperplazija (Slike 5, 6).

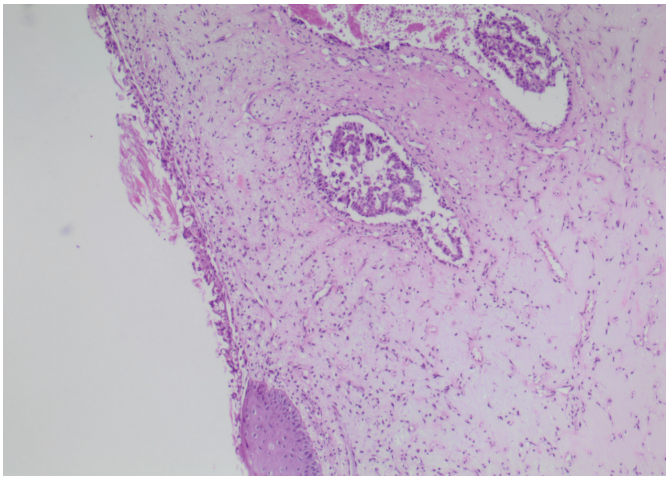
cupied the whole breast. Despite the obvious change, the parenchyma of the left breast could not be seen.

A simple mastectomy was performed with no axillary lymph node dissection (Figures 2,3,4). The histopathological examination upon surgery showed a borderline phyllodes tumor of the breast. In the cross-section, almost all the breast tissue was infiltrated by the tumor which was 18x17x7 cm in size. The tumor's intersection was found to contain numerous central cavities which were necrotic.



Slika 5. Histološki presek tumora dojke na kome se vidi filodni tumor (H&E boja x 4)

Figure 5. A histological section of the breast tumor showing phyllodes tumor (H&E stain x 40)



Slika 6. Histološki presek tumora dojke na kome se vidi filodni tumor (H&E boja x 4)

Figure 6. A histological section of breast tumor showing phyllodes tumor (H&E stain x 40)

DISKUSIJA

Filodni tumor (FT) se najčešće javlja kod žena u četvrtoj ili petoj deceniji života.

Bolest se prvenstveno sreće kod žena, ali postoji i nekoliko izveštaja o ovakvim tumorima kod muškaraca [7,8]. Etiologija ovih tumora je i dalje nepoznata.

The stroma of the tumor was moderately cellular. It was found to possess a mild pleomorphism and low mitotic index, which was partially hyaline modified. The epithelial component was found to be partly atrophic, and partly of a squamous metaplasia, and focal atypical hyperplasia (Figures 5, 6).

Benigni filodni tumori se najčešće prezentuju kao bezbolne izrasline u dojci. Široka lokalna ekscizija je najčešći tip operacije koji se izvodi u takvim slučajevima [9]. Inicijalna dijagnoza filodnog tumora zasniva se na kliničkom pregledu, mamografiji, ultrazvuku i aspiraciji tankom iglom (FNA), ali se konačna dijagnoza postavlja na osnovu histopatološkog nalaza. Dok se benigni tumori mogu lečiti parcijalnom resekcijom dojke, rekurentni, maligni i masivni tumori zahtevaju mastektomiju bez aksilarne disekcije. Bilo je pokušaja primene adjuvantne terapije uz radioterapiju i/ili hemioterapiju, iako je ova vrsta terapije imala samo ograničenu efikasnost [10,11].

Prema smernicama Svetske zdravstvene organizacije (SZO), filodni tumori se dele na benigne, granične (borderline) i maligne na osnovu tri glavne karakteristike: 1) stepena tumorske stromalne ćelijske atipije; 2) broja mitotičkih figura na 10 polja velike snage; i 3) stepena prerastanja strome. Nekroza tumora i izgled ivica resekcije takođe se uzimaju u obzir pri kategorisanju filodnih tumora [12,13].

Lokalni recidivi

Zabeležen je širok raspon stopa lokalnih recidiva od 10-40%, dok je u većini slučajeva u proseku bilo reč o 15%. Kada dođe do lokalnog recidiva, često je reč o tome da FT nije u potpunosti uklonjen tokom primarnog hirurškog zahvata. Hirurška margina je jedini nezavisni prediktivni faktor za lokalni recidiv prema multivarijantnim analizama. Kod većine pacijenata, takav recidiv je izolovan i stoga nije u vezi sa pojavom udaljenih metastaza. Ipak, ponovljeni lokalni recidivi se dešavaju kod manjeg broja pacijenata, što često nema veze sa histološkim tipom tumora ili obimom ivica resekcije. Lokalni recidivi se obično mogu izbeći primenom široke ekscizije (slobodne margine od 1 cm). Iako mastektomija u suštini nije obevezna, ipak je treba razmotriti kao opciju u slučaju lokalnog recidiva nakon lokalizovane operacije graničnih (borderline) ili malignih tumora. Ovo bi u velikoj meri moglo sprečiti dalje recidive ili komplikacije. Postoji rizik od agresivnog lokalnog recidiva koji rezultuje široko rasprostranjenom bolešću grudnog koša gde dolazi do direktne invazije plućnog parenhima. Kada je reč o slučajevima filodnog tumora, do sada su objavljeni izolovani izveštaji o pravilnoj palijaciji uz upotrebu radioterapije [14]. Radioterapija može imati ulogu u lečenju FT u zavisnosti od broja recidiva, mitotičkog indeksa, veličine tumora, statusa resekcionih margina, kao i ekspresije tumorskih p53 i Ki67 [15].

Metastaze

Kod oko 10% svih pacijenata sa FT pojave se udaljene metastaze, pri čemu približno 25% svih pacijenata sa

DISCUSSION

Phyllodes tumors (PTs) most commonly occur in females in the 4th or 5th decade of life. This disease is primarily found in women, but there have been a few reports of these tumors in male breasts as well [7,8]. The cause of these tumors has not been understood yet. Benign phyllodes are more commonly presented as painless breast lumps. The most frequently performed surgery in case of such tumors is a wide local excision [9]. Upon clinical examination, mammography, ultrasonography and FNAC, a preliminary diagnosis is made; however, the final diagnosis is made based on histological findings. Benign tumors can be treated with lumpectomy, but recurrent, malignant, and massive tumors require mastectomy without axillary dissection. Attempts have been made to use adjuvant therapy along with radiotherapy and/or chemotherapy, despite its limited effectiveness [10,11].

As per the guidelines given by the World Health Organization (WHO), phyllodes tumors are to be divided into benign, borderline, and malignant based on the three main characteristics: 1) the degree of cellular atypia of the stromal tumor; 2) the mitotic activity measured as the number of cells undergoing mitosis per area of tissue, typically counted in 10 high-power fields; and 3) the degree of stromal overgrowth. Tumor necrosis and margin appearance are also considered when categorizing a PT [12,13].

Local recurrence

Local recurrence rates have been reported to range from 10-40%, with most cases averaging approximately 15%. When local recurrence occurs, it is often due to an incomplete removal of the original PT during the primary surgical treatment. The only independent predictive factor for local recurrence is the surgical margin, according to multivariate analyses. In the majority of patients, such recurrence is found to be isolated and therefore disassociated with the occurrence of distant metastases. Nevertheless, repeated local recurrence does occur in a minority of patients, which is often unrelated to either the histological type of tumor or the extent of the specimen margins. Further wide excision (with a margin of 1 cm) can usually prevent local recurrence. If localized surgery for borderline or malignant tumors is followed by a recurrence at the same site, it may be worth considering mastectomy as a possible option, even though it is not typically necessary. This could help to increase the chances of preventing future recurrences or complications. There is a risk of aggressive local recurrence resulting in widespread chest-wall disease where direct invasion of the underlying lung parenchyma occurs. For PT cases, isolated reports of proper palliation using radiotherapy have

FT na kraju oboli od malignih tumora prema histopatološkoj klasifikaciji. Metastaze koje su najudaljenije od primarnog tumora, mogu se pojaviti bez ikakvih znakova koji bi ukazali na lokalni recidiv. Najčešća mesta na kojima se javljaju takve metastaze su pluća (66%), kosti (28%), i mozak (9%). U retkim slučajevima, metastaze se takođe mogu pojaviti u jetri ili srcu. Obim primarne operacije ne utiče na rizik od pojave metastatske bolesti. Čini se da je biologija tumora bolji prediktor rizika od drugih faktora. Metastatski filodni tumori imaju lošu prognozu i ne obećavaju dugoročno preživljavanje [10].

Praćenje

Zbog činjenice da postoji velika verovatnoća za pojavu lokalnih recidiva kod filodnih tumora, posebno kada nisu ekscizirani uz upotrebu jasnih ivica, i pošto su FT nepredvidivi u svom rastu i metastatskoj aktivnosti, od ključnog je značaja da se pacijent redovno kontroliše na svakih šest meseci tokom prve dve godine, imajući u vidu da su šanse za pojavu recidiva najveće u prve dve godine nakon inicijalne operacije. Nakon toga, praćenje treba da se sprovodi na godišnjem nivou. Pacijenti moraju biti obučeni kako da najbolje sprovode redovan samopregled dojki i da se konsultuju sa svojim lekarima ukoliko otkriju bilo kakvu abnormalnost. Na kontrolama je potrebno obaviti fizički pregled pacijenta. Ako se otkrije bilo kakva abnormalnost, potrebno je sprovesti dalja istraživanja, uz upotrebu ultrazvuka, mamografije, magnetne rezonance i/ili biopsije tkiva, u cilju postavljanja precizne dijagnoze i sprovođenja pravilnog lečenja[10].

Iako je hirurško lečenje FT detaljno obrađeno u literaturi, može biti i jasnije. U nekolicini izveštaja ili izvora su posebno komentarisani gigantski filodni tumori. Proizvoljna granična tačka za označavanje FT kao gigantskog filodnog tumora je 10 cm [16]. Takvi entiteti pred hirurga postavljaju nekoliko jedinstvenih problema.

Na osnovu inicijalnog kliničkog pregleda, ultrazvuka i mamografije, filodni tumor koji je ovde prikazan je dijagnostikovan pre operacije. Odlučeno je da se ne izvodi biopsija tumora bilo koje vrste zbog visokog rizika od krvarenja.

Pošto transformacija primarno benignog filodnog tumora u maligni tumor predstavlja mogući krajnji ishod za svakog pacijenta, od vitalnog je značaja da se operacija izvede što je pre moguće, pre nego što tumor dobije šansu da se transformiše u maligni [17].

Široka ekscizija sa čistim ivicama resekcije može biti najbolja početna terapija za maligne FT. Međutim, rutinska disekcija aksilarnih limfnih čvorova se ne preporučuje. Pacijenti koji imaju tumore sa infiltrirajućim marginama tumora, prekomernim rastom strome, ati-

also been published [14]. Radiotherapy may have a role in the treatment of PT depending on the number of recurrences, the mitotic index, the size of the tumor, the status of the resection margins, as well as the tumor's p53 and Ki67 expression [15].

Metastases

About 10% of all PT patients develop distant metastases, wherein approximately 25% of all PT patients eventually experience histologically malignant tumors. Metastases that are far away from the cancer's site of origin can develop without any signs of the cancer returning locally. The most common sites for metastases are the lungs (66%), bones (28%), and the brain (9%). In rare instances, metastases may also be found in the liver or the heart. The extent of the initial surgery does not affect the risk of metastatic disease. It appears that tumor biology is a better predictor of risk than other factors. Phyllodes tumors that metastasize have a poor prognosis and no long-term survival [10].

Follow-up

It is crucial for patients with phyllodes tumors to have regular follow-ups at 6-month intervals for the first two years upon the initial surgery. This is because these tumors have a high chance of recurrence, particularly if they were not excised using clear margins. Moreover, phyllodes tumors are unpredictable in their growth and metastatic activity. The chances of recurrence are at their highest in the first two years after the surgery. Thereafter follow-ups are to be done on an annual basis. It is crucial to provide thorough instructions to patients on the proper technique of regular breast self-examination. If any abnormality is detected, patients should immediately consult their doctor. It is important to physically examine patients during their follow-up appointments. This allows for thorough monitoring of their condition and progress. If any abnormalities are found, it is recommended to conduct further investigation using ultrasonography, mammography, MRI, and/or tissue biopsy to ensure an accurate diagnosis and prompt treatment [10].

Although literature has thoroughly addressed surgical management of PTs, it can still be made clearer. Some reports or sources have specifically mentioned giant phyllodes tumors. The arbitrary cut off point for designating a PT as a giant phyllodes tumor is 10 cm [16]. Such entities present the surgeon with several unique management problems.

Based on the initial clinical examination, ultrasonography, and mammography, the phyllodes tumor presented here had been conclusively diagnosed prior to surgery. It was decided against performing any type of biopsy of the tumor due to the high risk of bleeding.

pijom i celularnošću imaju visok rizik za pojavu metastaza i treba ih pomno pratiti [18].

Iako je pacijentkinja iz ove studije slučaja imala filodni tumor 15 godina, on nije prerastao u maligni i to je najznačajnije od svega.

Tokom prve godine praćenja, nije bilo pojave lokalnih recidiva.

ZAKLJUČAK

Filodni tumori dojke predstavljaju neuobičajen, ali intrigantan tip fibroepitelnih neoplazmi. Precizna preoperativna dijagnoza i adekvatna hirurška intervencija su od ključnog značaja za isključenje pojave pozitivnih margina koje mogu dovesti do lokalnog recidiva, metastaza, i smanjenih izgleda za preživljavanje, a pomažu i da se izbegnu ponovne operacije.

Sukob interesa: Nije prijavljen.

Since a malignant transformation of a primarily benign phyllodes tumor is an eventual outcome for any patient, it is vital that surgery is conducted as early as possible before the tumor transforms into a malignant one [17].

For malignant phyllodes tumors (PTs), it may be best to begin with wide excision that leaves a clear margin. However, routine axillary lymph node dissection is not recommended. Patients with tumors that have infiltrating tumor margins, severe stromal overgrowth, atypia, and cellularity have a high risk of metastases, and should be closely monitored [18-26].

Although the patient in this case report had had a phyllode tumor for 15 years, it did not transform into a malignant tumor and that is the most important thing of all.

During the first year of follow-up, no local recurrence was found.

CONCLUSION

Phyllodes tumor of the breast is a rare but intriguing type of fibroepithelial neoplasm. An accurate preoperative diagnosis and proper surgery are crucial for preventing positive margins, which can lead to local recurrence, metastases, and decreased survival rates. Avoiding new surgeries is also important.

Conflict of interest: None declared.

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KONAČAN ISHOD U LEČENJU LEG-KALVE-PERTESOVE BOLESTI KORISTEĆI KOMBINACIJU ILIZAROVOG METODA I TUNELIZACIJE – PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

THE FINAL OUTCOME IN THE TREATMENT OF LEGG-CALVE-PERTHES DISEASE USING THE COMBINATION OF ILIZAROV METHOD OF TREATMENT AND TUNELISATION (CASE REPORT)

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SAŽETAK

Uvod: Leg-Kalve-Pertesova bolest (LKPB) je relativno česta bolest kuka dečjeg doba, koja pogađa otprilike 0,8 slučajeva na 100.000 dece. Obično se javlja kod dece uzrasta između 4 i 8 godina i kod dečaka je prisutnija više nego kod devojčica. Primarno je zahvaćen jedan kuk, ali bilateralna lokalizacija je prisutna u 9-15 slučajeva. Primarni tretman u Leg-Kalve-Pertesovoj bolesti je koncept fokusiran na očuvanju glave butne kosti u acetabulumu, čime se sprečava omekšavanje i fragmentacija. Najčešći metod hirurškog tretmana sastoji se od butne ili pelvične osteotomije ili kombinacije oba. Ovaj rad ima za cilj da predstavi minimalno invazivnu alternativnu metodu za lečenje Leg-Kalve-Pertesove bolesti.

Prikaz slučaja: Predstavljamo izveštaj o slučaju 19-godišnjaka sa dugom istorijom bolesti. Njegovo lečenje počelo je u petoj godini života, i ovo je najnoviji izveštaj njegovog stanja 14 godina nakon operacije.

Zaključak: Artrodijastaza kuka korišćenjem Ilizarovljevog cirkularnog okvira u kombinaciji sa tunelizacijom glave i vrata butne kosti je minimalno invazivni hirurški zahvat. Sa tehničke tačke gledišta, ovo je relativno zahtevna procedura koja rezultira kraćim periodom hospitalizacije, smanjenim rizikom od komplikacija i troškovima, u poređenju sa karličnom i butnom osteotomijom.

Ključne reči: Leg-Kalve-Pertesova bolest, karlične kosti, Ilizarov tehnika, ishod lečenja

ABSTRACT

Introduction: Legg-Calve-Perthes disease (LCPD) is a common childhood hip disease, affecting approximately 0.8 in 100,000 children. It usually affects children between 4 and 8 years old, and boys are more affected than girls. One hip is initially affected, but bilateral localization is present in 9-15 of the cases. The primary treatment in LCPD focuses on containing the femoral head in the acetabulum, thus preventing mollification and fragmentation. The most common surgical treatment method consists of either femoral or pelvic osteotomy or a combination of both. This paper aims to present a minimally invasive alternative method for treating LCPD.

Case report: We are presenting a case report of a 19-year-old with a lengthy history of illness. His treatment started at the age of 5, and this is an update on his condition 14 years after the surgery.

Conclusion: Hip arthrodiastasis using the Ilizarov circular frame combined with femoral head and neck tunneling is a minimally invasive surgical procedure. From a technical standpoint, this is a relatively demanding procedure that results in shorter in-patient treatment, reduced risk of complications, and cost compared to pelvic and femoral osteotomy.

Keywords: Legg-Calve-Perthes disease, pelvic bones, Ilizarov technique, treatment outcome

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Primljeno • *Received*: July 26, 2023; **Revidirano • *Revised*:** October 19, 2023; **Prihvaćeno • *Accepted*:** October 21, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-45692

UVOD

Leg-Kalve-Pertersova bolest (LKPB) je relativno česta bolest kuka dečjeg doba, koja pogađa otprilike 0,8 slučajeva na 100.000 dece [1]. Bolest su 1910. godine prvi put opisali tri naučnika iz tri različite zemlje, ali su njena etiologija i načini lečenja još uvek predmet rasprave [2]. Obično se javlja kod dece uzrasta od 4 do 8 godina i češće se javlja kod dečaka nego kod devojčica [1,2]. Primarno je zahvaćen jedan kuk, ali bilateralna lokalizacija je prisutna u 9-15 slučajeva [1,2].

Leg-Kalve-Pertesova bolest je avaskularno stanje koje utiče na epifizu kapitela budne kosti (glava) [1,3]. Avaskularno stanje je praćeno usporavanjem rasta jezgra kostiju. Kostno jezgro se naknadno resorbuje, zamenjuje novom i preuređuje u skladu sa mehaničkim svojstvima. Glava butne kosti postaje sravnjena i uvećana nakon preuređenja. Proksimalni butni deo i metafiza takođe mogu biti zahvaćeni, što može dovesti do sekundarnih promena u acetabulumu. Tretman LKPB-a i dalje ostaje kontroverzan uprkos opsežnoj literaturi o ovoj temi [3].

Princip LKPB tretmana je koncept zadržanja glave butne kosti u acetabulumu, kao zaštite od omekšane i fragmentovane glave butne kosti [4,5]. Koncept suzbijanja se može postići korišćenjem konzervativne metode (kao što su odmor ili ortoza) ili hirurške metode lečenja. Ovaj princip lečenja u ranoj fazi LKPB-a u uzrastu mlađih od 8 godina je široko prihvaćen.

Lečenje kasnog LKPB-a (preko 8 godina) je još uvek izazovno. Lečenje kasnog LKPB-a butnom ili karličnom osteotomijom ili kombinacijom oba, imao je loš konačni ishod [6-9].

Mnogi autori preporučuju koncept distrakcije kuka (artrodijastaza) kao početni metod lečenja [10-16].

Artrodijastaza nema uticaja na anatomske promene u zglobu kuka. Smanjuje opterećenje zglobne površine kuka i podspešuje zarastanje glave butne kosti [17]. Takođe, može se kombinovati sa tuneliranjem vrata i glave butne kosti kako bi se poboljšalo izlečenje [13].

Ova studija ima za cilj da predstavi slučaj minimalno invazivne alternativne metode u lečenju LKPB-a kod 5-godišnjeg dečaka i praćenje početne procedure 14 godina kasnije.

PRIKAZ SLUČAJA

Predstavićemo izveštaj o slučaju 5-godišnjeg dečaka sa dugom LKPB istorijom. Žalio se na bolove u levom kuku i levom kolenu. Takođe je šepao na levu nogu. Nije imao opšte znake infekcije, noćne bolove ili prateće bolesti. U kliničkim nalazima, imao je ograničenje abdukcije (30 stepeni) i unutrašnje rotacije (5 stepeni) u levom kuku. Takođe, imao je pozitivan Trendelenburgov znak sa leve strane.

INTRODUCTION

Legg-Calve-Perthes disease (LCPD) is a common childhood hip disease, affecting approximately 0.8 in 100,000 children [1]. The disease was first described in 1910 by three scientists from three different countries, but its etiology and treatment modalities are still a matter of debate [2]. It usually occurs in children aged 4 to 8 years, and it is more common in boys than girls [1,2]. One hip is initially affected, but bilateral localization is present in 9-15 cases [1,2].

Legg-Calve-Perthes disease is an avascular condition that affects the capital femoral epiphysis (head) [1,3]. The avascular condition is followed by growth retardation of the ossific nucleus. The ossific nucleus is subsequently resorbed, replaced by a new bone, and remodeled according to mechanical properties. After remodeling the femoral head becomes flattened and enlarged. The proximal femoral physis and metaphysis could also be affected, leading to secondary acetabulum changes. The treatment of LSPD remains controversial despite the extensive literature on this topic [3].

The principle of LCPD treatment is the concept of containment of the femoral head in acetabulum, as a protection against a mollified and fragmented femoral head [4,5]. The containment concept could be attained using conservative methods (like rest or orthosis) or surgical treatment. This principle of treatment in the early stages of LCPD at the age of under 8 is widely accepted.

The treatment of late LCPD (over the age of 8) is still challenging. Late LCPD treated by femoral or pelvic osteotomy, or a combination of both has had poor outcomes [6-9].

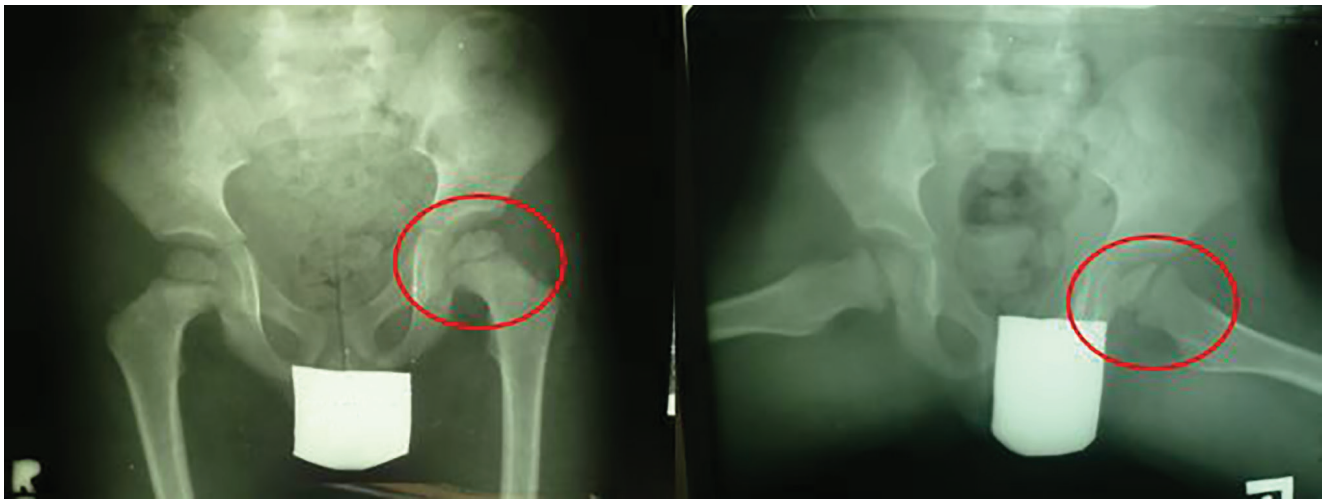
Many authors recommend the concept of hip distraction (arthrodiastasis) as the initial treatment method [10-16].

Arthrodiastasis does not have an impact on anatomic changes in the hip joint. It decreases the stress on the hip articular surface and enhances the healing of the femoral head [17]. It could also be combined with the femoral neck and head tunneling to improve healing [13].

This study aims to present a case of a minimally invasive alternative method in treating LCPD in a 5-year-old boy and a follow-up on the initial procedure 14 years later.

CASE REPORT

We will present the case report on a 5-year-old boy with long LCPD history. He complained of pain in the left hip and left knee. He had also been limping on the left leg. He had no general signs of infection, night pain, or concomitant diseases. In the clinical findings,



Slika 1. Inicijalni rendgenski snimak levog kuka u AP i u „žabljem" položaju Pertesove bolesti.

Figure 1. Initial X-ray in AP and in "frog-like" view of left hip Perthes disease

Nakon analize krvi i rendgenskih nalaza (u AP i „žabljem" položaju) LKPB je potvrđen. Prema Katarel i Hering klasifikaciji, on je klasifikovan je kao Katarel 3 i Hering B grupa.

Nakon prijema, počeli smo sa konzervativnim tretmanom koristeći perkutanu trakciju u blagoj abdukciji na nedelju dana (otprilike 10% ukupne težine pacijenta). Nakon vuče usledio je odmor bez opterećenja još nedelju dana. Nakon toga, pristupili smo protokolu zatezanja Atlanta ortozom, u položaju blage abdukcije i unutrašnje rotacije sa punim opterećenjem na obolelu nogu. Položaj glave butne kosti (suzbijanje) potvrđen je rendgenskim snimkom (u AP prikazu). Posle 4 meseca konzervativnog lečenja, ishod je bio loš i hirurško konsultantsko telo (troje specijalista ortopedske hirurgije) odlučilo je da obavi hirurški tretman.

Roditeljima su predstavljeni svi modaliteti hirurškog lečenja i oni su odobrili ovaj retko korišćeni hirurški tretman. Ova metoda je izvedena kao kombinacija artrodijastaze levog kuka pomoću Ilizarov okvira (kružni spoljni fiksator) i tuneliranja glave i vrata butne kosti korišćenjem Kiršnerovih žica od 2,0 mm (K žice).

Ova metoda lečenja je minimalno invazivna hirurška metoda. Glavni cilj artrodijastaze pomoću Ilizarovskog kružnog fiksatora je odvlačenje pažnje sa zgloba kuka i smanjenje pritiska na fragmentovanu glavu butne kosti.

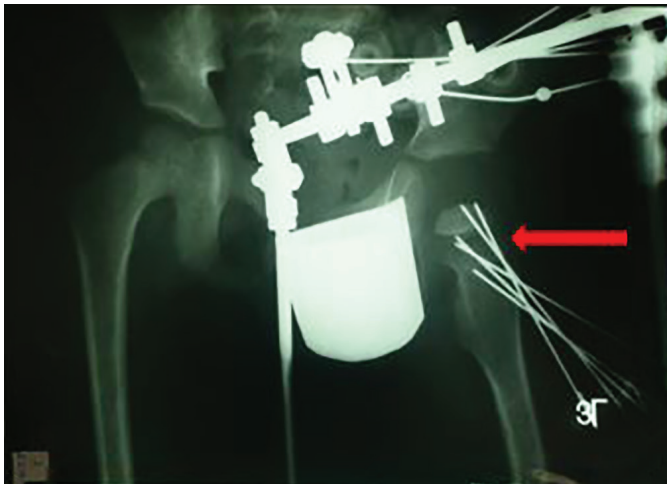
S druge strane, glavni cilj tuneliranja pomoću K žica je povećanje dotoka krvi u vrat i glavu butne kosti (Slika 2). Proces izlečenja glave butne kosti biće poboljšan u ishodu.

Tokom hirurškog zahvata i postoperativno nije došlo do komplikacija. Dva dana posle operacije pacijent je počeo sa fizikalnom terapijom, pasivnom kinezioterapijom sa delimičnim nošenjem težine na levoj nozi koristeći štake. Fizikalna terapija je bila obezbeđena u

he had the limitation of abduction (30 degrees) and internal rotation (5 degrees) in the left hip. He also had a left-side positive Trendelenburg sign.

Legg-Calve-Perthes disease was confirmed after blood analysis and X-ray findings (in AP and 'frog-like' position). According to Catarell and Herring classification he was classified as Catarell 3 and Herring B group.

After admission, we started with conservative treatment using percutaneous traction in slight abduction for one week (approximately 10% of the patient's total weight). The traction was followed by non-weight-bearing rest for one week more. After that, we started the bracing protocol using Atlanta orthosis, in the position of a slight abduction and internal rotation with full-weight bearing on the affected leg. The posi-



Slika 2. Intraoperativni rendgenski snimak u AP položaju (operativni postupak: Aplicatio aparatus pro distractio fixatione ad pelvis et femoris sinistri sec. Ilizarov. Transfixatio capitis femoris sinistri cum filli Kirshneri No V)

Figure 2. Intraoperative X-ray in AP position (Operative procedure: Aplicatio aparatus pro distractio fixatione ad pelvis et femoris sinistri sec. Ilizarov. Transfixatio capitis femoris sinistri cum filli Kirshneri No V)

Slika 3. Rendgen u AP položaju nakon uklanjanja K-žica sa glave i vrata butne kosti.

Figure 3. X-ray in AP position after K-wires removal from femoral head and neck

Slika 4. Rendgen u AP položaju nakon uklanjanja Ilizarovog cirkularnog okvira i K žica

Figure 4. X-ray in AP position after Ilizarov circular frame and K wires removal

bolnici u trajanju od dva meseca. Šest nedelja nakon operacije K žice su uklonjene sa vrata i glave butne kosti. Tri meseca posle operacije pacijent je primljen na ponovnu operaciju kada je izvađen Ilizarov kružni fiksator. Hirurški ishod je prikazan na slici 4.

Posle drugog hirurškog zahvata (uklanjanje Ilizarovljevog okvira) u bolnici je obezbeđen kratak tretman fizikalne terapije sa punim težinom; tokom prve dve nedelje oslonac je bio na štakama, a zatim sa nošenjem pune težine.

Pacijent je kontrolisan u intervalima od 6 nedelja, tri meseca i šest meseci posle druge operacije. Na slici 5 predstavljeni su 6-mesečni i 18-mesečni rendgenski nalazi posle druge operacije (uklanjanje hardvera).

U kliničkom ishodu, 18 meseci nakon uklanjanja hardvera pacijent je imao pun spektar kretanja u levom kuku i levom kolenu, bezbolno hodajući bez ikakve

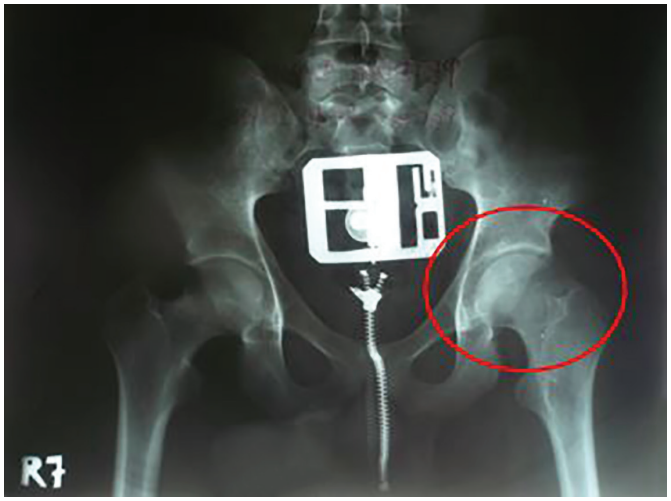
tion of the femoral head (containment) was confirmed by the X-ray (in AP view). After 4 months of conservative treatment, the outcome was poor and the surgical consulting body (3 specialists in orthopedic surgery) decided to perform a surgical treatment.

All modalities of the surgical treatment were presented to the parents, and they approved of this rarely used surgical treatment. This method was performed as a combination of left hip arthrodiastasis using the Ilizarov frame (circular external fixator) and the femoral head and neck tunneling using 2.0 mm Kirschner wires (K wires).

This method of treatment is a minimally invasive surgical method. The main goal of arthrodiastasis using the Ilizarov circular fixator is to distract the hip joint

Slika 5. Rendgen u AP položaju 6 meseci (A) i 18 meseci (B) nakon uklanjanja hardvera

Figure 5. X-ray in AP position 6 months (A) and 18 months (B) after hardware removal



Slika 2. Rendgen u AP položaju 14 godina nakon prve operacije

Figure 6. X-ray in AP position 14 years after the first surgery

podrške i obavljajući normalne fizičke aktivnosti osim skakanja.

Poslednje praćenje urađeno je kada je pacijent napunio 19 godina (14 godina posle prve operacije). Rendgenski snimak u AP položaju predstavio je kongruentnost glave butne kosti bez ikakvih znakova avaskularne nekroze. Estetski razlozi su takođe bili od suštinskog značaja; butni i ilijački ožiljci su bili skoro nevidljivi.

DISKUSIJA

Modaliteti lečenja LKPB-a su različiti, bilo konzervativni ili hirurški. Pacijenti mlađi od 6 godina imaju bolje ishode i prognoze uprkos metodi lečenja za razliku od pacijenata starijih od 6 godina [15,18]. Konzervativne metode lečenja (fizikalna terapija i upotreba ortoze) imaju mnoge prednosti kao neinvazivne metode: nema formiranja ožiljaka, nema rizika od infekcije i nema psiholoških efekata na dete i roditelje. Sa druge strane, potrebno je duže lečenje i dobra usaglašenost između lekara, deteta i roditelja. Da zaključimo, svi ovi faktori se moraju razmotri u donošenju konačne odluke [19].

Najvažniji faktori u LKPB lečenju su starosni rendgenski nalaz pacijenta u AP-u i pozicija „nalik žabi" (prema katarelovoj i Heringovoj klasifikaciji).

Pacijenti starosti preko 6 godina imaju bolje ishode koristeći hirurški pristup u LKPB lečenju [16]. Prema njihovim studijama, neki autori su zaključili da je rengenski nalaz glavni faktor u prognozi konačnog ishoda LKPB-a, odnosno nivo aseptičke narkoze glave butne kosti [20,21].

Pokazalo se da bušenje tunela utiče na manje od 10% ukupne površine hrskavice rasta, ne narušava rast ploče i ne smanjuje rast u predelu kuka [22]. Nekoliko autora lečilo je pacijente sa artrodijastazom koristeći monolateralni fiksator; međutim, koristili su biomeha-

and to reduce the pressure on the fragmented femoral head. On the other hand, the main goal of tunneling using K wires is to increase the blood supply to the femoral neck and head (Figure 2). The healing process of the femoral head will be improved in the outcome.

No complications occurred during the surgical procedure and postoperatively. Two days after the surgery, the patient started with physical therapy, passive kinesiotherapy with partial weight bearing on the left leg using crutches. All physical therapy treatments were provided in the hospital during the two months. Six weeks after the surgery K wires were removed from the femoral neck and head. Three months after the surgery, the patient was admitted for a redo-surgery procedure when the Ilizarov circular fixator was extracted. The surgical outcome is presented in Figure 4.

After the second surgical procedure (the Ilizarov frame removal), a short physical therapy treatment with full-weight bearing was provided during the stay; at first, it was supported with crutches during the first two weeks and afterward with full-weight bearing.

The patient was controlled at 6 weeks, three-month, and six-month intervals after the second surgery. Figure 5 presents 6-month and 18-month X-ray findings after the second surgery (hardware removal).

In the clinical outcome, 18 months after the hardware removal the patient had the full range of motion in the left hip and left knee, painlessly walked without any support, and carried out normal physical activities besides jumping.

The last follow-up was done when the patient turned 19 (14 years after the first surgery). The X-ray in the AP position presented the congruency of the femoral head without any signs of avascular necrosis. Aesthetic reasons were also essential; the femoral and iliac scars were almost invisible.

DISCUSSION

The treatment modalities of LCPD are various, whether conservative or surgical. Patients under the age of 6 have better outcomes and prognoses despite the method of treatment than patients over the age of 6 [15,18]. Conservative methods of treatment (physical therapy and orthotics usage) have many advantages as non-invasive methods: no scar formation, no infection risk, and no psychological effects on a child and parents. It takes, on the other hand, longer treatment and good compliance between a doctor, a child, and parents. To conclude, all these factors have to be considered in making a final decision [19].

The most important factors in LCPD treatment are the patient's age X-ray findings in AP and the "frog-like" position (according to Catarell and Herring classification).

nički slabiju metodu fiksatora i igle velikog prečnika za tuneliranje i njihovi pacijenti nisu nosili težinu tokom cele dužine lečenja [23,24]. Kočaoglu je predstavio i objavio rezultate upotrebe Ilizarovljevog aparata kod Pertesove bolesti. Koristio je snažan i složen Ilizarov okvir u ranoj fazi fragmentacije glave butne kosti, a njegova stopa uspeha nije bila impresivna. Da bi se održalo zadržavanje glave butne kosti neophodno je započeti tretman u fazi nekroze ili ranog stadijuma fragmentacije, odnosno pre kolapsa epifize butne kosti [25]. Uprkos pregledu literature o zlatnom standardu u hirurškom pristupu (osteotomiji karlice poput Saltera, Kjarija ili trostruke osteotomija karlice), artrodijazu kuka sa tuneliranjem treba smatrati alternativnom hirurškom tehnikom. Artrodijastaza kuka i tuneliranje glave i vrata butne kosti treba razmotriti u ranoj fazi LKPB-a i kasnom početku bolesti kada standarne hirurške procedure ne daju dobre ishode [26].

Primenom ove tehnike dobija se pun opseg bezbolnih pokreta, bez sekundarnih poremećaja ili smetnji u hodu. Rizik od lateralne subluksacije glave butne kosti smanjen je na rendgenskim snimcima, postignuta je kongruencija glave butne kosti bez anatomskih povreda u zglobu kuka. Takođe, ova tehnika se može primeniti kod starije dece i adolescenata sa lošim prognozama (prema rendgenskim nalazima) i u kontraindikacijama za osteotomiju karlice.

Ovaj izveštaj LKPB slučaja predstavlja najvažnije vrednosti u konačnom ishodu: starost, ocenu prema rendgenskim nalazima (prema Heringu i Katarelu) i adekvatnu strategiju u pristupu lečenja.

Odabrali smo manje invazivnu i retko korišćenu tehniku: artrodijastu kuka korišćenjem Ilizarov cirkularnog okvira u kombinaciji sa tuneliranjem vrata i glave butne kosti. To je minimalno invazivna hirurška procedura i tehnički manje zahtevna: kraće lečenje pacijenta, manji rizik od komplikacija i niži troškovi u poređenju sa osteotomijom karlice i butne kosti. Ova tehnika bi mogla pomoći u lečenju manje neusaglašenosti nogu, kao jednog od kliničkih i radioloških znakova u evoluciji Pertesove bolesti.

Želimo da naglasimo da artrodijastazu sa tuneliranjem, kao minimalno invazivnu operaciju, treba smatrati jednom od prvih opcija lečenja u ranoj fazi LKPB-a kada glava butne kosti još uvek nema nikakve strukturne promene i nakon neuspelog konzervativnog tretmana.

IZJAVE ZAHVALNOSTI

Zahvaljujemo Aleksandru Stevanoviću na kritičkom osvrtu na rukopis.

Sukob interesa: Nije prijavljen.

Patients over the age of 6 have better outcomes using the surgical approach in LCPD treatment [16]. According to their studies, some authors concluded that the major factor in LCPD prognosis of the outcome is an X-ray finding, precisely the level of aseptic narcosis of the femoral head [20,21].

It has been shown that drilling a tunnel affects less than 10% of the total area of the growth cartilage, it does not impair the growth plate and it does not reduce growth in the hip region [22]. Several authors treated patients with arthrodiastasis using monolateral fixator; however, they used a biomechanically weaker fixator method, and large diameter pins for tunneling and their patients did not weight bear during the whole length of treatment [23,24]. Kocaoglu presented and published results of the Ilizarov apparatus usage in Perthes disease. He used a robust and complex Ilizarov frame at the early stage of the femoral head fragmentation, and his success rate was not very impressive. To maintain the containment of the femoral head it is mandatory to initiate the treatment during the stage of necrosis or early fragmentation stage, thus before the collapse of the femoral epiphysis [25]. Despite the literature review on the gold standard in surgical approach (pelvic osteotomy like Salter, Chiari, or triple pelvic osteotomy), hip arthrodiastasis with tunneling should be considered as an alternative surgical technique. Hip arthrodiastasis and femoral head and neck tunneling should be considered at an early stage of LCPD and the late onset of disease when standard surgical procedures do not give great outcomes [26].

The usage of this technique has gained a full range of painless motion, without secondary disorders or gait disturbances. The risk of lateral subluxation of the femoral head was decreased in X-ray findings, the femoral head congruency was reached without anatomic violation in the hip joint. This technique might also be used in older children and adolescents with poor prognosis (according to X-ray findings) and in contraindications to do pelvic osteotomy.

This LCPD case report presents the most important values in the outcome: age, rating according to X-ray findings (according to Herring and Catarell), and adequate strategy in the treatment approach.

We chose the less invasive and rarely used technique: hip arthrodiastasis using the Ilizarov circular frame in combination with femoral neck and head tunneling. It is a minimally invasive surgery procedure and technically less demanding: shorter patient–in treatment, minor risk of complications, and lower costs in comparison to pelvic and femoral osteotomy. This technique might help treat a minor leg discrepancy, as one of the clinical and radiological signs in the evolution of Perthes disease.

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We want to emphasize that arthrodiastasis with tunneling, as a minimally invasive surgery should be considered as one of the first treatment options at an early stage of LCPD when the femoral head still does not have any structural changes and conservative treatment failed.

ACKNOWLEDGMENTS

We thank Aleksandar Stevanović for his critical review of the manuscript.

Conflict of interest: None declared.

NEUROPSIHIJATRIJSKI LUPUS – DVA LICA JEDNE BOLESTI (PRIKAZ DVA SLUČAJA)

PRIKAZ SLUČAJA

CASE REPORT

NEUROPSYCHIATRIC LUPUS – TWO FACES OF ONE DISEASE (TWO CASE REPORTS)

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SAŽETAK

Uvod: Neuropsihijatrijski lupus (neuropsihijatrijski sistemski eritemski lupus – NPSEL) je forma sistemske autoimunske bolesti – sistemskog eritemskog lupusa, sa dominantnim zahvatanjem centralnog i perifernog nervnog sistema. Nuklearna magnetna rezonanca (NMR) mozga se smatra zlatnim standardom za dijagnostiku pacijenata sa neuropsihijatrijskim lupusom. Lečenje NPSEL-a uključuje: visoke doze kortikosteroida, pulsnu terapiju metilprednizolonom, intravenske imunoglobuline, plazmaferezu, imunosupresive (ciklofosfamid, azatioprin, mikofenolat mofetil), te biološku terapiju – rituksimab.

Prikaz slučajeva: U ovom radu su prikazane dve pacijentkinje sa dijagnozom neuropsihijatrijskog lupusa, sa različitim kliničkim manifestacijama bolesti, kao i sprovedenu dijagnostika, te povoljni ishod imunosupresivne terapije postignut kod obe pacijentkinje.

Zaključak: Patogeneza NPSEL-a uključuje neuroinflamatorne (autoimunske) i ishemijske mehanizme. Neuroimidžing (engl. *neuroimaging*) je pokazao dobre rezultate u razlikovanju pacijenata sa sistemskim eritemskim lupusom (SEL) u odnosu na kontrolnu grupu. Cilj lečenja SEL-a je postizanje remisije ili niske aktivnosti bolesti kao i sprečavanje epizoda pogoršanja. Terapija intravenskim ciklofosfamidom, kao i sistemskim kortikosteroidima, pokazala je značajno pozitivne rezultate kod pacijenata sa NPSEL-om. Postoji velika potreba za novim biomarkerima u serumu i likvoru kao i inovativnijim radiološkim procedurama u budućnosti. Neophodna su dodatna klinička ispitivanja koja bi dovela do novih terapijskih opcija u lečenju NPSEL-a.

Ključne reči: neuropsihijatrijski lupus, NMR mozga, metilprednizolon, ciklofosfamid

ABSTRACT

Introduction: Neuropsychiatric lupus (neuropsychiatric systemic lupus erythematosus – NPSLE) is a form of a systemic autoimmune disease – systemic lupus erythematosus (SLE), with dominant central and peripheral nervous system involvement. Nuclear magnetic resonance imaging (NMRI) of the brain is considered the gold standard for diagnosing patients with NPSLE. Treatment of NPSLE includes the following: high doses of corticosteroids, methylprednisolone pulse therapy, intravenous immunoglobulins, plasmapheresis, immunosuppressants (cyclophosphamide, azathioprine, mycophenolate mofetil), and biological therapy – rituximab.

Case reports: In this paper, we present two patients diagnosed with neuropsychiatric lupus, with different clinical manifestations of the disease, as well as the diagnostics performed, and the good clinical outcomes of immunosuppressive therapy achieved in both patients.

Conclusion: The pathogenesis of NPSLE involves neuroinflammatory (autoimmune) and ischemic mechanisms. Neuroimaging has shown good results in differentiating patients with SLE from controls. The goal of SLE treatment is to achieve remission or low disease activity and to prevent episodes of exacerbation. Treatment with intravenous cyclophosphamide as well as with systemic corticosteroids has shown significantly positive results in patients with NPSLE. There is great need, in the future, for new biomarkers in the serum and cerebrospinal fluid (CSF), as well as for more innovative radiological procedures. Additional clinical trials that would lead to new therapeutic options for the treatment of NPSLE are necessary.

Keywords: neuropsychiatric lupus, brain NMRI, methylprednisolone, cyclophosphamide

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Primljeno • *Received*: November 29, 2023; **Revidirano • *Revised*:** December 8, 2023; **Prihvaćeno • *Accepted*:** December 12, 2023; ***Online first*:** December 25, 2023

DOI: 10.5937/smclk4-47964

UVOD

Neuropsihijatrijski lupus (neuropsihijatrijski sistemski eritemski lupus – NPSEL) je forma sistemske autoimunske bolesti – sistemskog eritemskog lupusa (SEL), sa dominantnim zahvatanjem centralnog i perifernog nervnog sistema [1]. Oko 50% pacijenata razvija neuropsihijatrijske simptome SEL-a, unutar jedne godine od početka sistemskog eritemskog lupusa [2]. NPSEL uključuje niz neuroloških i psihijatrijskih simptoma koji utiču na kvalitet života pacijenata, kao i na prognozu bolesti [3]. Kod pacijenata sa SEL-om, mortalitet od NPSEL-a je na drugom mestu, odmah iza lupusnog nefritisa [4]. Prevalencija NPSEL-a varira u rasponu od 37% do 95%. Na ovakav rezultat utiču različiti dijagnostički kriterijumi, dizajni studija, različite populacije i rase pacijenata, praćenje različitih kohorti pacijenata, kao i tipovi i težina kliničke slike bolesti [1]. Nuklearna magnetna rezonanca (NMR) mozga se smatra zlatnim standardom za dijagnostiku pacijenata sa NPSEL-om [5]. Lečenje NPSEL-a uključuje: visoke doze kortikosteroida, pulsnu terapiju metilprednizolonom, intravenske imunoglobuline, plazmaferezu, imunosupresive (ciklofosfamid, azatioprin, mikofenolat mofetil), te biološku terapiju – rituksimab [2].

Cilj ovog rada je da se prikažu dve potpuno različite manifestacije neuropsihijatrijskog lupusa, izazove u njihovoj dijagnostici, kao i postignuti povoljni odgovor na imunosupresivnu terapiju.

PRIKAZ DVA SLUČAJA

Prikaz prvog slučaja

Prvi slučaj jeste pacijentkinja stara 65 godina. Dijagnoza sistemskog eritemskog lupusa (SEL) je kod ove pacijentkinje postavljena 1991. godine, na osnovu kožnih promena, fotosenzitivnosti, poliartralgije, ranica u ustima i nosu, poliserozitisa, bicitopenije, + antinukleusnih antitela (ANA), + anti-Smit antitela (anti-Sm at), sniženih vrednosti C4 komponente komplementa, te zapaljenskog sindroma. U isto vreme je postavljena i dijagnoza sekundarnog Sjogrenovog sindroma, koja je potvrđena patohistološkim nalazom biopsije male pljuvačne žlezde.

Inicijalna terapija sa zadovoljavajućim efektom uključivala je primenu parenteralne (metilprednizolon 1 mg/kg) i *per os* (prednizon – doza održavanja 10 mg/dan) glukokortikosteroidne (GKS) terapije, uz antimalarik – hidroksihlorokin u dozi od 200 mg/dan. Tokom vremena javljala su se povremena pogoršanja u vidu poliserozitisa i kutanog diskoidnog lupusa sa dobrim odgovorom na pulsnu terapiju metilprednizolonom.

Novembra 2015. godine, po prvi put od početka bolesti, javlja se prvi *Grand mal* epileptični napad. Na

INTRODUCTION

Neuropsychiatric lupus (neuropsychiatric systemic lupus erythematosus – NPSLE) is a form of systemic autoimmune disease – systemic lupus erythematosus (SLE), with dominant involvement of the central and peripheral nervous system [1]. About 50% of patients develop neuropsychiatric symptoms of SLE within one year of the onset of systemic lupus erythematosus [2]. NPSLE includes a number of neurological and psychiatric symptoms that affect the quality of life of patients, as well as the prognosis of the disease [3]. In patients with SLE, mortality from NPSLE is second only to lupus nephritis [4]. The prevalence of NPSLE varies between 37% and 95%. This result is affected by different diagnostic criteria, study designs, different populations and races of patients, follow-up of different cohorts of patients, as well as the types and severity of the clinical presentation of the disease [1]. Nuclear magnetic resonance imaging (NMRI) of the brain is considered the gold standard for the diagnosis of patients with NPSLE [5]. Treatment of NPSLE includes the following: high doses of corticosteroids, pulse therapy with methylprednisolone, intravenous immunoglobulins, plasmapheresis, immunosuppressants (cyclophosphamide, azathioprine, mycophenolate mofetil), and biological therapy – rituximab [2].

The aim of this study is to present two completely different manifestations of neuropsychiatric lupus, the challenges in their diagnosis, as well as the favorable response to immunosuppressive therapy.

TWO CASE REPORTS

Case report I

The first case is a 65-year-old female patient. The diagnosis of systemic lupus erythematosus (SLE) was established in this patient in 1991, based on skin changes, photosensitivity, polyarthralgia, sores in the mouth and nose, polyserositis, bicytopenia, + antinuclear antibodies (ANAs), + anti-Smith antibodies (anti- Sm at), decreased values of the complement component 4 (C4), and inflammatory syndrome. At the same time, a diagnosis of secondary Sjögren's syndrome was made, which was confirmed by the pathohistological findings of a small salivary gland biopsy.

Initial treatment, which achieved a satisfactory effect included the use of parenteral (methylprednisolone 1 mg/kg) and *per os* (prednisone – maintenance dose of 10 mg/day) glucocorticosteroid (GCS) therapy, together with an antimalarial drug – hydroxychloroquine at a dose of 200 mg/day. Over time, there were occasional exacerbations, in the form of polyserositis and cutaneous discoid lupus with a good response to pulse therapy with methylprednisolone.

elektroencefalogramu (EEG) su opisane epileptiformne promene sa paroksizmalnim šiljcima i oštrim talasima. U terapiju je uvedena valproinska kiselina, kao i natrijum valproat. Januara 2016. godine, urađena je NMR endokranijuma gde su opisane supratentorijalne multiple mikroangiopatske lezije bele mase, suspektno vaskulitisne etiologije uz kortikalne reduktivne promene. Istog meseca, pacijentkinja je imala još jedan *Grand mal* napad. Nije bilo kliničkih i laboratorijskih kriterijuma za dijagnozu sekundarnog antifosfolipidnog sindroma. Uz konsultaciju sa neurologom, postavljena je dijagnoza NPSEL-a.

Početkom 2016. godine, započeta je pulsna terapija ciklofosfamidom (500 mg/m^2 telesne površine (TP)) uz dva pulsa metilprednizolona od po 500 mg. Nakon mesec dana, pacijentkinja je imala treći i poslednji *Grand mal* napad. Kod pacijentkinje je primenjeno ukupno 12 ciklusa terapije ciklofosfamidom u kumulativnoj dozi od 10 grama. Po završetku terapije, na kontrolnom EEG-u nisu opisane epileptiformne promene, kontrolna NMR endokranijuma je bila bez bitnijih promena u odnosu na početak bolesti. Po završetku lečenja ciklofosfamidom, u terapiju je, pored prednizona u dozi od 10 mg/dan i hidroksihlorokina od 200 mg/dan, uveden i azatioprin u dozi od 100 mg/dan. U nekoliko navrata tokom lečenja ciklofosfamidom, detektovane su asimptomatske urinarne infekcije sa blažom hipogamaglobulinemijom, koje su, pored antibiotske terapije, lečene i primenom humanih intravenskih imunoglobulina (IVIG).

Prikaz drugog slučaja

Drugi slučaj jeste pacijentkinja stara 53 godine. Njoj je, 2016. godine, postavljena dijagnoza Sjogrenovog sindroma, na osnovu pozitivnih antinukleusnih antitela, povišenih anti SSA antitela (anti-SSA at), suvog oka (keratokonjuktivitis *sicca* – KK *sicca*; lat. *keratoconjunctivitis sicca*), patološkog nalaza scintigrafije pljuvačnih žlezda koji je dokazao postojanje smanjene akumulacione i ekskrecione sposobnosti pljuvačnih žlezda, PH nalaza biopsije pljuvačnih žlezda sa fokusima limfocitne infiltracije, kseroftalmije, kserostomije, te poliartralgije.

Pacijentkinja je inicijalno lečena prednizonom u dozi od 1 mg/kg, uz postepeno smanjivanje doze do 15 mg/dan, kao i hidroksihlorokinom u dozi od 300 mg/dan. Nakon nekoliko meseci, javilo se akutno konfuzno stanje uz kognitivnu disfunkciju. Pacijentkinja je pregledana od strane neurologa i inicijalno je postavljena sumnja na *Morbus Alzheimer*. Urađena je NMR endokranijuma, na kojoj su opisane punktiformne mikroangiopatske lezije, fronto-parijetalno, obostrano, uz kortikalne reduktivne promene.

In November 2015, for the first time since the onset of the disease, the first grand mal epileptic seizure occurred. Epileptiform changes with paroxysmal spikes and sharp waves were recorded on the electroencephalogram (EEG). Valproic acid and sodium valproate were introduced as a part of the therapy. In January 2016, an NMRI of the endocranium was performed recording supratentorial multiple microangiopathic white matter lesions of suspected vasculitis etiology, with cortical reductive changes. In the same month, the patient had another grand mal seizure. There were no clinical or laboratory criteria for the diagnosis of secondary antiphospholipid syndrome. In consultation with a neurologist, the diagnosis of NPSLE was established.

In early 2016, cyclophosphamide pulse therapy (500 mg/m^2 body surface area (BSA)) was started, with two pulses of methylprednisolone – 500 mg each. After one month, the patient had her third and final grand mal seizure. The patient received a total of 12 cycles of cyclophosphamide therapy, with a cumulative dose of 10 grams. After the end of the therapy, no epileptiform changes were described on the follow-up EEG, while the follow-up NMRI of the endocranium was without significant changes, as compared to the beginning of the disease. After the end of treatment with cyclophosphamide, in addition to prednisone at a dose of 10 mg/day and hydroxychloroquine at a dose of 200 mg/day, azathioprine at a dose of 100 mg/day was also introduced into the therapy. On several occasions during treatment with cyclophosphamide, asymptomatic urinary infections with mild hypogammaglobulinemia were detected, which, in addition to antibiotic therapy, were also treated with the use of human intravenous immunoglobulins (IVIGs).

Case report II

The second case is a 53-year-old female patient. In 2016, she was diagnosed with Sjögren's syndrome, based on a positive ANA test, elevated anti-SSA antibodies (anti-SSA at), dry eye syndrome (keratoconjunctivitis sicca – KC sicca), a pathological finding of salivary gland scintigraphy proving reduced accumulation and excretory capacity of the salivary glands, the PH finding of salivary gland biopsy with foci of lymphocytic infiltration, xerophthalmia, xerostomia, and polyarthralgia.

The patient was initially treated with prednisone at a dose of 1 mg/kg, which was gradually reduced to 15 mg/day, as well as with hydroxychloroquine at a dose of 300 mg/day. After several months, acute confusional state with cognitive dysfunction occurred. The patient was examined by a neurologist, and Alzheimer's disease was initially suspected. NMRI of the endocranium was performed and punctiform microangiopathic le-

Marta 2017. godine, tokom prve hospitalizacije na Klinici za alergologiju i imunologiju Univerzitetskog kliničkog centra Srbije (UKCS) postavljena je dijagnoza neuropsihijatrijskog lupusa, na osnovu fotosenzitivnosti, poliartralgije, + ANA, + lupus antikoagulans testa (LA), bicitopenije, te neuropsihijatrijskih manifestacija. Od strane psihijatra je postavljena dijagnoza anksiozno-depresivnog sindroma i u terapiju je uveden selektivni inhibitor preuzimanja serotonina (engl. *selective serotonin reuptake inhibitor – SSRI*) – sertralin, u dozi od 50 mg/dan. Elektromioneurografskim pregledom (EMNG) isključeno je postojanje polineuropatije (PNP). Pregledom neurologa konstatovana je desnostrana slabost uz hod na širokoj osnovi.

Jula 2017. godine, započeta je imunosupresivna terapija ciklofosfamidom u dozi od 500 mg/m^2 telesne površine, i ukupno ordinirano 12 ciklusa sa kumulativnom dozom od 7,2 grama, uz pulseve metilprednizolona od po1.000 mg po ciklusu. Od postavljanja dijagnoze, pored prednizona i antimalarika, u terapiju je uključena i acetilsalicilna kiselina u dnevnoj dozi 100 mg, zbog + lupus antikoagulansa (LA). Nakon završenih 12 ciklusa terapije ciklofosfamidom, urađena je kontrolna NMR endokranijuma, čiji nalaz je bio značajnije neizmenjen u odnosu na prethodni, pre započinjanja terapije.

Od strane psihijatra, krajem 2018. godine, iz terapije je isključen antidepresiv, dok je produžena terapija benzodiazepinom, po potrebi. Već nakon prvog ciklusa ciklofosfamidom, nisu se više javljali napadi akutnog konfuznog stanja, dok su kognitivne funkcije bile značajno poboljšane. Terapija održavanja je u daljem toku, pored prednizona u dozi od 10 mg/dan, hidroksihlorokina u dozi od 200 mg/dan i acetilsalicilne kiseline u dozi od 100 mg/dan, uključivala i azatioprin u dozi od 100 mg/dan.

DISKUSIJA

Neuropsihijatrijska forma sistemskog eritemskog lupusa je oduvek predstavljala izazov za kliničare, kako na dijagnostičkom tako i na terapijskom nivou [1]. NPSEL se češće javlja kod afričke i azijske populacije, ali je uočeno da su teži oblici bolesti češći kod bele rase [5]. NPSEL ima široki spektar i visoku heterogenost kliničkih fenotipova, uključujući glavobolju, epilepsiju, moždani udar, perifernu neuropatiju, kognitivne poremećaje, gubitak pamćenja, te psihijatrijske simptome. [2,4].

Američki koledž za reumatologiju (engl. *American College of Rheumatology – ACR*) je 1999. godine predložio 19 entiteta u sklopu NPSEL-a (12 u sklopu centralnog nervnog sistema (CNS) i 7 u sklopu perifernog nervnog sistema (PNS), uz podelu još i na difuznu i fokalnu zahvaćenost nervnog sistema (NS)), (Tabela 1) [1]. Moždane manifestacije SEL-a se definišu kao fokalni i

sions were registered, fronto-parietally, bilaterally, with cortical reductive changes.

In March 2017, during the patient's first hospital stay at the Clinic of Allergology and Immunology of the University Clinical Center of Serbia (UCCS), a diagnosis of neuropsychiatric lupus was made, based on photosensitivity, polyarthralgia, + ANA, + lupus anticoagulant test (LA), bicytopenia, and neuropsychiatric manifestations. A psychiatrist diagnosed anxiety-depressive syndrome and selective serotonin reuptake inhibitor (SSRI) – sertraline, at a dose of 50 mg/day, was introduced as a part of the therapy. The electromyoneurography (EMNG) finding ruled out polyneuropathy (PNP). An examination by a neurologist revealed right-sided weakness with broad-based gait.

In July 2017, the patient was started on immunosuppressive therapy with cyclophosphamide at a dose of 500 mg/m^2 of body surface area, and a total of 12 cycles were prescribed with a cumulative dose of 7.2 grams, with methylprednisolone pulses of 1,000 mg per cycle. Since the diagnosis, in addition to prednisone and antimalarial drugs, the therapy included acetylsalicylic acid at a daily dose of 100 mg, due to + lupus anticoagulant (LA). After completing 12 cycles of cyclophosphamide therapy, a follow-up NMRI of the endocranium was performed, and the findings were significantly unchanged, as compared to the previous one, performed before the beginning of therapy.

In late 2018, the patient's psychiatrist discontinued antidepressant treatment, but continued treatment with benzodiazepine, as needed. As early as the first cycle with cyclophosphamide was completed, attacks of acute confusional state no longer occurred, while cognitive functions were significantly improved. In addition to prednisone at a dose of 10 mg/day, hydroxychloroquine at a dose of 200 mg/day, and acetylsalicylic acid at a dose of 100 mg/day, further maintenance therapy also included azathioprine at a dose of 100 mg/day.

DISCUSSION

The neuropsychiatric form of systemic lupus erythematosus has always been a challenge for clinicians, both at the diagnostic and at the therapeutic level [1]. NPSLE occurs more often in African and Asian populations, however, more severe forms of the disease have been observed as more common in Caucasians [5]. NPSLE has a wide spectrum and high heterogeneity of clinical phenotypes, including headache, epilepsy, stroke, peripheral neuropathy, cognitive impairment, memory loss, and psychiatric symptoms. [2,4].

In 1999, the American College of Rheumatology (ACR) proposed 19 entities within NPSLE (12 with-

Tabela 1. Manifestacije neuropsihijatrijskog SEL-a, prema Američkom koledžu za reumatologiju (ACR)

	Centralni nervni sistem (CNS)	Periferni nervni sistem (PNS)
Difuzne manifestacije (psihijatrijski poremećaji)	Akutno konfuzno stanje Anksiozni poremećaji Kognitivne disfunkcije Poremećaji raspoloženja Psihoze	
Fokalne manifestacije (neurološki poremećaji)	Aseptični meningitis Cerebrovaskularne bolesti Demijelinizacioni sindrom Glavobolje Poremećaji pokreta Mijelopatija Epilepsija	Gilen Bareov sindrom Bolesti autonomnog nervnog sistema Mononeuropatije Mijastenija gravis Kranijalna neuropatija Pleksopatija Polineuropatija

Table 1. Manifestations of neuropsychiatric SLE according to the American College of Rheumatology (ACR)

	Central nervous system (CNS)	Peripheral nervous system (PNS)
Diffuse manifestations (psychiatric disorders)	Acute confusional state Anxiety disorders Cognitive dysfunction Mood disorders Psychoses	
Focal manifestations (neurological disorders)	Aseptic meningitis Cerebrovascular diseases Demyelination syndrome Headaches Movement disorders Myelopathy Epilepsy	Guillain-Barre syndrome Diseases of the autonomous nervous system Mononeuropathies Myasthenia gravis Cranial neuropathy Plexopathy Polyneuropathy

difuzni neurološki deficiti, pri čemu su fokalni poremećaji uglavnom posledica tromboembolijskih događaja prouzrokovanih prisustvom antifosfolipidnih antitela. Patogeneza difuznih poremećaja (afektivni i kognitivni poremećaji) značajno je kompleksnija i za sada nedovoljno razjašnjena [3]. Većina simptoma NPSEL-a može se javiti i u sklopu komorbiditeta ili može biti posledica terapije glukokortikosteroidima (GKS), što značajno otežava dijagnostiku ove bolesti [4].

Patogeneza NPSEL-a uključuje neuroinflamatorne (autoimunske) i ishemijske mehanizme. Patološki mehanizam kod SEL-a uključuje gubitak imunološke tolerancije na ćelijski nuklearni antigen, proizvodnju autoantitela i taloženje imunskih kompleksa, što dovodi do aktivacije komplementa, upale tkiva i ćelijske apoptoze. Izmenjena je aktivacija B i T ćelija kao i produkcija interferona tip I. U većini slučajeva koegzistiraju oba patogenetska mehanizma [5].

Disfunkcija krvno-moždane barijere sa posledičnim prolaskom antitela u cerebrospinalnu tečnost kao

in the central nervous system (CNS) and 7 within the peripheral nervous system (PNS), with an additional distinction between diffuse and focal involvement of the nervous system (NS)), (Table 1) [1]. Cerebral manifestations of SLE are defined as focal and diffuse neurological deficits, whereby focal disorders are mainly due to thromboembolic events caused by the presence of antiphospholipid antibodies. The pathogenesis of diffuse disorders (affective and cognitive disorders) is significantly more complex and, as yet, insufficiently understood [3]. Most of the symptoms of NPSLE can occur within comorbidities or can be a consequence of glucocorticosteroid (GCS) therapy, which significantly complicates the diagnosis of this disease [4].

The pathogenesis of NPSLE involves neuroinflammatory (autoimmune) and ischemic mechanisms. The pathological mechanism in SLE involves the loss of immune tolerance to the cell nuclear antigen, production of autoantibodies, and build-up of immune complexes, leading to complement activation, tissue inflamma-

i intratekalna sinteza antitela, jesu poremećaji koji se javljaju u sklopu NPSEL-a. Prisustvo antifosfolipidnih antitela povezano je pre svega sa pojavom trombotičkih događaja, kao što je moždani udar, u sklopu NPSEL-a, ali i sa pojavom epileptičnih napada, poremećaja pokreta, kognitivne disfunkcije i mijelopatije. Anti-akva porin 4 antitela su povezana sa pojavom transferzalnog mijelitisa i optičkog neuromijelitisa. Anti-P ribozomska antitela najčešće su povezana sa pojavom psihoze. U sklopu NPSEL-a se javljaju i anti-N metil D aspartat receptorska antitela koja zajedno sa anti-P ribozomalnim antitelima učestvuju u patofiziologiji difuznih oštećenja preko toksičnog oštećenja neurona i izazivanja apoptoze [1]. Kod difuznih formi NPSEL-a sa kliničkom slikom akutnog konfuznog stanja, uočen je povišen nivo IL-6 u cerebrospinalnoj tečnosti. Zbog nedostatka specifičnosti, za sada se ne radi rutinska provera prisustva ovog citokina u cerebrospinalnoj tečnosti [1,5].

Neuroimidžing je pokazao dobre rezultate u razlikovanju pacijenata sa SEL-om, u odnosu na kontrolnu grupu [3]. Neuroimidžing nije specifičan za postavljanje dijagnoze NPSEL-a, ali je od značaja za isključivanje drugih uzročnika (infektivni, neoplastični, aneurizme, i drugi) neuropsihijatrijskih simptoma kod ovih pacijenata [4]. Uobičajeni nalaz konvencionalnog NMR snimanja mozga kod pacijenata sa SEL-om uključuje hiperintenzivne promene bele mase kao i atrofiju mozga, ali ove promene nisu specifične [6].

Cilj lečenja SEL-a je postizanje remisije ili niske aktivnosti bolesti, kao i sprečavanje epizoda pogoršanja. Kod svih pacijenata sa SEL-om se preporučuje primena hidroksihlorokina u dozi ne većoj od 5 mg/kg telesne mase (TM). Doza održavanja prednizona ne treba da prelazi 7,5 mg/dan, sa tendencijom potpunog isključivanja kada se steknu uslovi. Primena imunomodulatornih agenasa (metotreksat, azatioprin, mikofenolat) može skratiti vreme potrebno za smanjenje doze GKS-a ili njihovo potpuno isključivanje iz terapije. Kod svih pacijenata sa pozitivnim antifosfolipidnim antitelima (aFL at) preporučuje se primarna profilaksa niskim dozama acetilsalicilne kiseline. Primena antikoagulante terapije – niskomolekularni heparini (engl. *low molecular weight heparins – LMWHs*), preporučuje se naročito tokom trudnoće kao i u postoperativnom toku. U zavisnosti od manifestacije bolesti, potrebna je i simptomatska terapija (antipsihotici, anksiolitici, i dr.) [7]. Hidroksihlorokin se koristi kao prva terapijska linija kod pacijenata sa SEL-om bez značajnijih oštećenja organskih sistema. Predložena je i njegova primena za primarnu prevenciju NPSEL-a, posebno za cerebrovaskularne događaje i epileptičke napade [2]. Terapija intravenskim ciklofosfamidom, kao i sistemskim kor-

tion, and cell apoptosis. The activation of B and T cells, as well as the production of interferon type I, is altered. In most cases, both pathogenetic mechanisms coexist at the same time [5].

Dysfunction of the blood-brain barrier with consequent passage of antibodies into the cerebrospinal fluid, as well as intrathecal synthesis of antibodies, are disorders that occur as a part of NPSLE. The presence of antiphospholipid antibodies is primarily associated with the occurrence of thrombotic events, such as stroke, in NPSLE, but also with the occurrence of epileptic seizures, movement disorders, cognitive dysfunction, and myelopathy. Anti-aqua porin 4 antibodies are associated with the occurrence of transverse myelitis and neuromyelitis optica. Anti-P ribosomal antibodies are most often associated with the onset of psychosis. As a part of NPSLE, anti-N methyl D aspartate receptor antibodies also appear, and, together with anti-P ribosomal antibodies, participate in the pathophysiology of diffuse damage through toxic damage to neurons and the induction of apoptosis [1]. In diffuse forms of NPSLE with clinical presentation of acute confusional state, an elevated level of IL-6 in the cerebrospinal fluid has been observed. Due to the lack of specificity, the presence of this cytokine in the cerebrospinal fluid is not routinely tested for, as yet [1,5].

Neuroimaging has shown good results in differentiating patients with SLE, as compared to the control group [3]. Neuroimaging is not specific for the diagnosis of NPSLE, but it is important for excluding other causes (infectious agents, neoplastic causes, aneurysms, and others) of neuropsychiatric symptoms in these patients [4]. A common finding of conventional NMRI brain imaging in patients with SLE includes hyperintense white matter changes as well as brain atrophy, but these changes are not specific [6].

The goal of SLE treatment is to achieve remission or low disease activity, as well as to prevent episodes of exacerbation. In all patients with SLE, the administration of hydroxychloroquine at a dose not exceeding 5 mg/kg of body weight (BW) is recommended. The maintenance dose of prednisone should not exceed 7.5 mg/day, with a tendency to completely discontinue the drug, when the conditions for this are met. The use of immunomodulatory agents (methotrexate, azathioprine, mycophenolate) can shorten the time required to reduce the dose of GCSs or to completely exclude them from therapy. In all patients with positive antiphospholipid antibodies (aPL at), primary prophylaxis with low doses of acetylsalicylic acid is recommended. The use of anticoagulant therapy – low molecular weight heparins (low molecular weight heparins – LMWHs) is recommended, especially during pregnancy,

tikosteroidima, pokazala je značajno pozitivne rezultate kod pacijenata sa NPSEL-om, i danas je u većini slučajeva ovo prva terapijska opcija kod formi bolesti sa zahvatanjem organskih sistema (bubrezi, centralni i periferni nervni sistem) [5]. U randomizovanim kontrolisanim studijama, poređena je primena ciklofosfamida sa pulsnim dozama kortikosteroida i zaključeno je da bolji efekat ima lečenje ciklofosfamidom. Pokazano je da primena azatioprina, kao terapije održavanja, smanjuje relapse bolesti [2]. Isti efekat sa još bezbednijim terapijskim profilom ima i primena mikofenolat mofetila. Rituksimab je anti-CD20 IgG1 monoklonsko antitelo koje uništava B limfocite delujući na CD20 molekule koji se nalaze na njihovoj površini [2]. Postoje ograničeni podaci o efikasnosti biološke terapije u lečenju NPSEL-a. Upotreba rituksimaba pokazala je povoljne efekte ali potrebne su dodatne studije o efikasnosti. Belimumab je pokazao pozitivan efekat kod pacijenata sa blažom formom bolesti [5]. Kod pogoršanja ekstrarenalne forme bolesti, može se primeniti belimumab, dok se kod pogoršanja i aktivnosti SEL-a sa potencijalnim ugrožavanjem organskih sistema, može primeniti rituksimab [7].

Novija saznanja pokazuju da farmakološka modulacija mikroglije može uticati na ublažavanje simptoma bolesti (imunomodulator fingolimod; modulator sfingozin 1 fosfat receptora, koji deluje na limfocite tako što ih sekvestrira u limfne čvorove i sprečava njihovu migraciju na mesto autoimunskog procesa) [3]. Postoji potreba za novim terapijskim opcijama koje bi bile usmerene na poremećaj krvno-moždane barijere, citokine i mikroglijalne ćelije [5].

Uprkos opsežnim kliničkim istraživanjima, do sada se nijedan laboratorijski ni neuroimidžing biomarker nije pokazao kao potpuno precizan u dijagnozi NPSEL-a. Postoji velika potreba za novim biomarkerima u serumu i likvoru kao i za inovativnijim radiološkim procedurama u budućnosti [5]. Neophodna su dodatna klinička ispitivanja koja bi dovela do novih terapijskih opcija u lečenju NPSEL-a.

SPISAK SKRAĆENICA

NPSEL – neuropsihijatrijski sistemski eritemski lupus
NMR – nuklearna magnetna rezonanca
SEL – sistemski eritemski lupus
ANA – antinukleusna antitela
Anti-Sm at – anti-Smit antitela
GKS – glukokortikosteroidi
EEG – electroencefalogram
IVIG – intravenski imunoglobulini
Anti-SSA at – anti-Sjogren sindrom A antigen
KK *sicca* – keratokonjuktivitis *sicca*
LA – lupus antikoagulans

as well as during postoperative recovery. Depending on the manifestation of the disease, symptomatic therapy is also necessary (antipsychotic drugs, anxiolytic drugs, etc.) [7]. Hydroxychloroquine is used as first-line treatment in patients with SLE without significant damage to organ systems. Its application has also been suggested for the primary prevention of NPSLE, especially for cerebrovascular events and epileptic seizures [2]. Therapy with intravenous cyclophosphamide, as well as with systemic corticosteroids, has shown significantly positive results in patients with NPSLE, and nowdays, in most cases, this is the therapeutic option of choice for forms of the disease that involve organ systems (kidneys, the central and peripheral nervous system) [5]. In randomized controlled trials, the use of cyclophosphamide was compared with pulsed doses of corticosteroids, and it was concluded that treatment with cyclophosphamide had a better effect. It has been shown that the use of azathioprine, as maintenance therapy, reduces disease relapses [2]. The use of mycophenolate mofetil has the same effect with an even safer therapeutic profile. Rituximab is an anti-CD20 IgG1 monoclonal antibody that destroys B lymphocytes by acting on CD20 molecules located on their surface [2]. There are limited data on the effectiveness of biological therapy in the treatment of NPSLE. The use of rituximab has shown favorable effects, but additional studies on efficacy are needed. Belimumab has shown a positive effect in patients with the mild form of the disease [5]. In case of exacerbation of the extrarenal form of the disease, belimumab can be used, while in the case of exacerbation and activity of SLE, with a potential threat to organ systems, rituximab can be used [7].

More recent findings have shown that pharmacological modulation of microglia can affect the alleviation of disease symptoms (immunomodulator fingolimod; modulator of the sphingosine 1 phosphate receptor, which acts on lymphocytes by sequestering them in lymph nodes and preventing their migration to the site of the autoimmune process) [3]. There is a need for new therapeutic options that would target the disruption of the blood-brain barrier, cytokines, and microglial cells [5].

Despite extensive clinical research, to date, no laboratory or neuroimaging biomarker has proven to be completely accurate in the diagnosis of NPSLE. There is great need for new biomarkers in the serum and CSF, as well as for more innovative radiological procedures in the future [5]. Additional clinical trials are necessary that would lead to new therapeutic options in the treatment of NPSLE.

SSRI – selektivni inhibitor preuzimanja serotonina (engl. *selective serotonin reuptake inhibitors*)
EMNG – elektromioneurografija
PNP – polineuropatija
CNS – centralni nervni sistem
PNS – periferni nervni sistem
IL-6 – interleukin-6
aFL at – antifosfolipidna antitela
LMWHs – niskomolekularni heparini (engl. *low molecular weight heparins*)

Sukob interesa: Nije prijavljen.

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LIST OF ABBREVIATIONS AND ACRONYMS

NPSLE - neuropsychiatric systemic lupus erythematosus
NMRI – nuclear magnetic resonance imaging
SLE – systemic lupus erythematosus
ANAs – antinuclear antibodies
Anti-Sm at – anti-Smith antibodies
GCSs – glucocorticosteroids
EEG – electroencephalogram
IVIGs – intravenous immunoglobulins
Anti-SSA at – anti-Sjogren syndrome A antigen
KC sicca – keratoconjunctivitis sicca
LA – lupus anticoagulant
SSRIs – selective serotonin reuptake inhibitors
EMNG – electromyoneurography
PNP – polyneuropathy
CNS – central nervous system
PNS – peripheral nervous system
IL-6 – interleukin-6
aPL at - antiphospholipid antibodies
LMWHs - low molecular weight heparins

Conflict of interest: None declared.

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The sections of the paper are: the cover page, the abstract and keywords, the text of the paper, acknowledgements (optional), literature, and attachments.

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ABSTRACT should be up to 250 words, including acronyms (third page). For original papers, preliminary and short communications, meta-analyses and review papers, the abstract should have the following structure: Introduction, Aim, Methods, Results, Conclusion. Each of these segments should be written as a separate paragraph. For case report, the summary should have the following sections: Introduction, Case Report, Conclusion; each part should be written as a separate paragraph. For other types of papers, the abstract does not have a special structure. List three to six key words or phrases below the abstract. Words from the

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Ukoliko je moguće, sve numeričke vrednosti zaokružiti na jedno decimalno mesto. Ne duplirati prikaz rezultata u tabelama i grafikonima. Za prikaz rezultata u tabelama i tekstu preporuka je da se: numerički podaci sa normalnom raspodelom i bez ekstremnih vrednosti prikazuju kao aritmetička sredina ± standardna devijacija; numerički podaci čija raspodela odstupa od normalnosti ili kada postoje ekstremne vrednosti, i ordinalni podaci prikazuju kao medijana i opseg (minimalna – maksimalna vrednost); nominalni podaci i ordinalni podaci sa malim brojem kategorija prikazuju kao n (%).

Prilikom opisa primenjenih statističkih metoda, prikaza i interpretacije rezultata u radu pridržavati se *SAMPL Guidelines (Lang TA, Altman DG. Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines. Int J Nurs Stud 2015;52(1):5-9.).* Primenjene statističke metode treba opisati dovoljno detaljno da ih čitalac može ponoviti na svojim podacima. Navesti korišćeni statistički test i nivo značajnosti. Saopštiti tačnu *p*-vrednost na 3 decimalna mesta.

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The number of pages provided for the appropriate structure of the paper is counted from the fifth page.

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(mol), a pritisak krvi u milimetrima živinog stuba (mm Hg). Sve rezultate hematoloških, kliničkih i biohemijskih merenja navoditi u metričkom sistemu prema Međunarodnom sistemu jedinica (SI).

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SRPSKI medicinski časopis Lekarske komore
= Serbian journal of the Medical chamber / glavni i odgovorni urednik Milena Šantrić-Milićević. - [Štampano izd.]. - Vol. 1, br. 1 (sep. 2020)- . - Beograd : Lekarska komora Srbije, 2020- (Novi Sad : Sajnos). - 30 cm

Tromesečno. - Tekst na srp. i engl. jeziku. - Drugo izdanje na drugom medijumu: Srpski medicinski časopis Lekarske komore (Online) = ISSN 2737-9752
ISSN 2737-971X = Srpski medicinski časopis Lekarske komore (Štampano izd.)
COBISS.SR-ID 19685641