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HISTORY OF THE SURGERY FOR OTOSCLEROSIS AND COCHLEAR IMPLANTS

ISTORIJA HIRURGIJE OTOSKLEROZE I KOHLEARNIH IMPLANTA

Dragan DANKUC

Surgery for Otosclerosis

At the turn of the 20th century, stapes surgery, and in general surgery for deafness was condemned by most otologists. A number of chance observations were made which encouraged further attempts to relieve deafness in otosclerosis. In 1897 Karl Adolf Passow made a window in the promontory and covered it with the tympanic membrane. His patient reported a slight improvement in hearing. Charles Ballance wrote about an earlier case in 1919, in which he had discovered a fistula into the lateral semicircular canal during the course of mastoid surgery. He covered it with a skin graft and found to his great satisfaction that not only was the patient free of vertigo but that there was an improvement in hearing as well. George J. Jenkins (1874-1939) from London believed that otosclerosis was caused by hypersecretion of labyrinthine fluids and thus attempted to decompress the labyrinth by making a window into the lateral semicircular canal and covering it with a skin graft.

Gunnar Holmgren started to use the first binocular microscope in 1922 and for the first time he was able to demonstrate the otosclerotic focus fixing the stapes footplate. He recognized that osseous closure of the labyrinthine window was the great stumbling block to permanent hearing improvement. Maurice Sourdille (1885-1961) presented first cases of "tympanolabyrinthopexy". His technique of covering a fistula in the horizontal semicircular canal with a meatal flap attached to the tympanic membrane was initially performed in three stages, later was reduced to two, in order to avoid infection and labyrinthitis.

Julius Lempert [1] was inspired by the technique which he followed closely but he applied the endaural approach in one stage. He called this the "fenestration operation" and published his first successful results in 1938. George Shambaugh Jr. (1903-1999) chose from the outset to use the binocular operating microscope and suction irrigation in order to endochondralize the fenestra and to remove all bone dust particles. These two factors greatly reduced the tendency towards osteogenic closure of the fenestra.

Figure 1. Maurice Sourdille (1885-1961)
Slika 1. *Moris Surdil (1885-1961)*

The fenestration operation was introduced in the pre-antibiotic era and gained in popularity as the operation of choice for otosclerosis until the re-establishment of stapes mobilization at the beginning of the 1950s.

Stapedectomy was reintroduced by Sir Terence Cawthorne (1902-1970) from London in 1947 and

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Figure 2. Samuel Rosen (1897-1981)
Slika 2. *Samjuel Rozen (1897-1981)*

Figure 3. John Shea (born 1924)
Slika 3. *Džon Šej (rođen 1924)*

Gino Cornelli [2] from Milan in 1949; the former covered the oval window with a tympanomeatal flap, which produced little hearing improvement, whilst the latter achieved better hearing results simply by opening the oval window after removal of the stapes. Samuel Rosen [3] (1897-1981) from New York rediscovered stapes mobilization by chance in 1952 when he was palpating the stapes to assess its degree of fixation prior to proceeding to a fenestration operation under local anesthesia. He was surprised by the sudden restoration of the patient's hearing. There was less postoperative vertigo, a normal ear canal and drum and an initial hearing improvement in about 70 per cent of cases. Stapes mobilization rapidly enjoyed worldwide popularity and was an important advance in the surgical treatment of otosclerosis.

Various modifications to the operation were made including the anterior crurotomy mobilization described by Milos Basek [4] from New York and Edmund Prince Fowler [5] in 1956. Two years later, the scene changed again with the re-introduction of stapedectomy by John Shea [6] (born 1924) from Memphis, Tennessee. He removed the whole stapes, covered the open oval window initially with "a thin slice of connective tissue" and replaced the stapes with a nylon replica. He later used a short length (4.5 mm) of fine polythene tubing, placed between the incus and vein, which replaced the connective tissue. John Shea thus established the two important principles: the oval window should be sealed and the ossicular continuity restored.

Many modifications followed, most of them being presented during the International Symposium on Otosclerosis in Detroit in 1960. They were the Gel-

Figure 4. Howard House (1907-2003)
Slika 4. *Hauard Haus (1907-2003)*

foam® wire prosthesis by Howard House [7] (1907-2003) from Los Angeles, the fat wire prosthesis by Harold Schuknecht [8] from Boston, the operation of anterior crurotomy with removal of the footplate and replacement of the posterior crus to rest on a vein graft „interposition“ described by Michel Portmann [9] (born 1926) from Bordeaux, the stainless steel by Manford McGree from Detroit and the Teflon® wire by Frederick R. Guilford [10] from Houston. In 1962 John Shea [11] introduced the idea of making a limited opening in the stapes footplate “stapedotomy“ through which he placed a Teflon® piston prosthesis. Progressively, various types of pistons have been developed by different schools of otologic surgery.

Taking into consideration the history of treatment of otosclerosis at the Department of Ear, Nose and Throat Diseases in Novi Sad, it can be said that fenestration surgery has never been applied as a method of treating otosclerosis. Surgical treatment of otosclerosis at our Department began with stapes mobilization. The first mobilization of the stapes was performed in 1958 by Radivoj Topolac (born 1927). The method of House was applied to perform the first stapedectomy in 1962, and Radivoje Topolac performed the stepedotomy in 1974 [12].

Cochlear Implants

William House’s desire to help the profoundly deaf led to his involvement in the early research into cochlear implants. William House was the first to place such an implant inside the cochlea. The concept of electrical stimulation producing hearing sensations in the deaf was not new. Towards the end of the 19th century both Adam Politzer, and Giuseppe Gradenigo were interested in the fact that the passage of an alternating current through electrodes applied around the ear produced sounds. In fact these sound waves were transmitted to the cochlea. By 1930, Ernest Glen Wever and Charles Bray from Princeton observed that an amplified output from an electrode placed intracranially in the acoustic nerve of a cat produced a copy of the speech waveform in both frequency and amplitude.

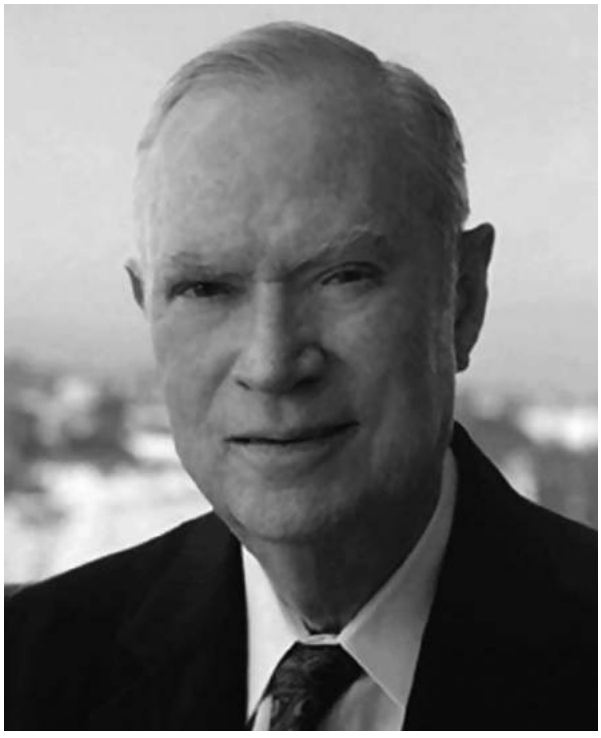

Figure 5. William F. House (1923-2012)
Slika 5. *Vilijam F. Haus (1923-2012)*

A true direct stimulation of the human auditory nerve was perhaps first achieved by Russians Andreef A.M, Gersuni G.V, and Volokhov A.A. [13] in 1934. They placed an electrode near the round window and described various hearing sensations ranging from separate short noises to a smooth buzzing sound. Later, in 1940, the Americans Clark Jones, Smith Stevens (1906-1973) and Moses H. Lurie [14] applied a saline-soaked cotton ball electrode on the round window in nine subjects. The sound of “the chirping cricket“ was described.

The first auditory implantation was performed by André Djourno [15] (1904-1996) and Charles Eyriès (1908-1996) in France in 1957. They inserted a single copper wire near a small segment of cranial nerve VIII in a 50-year old man who was totally deaf. It enabled him to perceive speech rhythm. This report stimulated others and in particular two groups in the United States of America; William House and the Doyle brothers in Los Angeles, and Blair Simmons (1930-1998) and Robert White in Stanford.

In 1961 William House [16] with John Doyle implanted two patients with a single gold electrode placed in the scala tympani. One of these was later replaced with a multiple electrode system. Blair Simmons [17] implanted a six-electrode device in 1964 and found that the patient was able to hear a wide range of sounds. The patient suffered an unforeseen complication of loss of vision due to retinitis pigmentosa, which greatly affected his progress as he was unable to speech-read. Caution was advised by the leading otologists of the day and further clinical work was completely stopped for several years. In 1969 William House [18] again implanted another patient, this time with a six-electrode system developed by his new collaborator Jack Urban. The success with this case led to further implants and the technique became established as a means of alleviating total deafness.

Robert Schindler [19] (born 1943), Michael Merzenich (born 1942), and Robert Michelson (1914-1997) from San Francisco, Claude Henri Chouard [20) from France, Paul Banfai [21] from Germany and Kurt Burian [22] from Austria began clinical work in the 1970s. In Australia Graeme Milbourne Clark [23] (born 1935) used a prototype ten-electrode system in 1978 which, although initially complex, was the first commercialized im-

plant. Ellis Doueck [24] and his group in London pioneered the extracochlear implant in 1977.

Cochlear implants are now produced commercially and nationally approved for clinical use. William House was the first to use a cochlear implant in a prelingually deaf child in 1980.

Cochlear implants are now established as being beneficial to the totally postlingually deaf adult and multichannel implants are superior to those with a single channel. The benefits for the prelingually deaf child are still being fully evaluated. The success of a cochlear implant depends on a fully developed team of otologist, audiology technicians and scientists and teachers of the deaf and, above all, a willing patient.

Yearlong activities had preceded the first cochlear implant surgery performed at the Center for Cochlear Implantation of the Department of Ear, Nose and Throat Diseases, Clinical Center of Vojvodina in 2002, laying the groundwork for its further activities. The first successful cochlear implantation in Serbia was performed at our Center.

The first modern cochlear implant, Nucleus R 24, was placed on November 20, 2002 in a female patient with postlingual hearing impairment (patient I. J., age 40). The surgery was performed by J. Jori, J. G. Kiss from the Ear, Nose and Throat Clinic Szeged, Hungary and Dankuc D. [25] from the Department of Ear, Nose and Throat Diseases in Novi Sad.

Subsequently, Dankuc D, assisted by J. Jori, performed the first implantation of an artificial inner ear in Serbia – a cochlear implant Nucleus R 24. Ever since, the cochlear implant surgery in Novi Sad has been exclusively performed by an experienced team led by Komazec Z. [26], Dankuc D, Vlaški Lj, Lemajić Komazec S, specialized surdopedagogists Nedeljkov S, Sokolovac I, and Vajs O. as well as engineers Mendrei T, and Mrđanov V.

Bone Anchored Hearing Aid

During the 19th century and beginning of the 20th century, various teeth-bone conduction devices were produced; however, they were unsuccessful. The development of the carbon microphone and the magnetic receiver at the beginning of the 1920s enabled the construction of the bone conduction vibrator. In the 1950s the first commercialized bone conduction spectacles were produced by different companies. To enhance the transmission of sound, some of which was lost in the soft tissue, the idea of implanting the vibrator percutaneously into the mastoid bone was pioneered by Per-Ingvar Branemark (born 1929) and Anders Tjellström [27] (born 1937) from Goteborg, Sweden using the principle of osseointegration. In 1977, they implanted the first Baha® (bone anchored hearing aid). In 1981 and in the same spirit, Jack Hought, from Oklahoma City, developed a fully implantable bone conduction device, without much success. By the 1990s the Baha® had become used worldwide.

Figure 6. Anders Tjellström (born 1937)
Slika 6. *Anders Ćelstrem (rođen 1937)*

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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

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Original study
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DATA MINING APPROACH FOR IN-HOSPITAL TREATMENT OUTCOME IN PATIENTS WITH ACUTE CORONARY SYNDROME

PROCENA INTRAHOSPITALNOG ISHODA LEČENJA PACIJENATA SA AKUTNIM KORONARNIM SINDROMOM METODOM ISTRAŽIVANJA PODATAKA

Miroslava SLADOJEVIĆ[1], Milenko ČANKOVIĆ[2], Snežana ČEMERLIĆ[1], Bojan MIHAJLOVIĆ[1], Filip AĐIĆ[1] and Milana JARAKOVIĆ[1]

Summary

Introduction. Risk stratification is nowadays crucial when estimating the patient's prognosis in terms of treatment outcome and it also helps in clinical decision making. Several risk assessment models have been developed to predict short-term outcomes in patients with acute coronary syndrome. This study was aimed at developing an outcome prediction model for patients with acute coronary syndrome submitted to percutaneus coronary intervention using data mining approach. **Material and Methods.** A total of 2030 patients hospitalized for acute coronary syndrome and treated with percutaneous coronary intervention from December 2008 to December 2011 were assigned to a derivation cohort. Demographic and anamnestic data, clinical characteristics on admission, biochemical analysis of blood parameters on admission, and left ventricular ejection fraction formed the basis of the study. A number of machine learning algorithms available within Waikato Environment for Knowledge Discovery had been evaluated and the most successful was chosen. The predictive model was subsequently validated in a different population of 931 patients (validation cohort), hospitalized during 2012. **Results.** The best prediction results were achieved using Alternating Decision Tree classifier, which was able to predict in-hospital mortality with 89% accuracy, and preserved good performance on validation cohort with 87% accuracy. Alternating Decision Tree classifier identified a subset of 6 attributes most relevant to mortality prediction: systolic and diastolic blood pressure, heart rate, left ventricular ejection fraction, age, and troponin value. **Conclusion.** Data mining approach enabled the authors to develop a model capable of predicting the in-hospital outcome following percutaneous coronary intervention. The model showed excellent sensitivity and specificity during internal validation.

Key words: Data Mining; Treatment Outcome; Acute Coronary Syndrome; Risk Assessment; Mortality

Sažetak

Uvod. Stratifikacija rizika je danas krucijalna u proceni prognoze ishoda lečenja i pomoć za donošenje odluka u kliničkoj praksi. Razvijeno je nekoliko skorova rizika za predviđanje kratkoročnog ishoda lečenja pacijenata sa akutnim koronarnim sindromom. Cilj rada bio je da se razvije prediktivni model za procenu ishoda lečenja kod pacijenata sa akutnim koronarnim sindromom, primljenih radi perkutane koronarne intervencije, upotrebom metode istraživanja podataka. **Materijal i metode.** Ukupno 2 030 pacijenata hospitalizovanih zbog akutnog koronarnog sindroma i podvrgnutih perkutanoj koronarnoj intervenciji, od decembra 2008. do decembra 2011. godine, činili su derivacionu kohortu. Analizirani su demografski i anamnestički podaci, kliničke karakteristike pri prijemu, parametri biohemijskih analiza krvi pri prijemu i ejekciona frakcija leve komore. Evaluiran je veliki broj algoritama mašinskog učenja dostupnih u Vaikato okruženju (*Waikato*) za istraživanje podataka i najuspešniji je izabran. Prediktivni model je naknadno validiran kod novih 931 pacijenta (validaciona kohorta), hospitalizovanih tokom 2012. **Rezultati.** Najbolja predikcija ostvarena je upotrebom klasifikatora Alternativnog stabla odluke, koji je mogao da predvidi intrahospitalni mortalitet sa 89% tačnosti i sačuva dobre performanse na validacionoj kohorti sa 87% tačnosti. Izdvojeno je 6 atributa koji su najrelevantniji za predviđanje smrtnog ishoda: sistolni i dijastolni krvni pritisak, srčana frekvencija, ejekciona frakcija leve komore, godine i vrednost troponina. **Zaključak.** Metodom istraživanja podataka, uspeli smo da razvijemo model sposoban da predvidi intrahospitalni ishod nakon perkutane koronarne intervencije. Model je pokazao odličnu senzitivnost i specifičnost tokom interne validacije.

Ključne reči: Istraživanje podataka; Ishod lečenja; Akutni koronarni sindrom; Procena rizika; Mortalitet

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Abbreviations

ACS – acute coronary syndrome
GRACE – Global Registry of Acute Coronary Events
TIMI – Thrombolysis in Myocardial Infarction
PCI – percutaneous coronary intervention
UA – unstable angina
AMI – acute myocardial infarction
STEMI – ST elevation myocardial infarction
NSTEMI – non-ST elevation myocardial infarction
LVEF – left ventricular ejection fraction
WEKA – Waikato Environment for Knowledge Analysis
AUROC – accuracy and area under the receiver operating curve
ADTree – Alternating Decision Tree

Introduction

Acute coronary syndrome (ACS) is defined as a spectrum of life-threatening conditions, representing a substantial proportion of all acute hospitalizations [1]. Mortality rates have declined during recent years [2] as a result of therapeutic options which have been expanded largely due to the optimization of timely reperfusion and innovations in pharmacological therapy.

Risk assessment is needed to guide triage and key management decisions in contemporary practice. Several risk models have been developed to predict short term outcomes in patients with ACS. Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk scores are the most popular and valuable ACS prediction models, recommended by current guidelines [3,4].

Knowledge discovery and data mining have achieved numerous successful applications in the domain of medicine over the last 30 years. However, this practice has not been widely adopted in some fields, such as cardiology, regardless of the potential benefits.

This study was aimed at developing an in-hospital outcome prediction model based on data mining approach for ACS patients submitted to percutaneous coronary intervention (PCI).

Material and Methods

Data were collected retrospectively. A set of patient-related data was obtained from the hospital information system of the Institute for Cardiovascular Diseases of Vojvodina, situated in Sremska Kamenica, Serbia. The Institutional Review Board approved the study and waived the need for informed consent.

A total of 2030 patients hospitalized for ACS and submitted to PCI between December 2008 and December 2011 were assigned to a derivation cohort. Validation cohort contained 931 ACS patients hospitalized during 2012 also submitted to PCI. All patients were examined by an experienced cardiologist immediately after admission.

ACS is defined as "any group of clinical symptoms compatible with acute myocardial ischemia", which includes unstable angina (UA) and myocardial infarction, with or without ST-segment elevation according to the American Heart Association [5].

All patients underwent an invasive strategy {primary PCI for STEMI (ST elevation myocardial infarction)/urgent PCI for NSTEMI (non-ST elevation myocardial infarction) and UA}, within two hours upon admission to hospital. Coronary stenting directly, or followed by balloon angioplasty, was performed where eligible. After the procedure, the patients were followed in the intensive coronary unit until stabilization.

The initial set of features including demographic and anamnestic data (age, gender, history of hypertension, diabetes, hyperlipidemia requiring treatment, smoking habits, alcohol consumption), clinical characteristics on admission (systolic and diastolic blood pressure, and heart rate), biochemistry and biohumoral response on admission (hemoglobin, troponin, urea, creatinine), and left ventricular ejection fraction (LVEF) formed the basis of the study.

The echocardiography examination was performed by a Vivid 7 (GE Medical Systems, Horten, Norway) with a phased-array 3.5-MHz transducer. Echocardiographic examination was performed after primary PCI in STEMI patients mostly within 24 hours upon admission to hospital. In the patients with NSTEMI and UA, echocardiographic examination was performed before the invasive strategy. Echocardiographic examination was performed in a standard manner [6].

In-hospital treatment outcome was defined as the in-hospital all-cause mortality. We defined all-cause mortality as death from any cause.

Using Waikato Environment for Knowledge Analysis (WEKA), an open source data mining tool [7], various machine learning algorithms have been applied in order to build a predictive model and the most successful was chosen. Several of these algorithms are of interest when it comes to the research presented in this study (listed by their WEKA denominations): ADTree, RandomTree, RandomForest, J48, J48graft, IB1, Naive Bayes and meta Cost Sensitive Classifier. Ten-fold cross validation was used for model validation. Both the accuracy and area under the receiver operating curve (AUROC) parameters were used for evaluation of algorithm performances [8-10]. After the best performing algorithm had been selected, the key attributes were extracted. Records containing only those attributes comprised the reduced "training set". Cost sensitive classification was explored as an additional methodology to enhance results. Additional validation of the developed predictive model was performed on the "test set" containing 931 patients (validation cohort), hospitalized during 2012.

Statistical analysis was performed using SPSS version 17. Continuous variables were presented as mean ± SD or median (25th percentile – 75th percentile). Comparisons between groups were analyzed by an unpaired t-test or a Mann-Whitney test. Differences were considered significant at $p < 0.05$.

Results

A total of 2030 patients (aged 61.29 ± 11.70 years, 66.79% males), diagnosed with ACS and treated with PCI from December 2008 to December 2011 were assigned to a derivation sample. Of these, 1495 (73.64%) were STEMI patients, 474 (23.35%) were NSTEMI patients and 61 (3.01%) were UA patients.

Table 1. Demographic and anamnestic data, clinical profile and echocardiographic parameters of patients from Derivation Cohort
Tabela 1. *Demografski, anamnestički podaci, kliničke karakteristike i ehokardiografski parametri pacijenata iz derivacione grupe*

Demographic and anamnestic data *Demografski i anamnestički podaci*	Total (n=2030, 100%) *Ukupno (n=2030, 100%)*	Mortality = YES (n=157, 7.74%) *Mortalitet = DA (n=157, 7.74%)*	Mortality = NO (n=1873, 92.27%) *Mortalitet = NE (n=1873, 92.27%)*	P-value *P-vrednost*
Age (year)/*Starost (godine)*	61 (53-71)	71 (62-77)	60 (53-70)	< 0.0005
Gender/*Pol*				
Male/*Muški*	1356 (66.8%)	85 (6.3%)	1271 (93.7%)	< 0.001
Female/*Ženski*	674 (33.2%)	72 (10.7%)	602 (89.3%)	
History of hypertension/*Od ranije podatak o hipertenziji*				
No/*Ne*	651 (32,1%)	45 (6.9%)	606 (93.1%)	0.381
Yes/*Da*	1376 (67.9%)	112 (8.1%)	1264 (91.9%)	
Diabetes mellitus/*Dijabetes melitus*				
No/*Ne*	75.3%			
Dietary modifications/*Modifikovana ishrana*	6.9%			
Oral antidiabetics/*Oralni antidijabetici*	13.2%			
Insulin/- *Insulin*	4.4%			
Combination therapy/*Kombinovana terapija*	0.1%			
Hyperlipidemia requiring treatment/*Hiperlipidemija koja zahteva lečenje*				
No/*Ne*	1364 (67.3%)	115 (8.4%)	1249 (91.6%)	0.117
Yes/*Da*	663 (32.7%)	42 (6.3%)	621 (93.7)	
Smoking habit/*Pušenje*				
No/*Ne*	901 (44.4%)			
Yes/*Da*	869 (42.9%)			
Smoking history/*Ranije pušenje*	257 (12.7%)			
Alcohol consumption/*Konzumiranje alkohola*				
No/*Ne*	2003 (98.8%)	157 (7.8%)	1846 (92.2%)	0.252
Yes/*Da*	24 (1.2%)	24 (100%)	0 (0%)	
Systolic blood pressure/*Sistolni krvni pritisak (mmHg)*	140 (120-160)	120 (90-140)	140 (120-160)	< 0.0005
Diastolic blood pressure/*Dijastolni krvni pritisak (mmHg)*	80 (70-100)	70 (60-85)	85 (70-100)	< 0.0005
Heart rate (bat/min.)/*Srčana frekvencija (otkucaja/min.)*	80.15 ± 22.90	109.80 ± 19.63	78.22 ± 21.84	0.002
LVEF (%)	52.00 (45.00-57.00)	38 (28-47)	52 (45-58)	< 0.0005

Values are reported as mean ± SD or median (25-75) percentile or (%) where indicated
Vrednosti su izražene kao srednja ± SD ili medijana (25-75) procenat ili (%) gde je indikovano

Demographic and anamnestic data are shown in **Table 1**. The survivors were significantly younger. One-third of patients from derivation cohort were women, and they had frequent lethal outcome (10.7%). The patients with already diagnosed hypertension accounted for more than two-thirds of the sample, but hypertension was not associated with the fatal outcome ($p = 0.767$). Diabetes mellitus was present in 24.7%, while hyperlipidemia occurred in 32.7% (there is no correlation with fatal outcome) of patients. Smoking habit and alcohol consumption was recorded in 42.9% and 1.2% of patients, respectively.

The patient's profile based on clinical examination during admission was associated with lethal outcome following PCI (**Table 1**). The patients with lethal outcome were found to have higher heart rate on admission. Biochemical analysis of blood parameters on admission is shown in **Table 2**.

The patients with lethal outcome tended to have lower hemoglobin values than the survivors, while urea and creatinine were higher in the patients with lethal outcome. Troponin was more frequently positive in the patients with mortality. The survivors had higher LVEF (**Table 1**).

In-hospital mortality was 7.73% and 6.64% in the derivation and the validation cohort, respectively.

Machine Learning Algorithm Evaluation

A number of algorithms available within WEKA were evaluated. The results, in terms of accuracy, AUROC and confusion matrix achieved by different algo-

Table 2. Biochemical analysis of blood parameters in the derivation sample
Tabela 2. *Parametri biohemijske analize krvi pacijenata iz derivacione grupe*

Biochemical analysis of blood parameters on admission *Parametri biohemijske analize krvi pri prijemu*	Total (n=2030, 100%) *Ukupno (n = 2 030, 100%)*	Mortality = YES (n=157, 7.74%) *Mortalitet = DA (n = 157, 7,74%)*	Mortality = NO (n=1873, 92.27%) *Mortalitet = NE (n = 1873, 92,27%)*	P-value *P-vrednost*
Hemoglobin (g/l)/*Hemoglobin (g/l)*	142.0 (131.0-152.0)	109.0 (106.5-141.5)	139.0 (125.5-150.5)	<0.0005
Urea (mmol/l)/*Urea (mmol/l)*	6.40 (5.10-8.20)	14.70 (9.75-20.10)	6.40 (5.00-8.20)	<0.0005
Creatinine/*Kreatinin (μmol/l)*	93.0 (81.0-108.0)	142.0 (115.0-196.5)	95.0 (79.5-107.5)	<0.0005
Troponin positive/*Pozitivan troponin (%)*	51.87	63.69	50.99	<0.0005

rithms, were analyzed. The ADTree decision tree performed better than other evaluated algorithms.

The initial dataset was reduced to contain only parameters shown by ADTree algorithm as significant. Cost sensitive classification was explored afterwards as an additional methodology to enhance the results. The best results were achieved by applying the following cost matrix [0, 6, 60, 0].

Alternating Decision Tree (ADTree) classifier which was able to predict in-hospital mortality with 89% accuracy (AUROC=0.91) identified a subset of six attributes most relevant to the mortality prediction. These attributes represent: systolic and diastolic blood pressure, heart rate, LVEF, age, and troponin value.

The developed model was subsequently tested on 931 new patients (the validation sample), and preserved good performance with 87% accuracy (AUROC=0.82).

Discussion

The application of data mining when solving the issue of predicting in-hospital outcome in ACS has not been explored extensively in the literature [11-14]. This study includes ACS patients after an invasive strategy (primary PCI for STEMI/urgent PCI for NSTEMI and UA) and focuses on in-hospital mortality. Our model, based on 6 attributes, is able to estimate in-hospital patient outcomes. Hynek Kruzk et al. designed and verified a predictive model of hospital mortality in STEMI patients based on clinical data, and presented results of an experimental evaluation of different machine learning methods. The best performed classifications were based on logistic regression and on simple Bayesian networks [15]. The best prediction results in this study, as well as in those done by Sladojevic et al. [16] and Vaithiyanathan V. et al. [17], were achieved by decision tree classifiers although the applications of data mining in this domain are not always restricted to classification [18].

LVEF, one of the main indicators of left ventricular systolic function, is already known as a key prognostic factor of mortality described in many studies [19,20]. Lilian P. Souza et al. demonstrated that LVEF was the single independent variable, significantly related to in-hospital heart failure in patients with a first STEMI and an LVEF ≤ 0.45 on admission [21]. The result obtained in this study indicates that all patients who died had a low LVEF, with average of 38%.

Similar to the results of our study, approximately two-thirds of patients were men, but this proportion decreased with age [22]. In a study covering more than 2-decade-long experience on more than 8000 patients with acute myocardial infarction (AMI), Robert J Goldberg et al. compared the outcome in the patients under 55 years of age with the outcome in the patients 55 to 64 years old, and concluded that the latter were 2.2 times more likely to die during hospitalization for AMI, whereas patients aged 65 to 74, 75 to 84, and ≥85 years were at 4.2, 7.8, and 10.2 times greater risk of dying, respectively [23].

In GRACE and TIMI risk scores, with the former considered the strongest one in evaluating the risk of adverse outcomes in the patients with initial presentation of ACS, age, heart rate and systolic blood pressure appeared as the most important variables [3, 4]. The same parameters occur in the predictive model developed in the study presented. Eric Boersma et al. analyzed the relation between the baseline characteristics and the 30-day incidence of death and the composite of death or myocardial (re)infarction in almost 9500 patients with ACS without persistent ST-segment elevation. More than 20 significant predictors for mortality and for the composite end point were identified. The most important were age, heart rate, systolic blood pressure, ST-segment depression, signs of heart failure, and elevated cardiac enzymes [24]. In our study, elevated troponin values appeared as one of six attributes most relevant to mortality prediction. Cardiac troponin I levels provide useful prognostic information and enable the early identification of patients with an increased risk of death in ACS, as emphasized by Antman EM et al. [25].

Conclusion

The proposed model might prove to be very helpful in decision-making and optimization of the treatment strategy in selected high-risk patients with acute coronary syndrome submitted to percutaneous coronary intervention. Although the presented study was done on a large number of patients and faithfully illustrates the actual state of patient population of the region where it was developed, the authors believe the model may prove to be useful in the daily work of clinicians worldwide.

Finally, the model for prediction of in-hospital mortality was developed, but fatal outcome cannot be excluded after discharge, so a follow-up of this study is preferable.

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MENTAL HEALTH PROBLEMS AND SPEECH DEVELOPMENT IN TODDLERS WITH PHYSICAL ILLNESSES

PROBLEMI MENTALNOG ZDRAVLJA I RAZVOJ GOVORA KOD DECE SA TELESNIM BOLESTIMA U PERIODU RANOG DETINJSTVA

Jasminka MARKOVIĆ[1,2] and Teodora ROMIĆ[3]

Summary

Introduction. Mental health problems develop more and more frequently in children and adolescents. Children with physical illnesses are at a particular risk of developing associated mental health problems and it is important to study this association in order to detect and treat these problems on time. This study was aimed at determining whether there were differences in the presence of mental health problems and delayed speech development in children with physical illnesses between 18 and 36 months of age compared to the presence of these problems in healthy children. **Material and Methods**. The study was carried out as an observational cross-sectional study. It included 100 children, of both sexes, aged up to 3 years. The first group consisted of 50 children with physical illnesses that were hospitalized at the Institute for Child and Youth Health Care of Vojvodina, and the control group consisted of 50 healthy children of the same age who attended kindergarten "Radosno detinjstvo" in Novi Sad. The instrument of the study was "A checklist of child behavior for children aged 1.5 to 5 years". The hypothesis was checked with t-test for independent samples. "A survey of language development for children aged 18 to 35 months" was used for assessing the language development. The second part of the hypothesis was checked with chi-square test. **Results.** A **s**tatistically significant difference was detected in the following dimensions of the questionnaire: emotional reactivity, anxiety / depression, withdrawal, aggression, stress, internalization, externalization, and total problems. A statistically significant difference was also found in the area of language delay. **Conclusion**. It has been concluded that mental health problems, as well as the language delay, are more pronounced among the children with physical illnesses than in the control group of children.

Key words: Mental Health; Language Development Disorders; Infant; Child, Preschool; Psychopathology; Disease

Sažetak

Uvod. Problemi mentalnog zdravlja su sve učestaliji kod dece i mladih. Deca sa telesnim bolestima su pod posebnim rizikom i za pojavu problema mentalnog zdravlja i ispitivanje njihove povezanosti je posebno značajno zbog pravovremenog otkrivanja i tretmana problema. Cilj rada je da se utvrdi da li postoje razlike u izraženosti problema mentalnog zdravlja i kašnjenja u razvoju govora kod dece sa telesnim bolestima uzrasta 18−36 meseci u odnosu na izraženost ovih problema kod zdrave dece. **Materijal i metode.** Istraživanje je vršeno po tipu opservacione studije preseka. Uključeno je 100 dece, oba pola, uzrasta do 3 godine. Ispitivanu grupu činilo je 50 dece sa telesnim bolestima, lečenih u Institutu za zdravstvenu zaštitu dece i omladine Vojvodine u Novom Sadu, dok je kontrolnu grupu činilo 50 zdrave dece, istog uzrasta, koja pohađaju predškolsku ustanovu *Radosno detinjstvo* u Novom Sadu. Instrument studije bio je *Lista provere dečjeg ponašanja za decu od 1,5 do 5 godina*. Hipoteza je proveravana pomoću t-testa za nezavisne uzorke. Za procenu razvoja govora korišćena je *Anketa o razvoju govora za decu starosti od 18 do 35 meseci*. Drugi deo hipoteze je proveravan pomoću χ^2 testa. **Rezultati.** Statistički značajna razlika je utvrđena na sledećim dimenzijama upitnika: emocionalna reaktivnost, anksioznost/depresivnost, povlačenje, agresivnost, stres, internalizacija, eksternalizacija i ukupni problemi. Statistički značajna razlika je prisutna i u oblasti razvoja govora. **Zaključak.** Konstatujemo da su problemi mentalnog zdravlja kao i kašnjenje u razvoju govora više izraženi kod dece sa telesnim bolestima u odnosu na kontrolnu grupu dece.

Ključne reči: Mentalno zdravlje; Poremećaji razvoja govora; Odojče; Predškolsko dete; Psihopatologija; Bolest

Introduction

Mental health is the basis of the child's social and emotional development, and, consequently, their well-being and functioning throughout life. Although it represents the fundamental component of general health, mental health of children is often neglected throughout the world, and mental and behavior disorders during childhood have become a serious public health problem. According to the World Health Organization (WHO), child's mental or behavioral disorders will become one of five causes of morbidity, mortality and incapacity by 2020 [1].

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Abbreviations
CBCL – Child Behavior Checklist

Mental health of children is particularly neglected in their early childhood and preschool age. However, not sufficient research work has been done regarding this age, which can result in many problems for several reasons. Firstly, some disorders such as oppositional defiant disorder (ODD), and hyperkinetic disorder begin in this period and they are relatively stable over time with a long term negative consequences. Then, some psychopathological syndromes change under the influence of developmental changes in the domain of cognition, language and emotional regulation. For example, oppositional defiant disorder in the preschool period can be a precursor of developing anxiety and depression later. The third important fact is that there is clear evidence of efficiency of the treatment at this age, and the studies about the problems in mental health of preschool children are the first step to understanding the burden of these illnesses as well as planning early interventions and prevention.

Physical, acute or chronic illness of a child may be the cause of the child's mental health problem as confirmed by the earlier studies [3–6]. Rutter found that children with asthma, epilepsy and neurological disorders in general were far more prone to these problems. A national research conducted in Great Britain indicated a large percentage of mental health problems among the children with physical handicap [3]. Almost all children with severe physical disability had a mental health problem. Children with emotional difficulties experienced problems with digestive tract, migraines, headaches, most probably reflecting the somatic symptoms associated with anxiety and depression [3].

Speech development is an important component of child's cognitive and social development in the early childhood, and its assessment serves as essential component of the psychomotor development assessment. Speech development delay is associated with intellectual disability, hearing impairment and pervasive developmental disorders. It is also a central symptom of the specific language impairment [7, 8]. Previous studies have confirmed that every child who spontaneously pronounces less than 50 words and does not combine sentences by the age of 2 (two), shows a distinct delay in speech development [8, 9]. Factors associated with disorders in speech development of 30-month-old children are male gender, behavioral and developmental problems of the child or a member of the family, and a bilingual environment [10]. Earlier studies confirmed a connection between a delay in speech development of the children and high level of timidity, fear and problematic behavior [11, 12].

The aim of this research was to determine whether there was a difference in the extent of the problems of mental health among the children with physical illnesses between 18 and 36 months of age, and if there was a difference in speech development delay in both groups of children. The hypothesis was that those problems occurred more often in children with physical illnesses than in healthy children of the same age, with a significant presence of speech development delay.

Material and Methods

This research was conducted as an observational study of interface from October 2012 until November 2013 at the Institute of Child and Youth Health Care of Vojvodina and the preschool facility 'Radosno Detinjstvo'. The study sample consisted of a hundred children of both genders who were divided into two groups: there were 50 children with physical illnesses in the study group and 50 healthy children in the control group, their average age being 29.6 and 27.4 months, respectively. The exclusion criterion was the age under 18 and over 36 months.

The study instrument was the Child Behavior Check List (CBCL/1.5-5) questionnaire for assessment of behavior of the children between 18 months to 5 years of age [13]. This is one of widely used standardized instruments for identifying child's behavior and emotions. It has proved its efficiency and reliability in many international studies. The questionnaire was completed voluntarily and anonymously by the parents. In both groups the questionnaires were mainly completed by mothers (in 92%) and in 8% of fathers. One part of the questionnaire used for this study was the Problem scale consisting of 100 statements. Each statement offered three replies: 0 = Not True (as far as I know), 1 = Somewhat or Sometimes True, 2 = Very True or Often True to give the best description of the child at the time of the study or over the last two months. Using factor analysis of 100 items of the Problem scale, 7 empirically based syndrome scales were constructed: emotional reactivity, anxiety/depression, somatic complaints, detachment, sleeping disorders, attention deficit and aggression. The scale syndrome was further organized into large problem groups (based on the second order factor analysis): Internalizing (internal problems of the person, individual) and Externalization (problems with other people). Internalizing group of problems were the first four syndrome scales: emotional reactivity, anxiety/depression, somatic complaints and detachment. Externalizing group of problems were the last syndrome scales: attention deficit and aggression. The total number of problems on the Problem scale was the sum of scores on all items which could range from 0 to 200 [14]. Each syndrome scale was determined by the T score with a margin of normal, borderline and clinical cases. According to the author, the T score syndrome scale over 70 was considered clinically significant, whereas the scores from 65 to 69 were marginal/borderline scores. T score under 64 was considered normal. Internalization and Externalization scales and the total number of problems had slightly lower T score rates, which was the reason why the results on these scales were

Table 1. Causes of children's hospitalization by wards at the Institute of Child and Youth Health Care of Vojvodina
Tabela 1. *Prikaz uzroka hospitalizacije dece po odeljenjima u Institutu za zdravstvenu zaštitu dece i omladine Vojvodine*

Ward *Odeljenje*	Cause of hospitalization *Uzrok hospitalizacije*	Number of children *Broj dece*
Nephrology *Nefrologija*	Post-streptococcal glomerulonephritis/*Poststreptokokni glomerulonefritis*	1
	Nephrotic syndrome/*Nefrotski sindrom*	1
	Hydronephrosis/*Hidronefroza*	1
	Urinary tract infection/*Urinarna infekcija*	2
Endocrinology *Endokrinologija*	Diabetes mellitus type 1/*Dijabetes melitus tip 1*	1
	Growth hormone deficiency/*Nedostatak hormona rasta*	1
	True precocious puberty/*Pravi prevremeni pubertet*	1
Gastroenterology *Gastroenterologija*	Diarrhea and vomiting/*Proliv i povraćanje*	5
Cardiology/*Kardiologija*	Congenital heart defect/*Urođena srčana mana*	1
Neurology/*Neurologija*	Loss of consciousness/*Kriza svesti*	1
	Epilepsy/*Epilepsija*	2
Pulmonology *Pulomolgija*	Pneumonia/*Upala pluća*	5
	Bronchitis/*Bronhitis*	2
	Asthma/*Astma*	2
	Purulent angina/*Gnojna angina*	1
	Acute otitis media/*Upala srednjeg uva*	7
	Cough/*Kašalj*	6
General/*Opšte*	Fever/*Povišena telesna temperatura*	7
	Exhaustion/*Malaksalost*	2
	Poisoning/*Trovanje*	1
Total/*Ukupno*		50

interpreted as clinical for scores over 64, marginal for scores from 60 to 63, and normal for those under 60.

The second part of the questionnaire was 'Language Development Survey-LDS' for the children from 18 to 35 months of age serving as a screening tool for detection and identification of speech delay in children. It included 310 words organized in 14 semantic categories [15]. It provided the words pronounced by a child correctly or in 'baby talk'. Identification of the language delay in children was when they knew less than 11 words (boys) or less than 25 words (girls) at 18 to 23 months of age; when they knew less than 40 words (boys) or less than 84 words (girls) at 24 to 29 months of age; and when they knew less than 88 words (boys) or less than 115 words (girls) at 30 to 35 months of age.

The database was created in Microsoft Excel 2010. The analysis was done using ADM, Microsoft Excel and SPSS programs. Hypothesis testing was done using an independent samples t-test and chi-square test.

Results

The research included 100 children of both genders, 50 with physical illnesses and 50 healthy children. The study group had 44% of girls and 56% of boys whereas the control group had 48% of girls and 52% of boys. The majority of the children were hospitalized at the Pulmonary Diseases Ward (46%), a large number with symptoms of middle ear infection (30%) and cough (26%), and at the General Pediatrics Ward (20%) with the highest number of cases of fever (70%), followed by Nephrology and Gastroenterology Ward with 10% (per ward) of the total number of hospitalized children **(Table 1)**.

Statistical data analysis yielded the results indicating that the children with physical illnesses had higher scores compared to the children in the control group within the following syndrome scales: emotional reactivity, anxiety/depression, detachment, aggression, stress, internalization, externalization and overall problems ($p<0.05$). No statistically significant difference in expression of emotional and behavior problems of the children with physical illnesses and the children from the control group was found on the following syndrome scales: somatic complaints, sleeping disorders and attention deficits ($p<.05$) **(Table 2)**.

The largest difference between the two groups was found on the internalization scale ($p<0.00004$) and the smallest one was seen on the attention deficit scale ($p<0.26$). These two groups of children differed more in the dimension of internalization ($p<0.00004$) than in externalization dimension ($p<0.0089$). Interestingly, the problems in the dimension of stress seem to be predominant in the group of children with physical illnesses (AS 55.48) as well as in the control group of children (AS 53.24) **(Table 2).**

It is important to stress that, regardless of the high scores of the study group in almost all dimensions, these scores, nevertheless, did not reach the borderline level (the highest value of T score was 55), and therefore fell into the category of normal results **(Table 2)**.

As for speech development delay, out of 50 children in the study group 14 had speech delay: 6 boys and 8

Table 2. Testing differences in T scores on the syndrome scales using t-test
Tabela 2. *Prikaz testiranja razlike u T-skorovima na skalama sindroma pomoću t-testa*

Dimensions of the CBCL/*Dimenzije CBCL**	Groups/*Grupe*	AS	SD	t	df	p
Emotional reactivity *Emocionalna reaktivnost*	Study/*Ispitivana* Control/*Kontrolna*	55,14 51,96	5,6928 3,3924	3,39	98	0,0009
Anxiety/Depression *Anksioznost/Depresivnost*	Study/*Ispitivana* Control/*Kontrolna*	54,94 51,82	5,1603 2,9602	3,70	98	0,0003
Somatic complaints *Somatske žalbe*	Study/*Ispitivana* Control/*Kontrolna*	53,86 52,34	5,1627 3,8151	1,67	98	0,0972
Withdrawal *Povlačenje*	Study/*Ispitivana* Control/*Kontrolna*	55,26 52,44	6,6511 4,4131	2,49	98	0,0141
Sleeping problems *Problemi sa spavanjem*	Study/Ispitivana Control/*Kontrolna*	54,26 52,82	5,3597 3,4504	1,59	98	0.1133
Attention problems *Problemi pažnje*	Study/*Ispitivana* Control/*Kontrolna*	54,26 53,14	5,6597 4,1748	1,12	98	0,2628
Aggressiveness *Agresivnost*	Study/*Ispitivana* Control/*Kontrolna*	53,82 51,60	4,8221 3,2763	2,69	98	0,0083
Stress *Stres*	Examined/*Ispitivana* Control/*Kontrolna*	55,48 53,24	5,5152 4,0736	2,31	98	0,0229
Internalization *Internalizacija*	Study/*Ispitivana* Control/*Kontrolna*	52,26 44,76	8,8359 8,6768	4,28	98	0,00004
Externalization *Eksternalizacija*	Study/*Ispitivana* Control/*Kontrolna*	50,08 45,62	8,6751 8,0226	2,66	98	0,0089
Total problems *Ukupni problemi*	Study/*Ispitivana* Control/*Kontrolna*	51,20 44,92	8,9897 7,9020	3,71	98	0,0003

CBCL - lista provere dečjeg ponašanja

girls. Namely, speech development delay was observed in 6 children (3 boys and 3 girls) between 18 to 23 months of age, in 3 children (2 boys and 1 girl) between 24 to 29 months of age and 5 children (1 boy and 4 girls) aged from 30 to 35 months **(Table 3)**.

The total number of children with speech development delay in the control group was 5 (3 boys and 2 girls) out of 50. Speech development delay was observed in 3 children (1 boy and 2 girls) between 18 and 23 months of age, and in one boy from the age group 24 to 29 months and 30 to 35 months, each **(Table 3)**.

Chi-square test indicated a statistically significant difference in speech development delay between the children with physical illnesses and healthy children in early childhood **(Table 4)**.

Discussion

This study was aimed at determining whether there was a statistically significant difference in manifestation of mental health problems among the children with physical illnesses in early childhood in comparison to their healthy peers. The results of our research showed a statistically significant difference between the two groups of children thus indicating that the children with physical illnesses had higher scores on scales assessing the emotional and behavior problems than the control group. In spite of the difference between these two groups, it is important to stress that the results of assessment of the extent of mental health problem in both groups were within a normal range.

Studies addressing the similar issue established a statistically significant difference in the manifestation of mental health problem between the children with physical illnesses and the healthy children from the control group [14, 16, 17]. Lavigne and Faier-Routman's study has shown a connection between the physical illness of a child aged 2 to 5 years with later occurrence of disorder in the form of opposition and defiance, disturbed parent-child relationship, hyperkinetic disorder and depression [18]. The only study performed in our environment, which used CBCL/1.5-5 questionnaire to assess the mental health problem rate among children from 4 to 11 years of age, has not found a connection between these problems and chronic illnesses, which can be explained by methodological factors. In addition, this study included older children and did not take into account the acute physical illnesses found in most children in our study.

The difference was not determined in the following dimensions: somatic complaints, sleeping disorders and attention deficit. Somatic complaint dimension had a low reliability (Cronbach's alpha measured only 0.28) in a study conducted on a large number of children in our environment, which can explain the absence of difference in this dimension. It is definitely an unexpected result to see that the children with physical illnesses have similarly manifested attention deficit and sleeping problems as the healthy children. One explanation could be that

Table 3. Language delay in children by age
Tabela 3. *Prikaz kašnjenja razvoja govora kod dece po uzrastima*

Age/groups/*Uzrast/grupe*	Study/*Ispitivana*		Control/*Kontrolna*	
	Boys/*Dečaci*	Girls/*Devojčice*	Boys/*Dečaci*	Girls/*Devojčice*
18 – 23 months/*meseci*	3	3	1	2
24 – 29 months/*meseci*	2	1	1	/
30 – 35 months/*meseci*	1	4	1	/
Total	6	8	3	2
Ukupno	14		5	

the children were more bedridden because of the physical illnesses, less active, aching, which could be the reason for the lack of differences in these dimensions. It could also be that the children at this age have more pronounced problems with sleeping and attention at this stage of development, and these dimensions are not sensitive enough to produce a clear picture of difference existing between these two groups of children.

The biggest difference was obtained in the internalization dimension which is very important for the clinical practice. Since these problems are less visible and they often pass unnoticed, they should be approached with more sensibility and their possible existence in children with physical illnesses should be studied thoroughly. Early recognition is a prerequisite for timely treatment of these problems that can be serious obstacles in a child's daily functioning.

The association between a mental health problem and physical illnesses can be explained by high-concern parental behavior which commonly occurs when a child is sick. This concern is related to parental perception of the child being extremely vulnerable when physically ill, including a hyper protective attitude which contributes to the occurrence of a mental health problem in children.

Another aim of this study was to determine whether the speech development delay was more pronounced in children with physical illnesses in their early childhood than in the healthy children of the same age. Almost one third of the children in the study group had a speech development delay in comparison to 10% of the children from the control group. According to the opinion of the author [9], an attempt to determine the speech development delay before the child is 2 years old can lead to falsely positive results. This study showed that the largest number of children with speech development delay, in both study and control group, was recorded between 18 and 23 months of age, so these data should be accepted with reservation. Furthermore, in the population with a middle socio-economic status, the speech development delay rate at the age of 2 is 10% [8]. A delay was recorded in 21% of cases in this study group. Typical delay in speech development at the age of 3 occures in 3-5% of children, that being less than at the age of two. This is expected because some children who have a delay in speech development at 2 years of age can have normal development when they are 3 years old [8]. However, speech development delay was reported in 36% of children from this study sample. An increasing number of studies have been dealing with the association between the middle ear infection and potentially resulting hearing loss, speech development, language and cognitive skills. Regardless of the methodological flaws in certain studies, an increasing data volume indicates the presence of a significant association [19, 20]. This study had the largest number of children who were hospitalized because of the middle ear infection which affected their speech development.

Among previously mentioned risk factors contributing to speech development delay is also the male gender [10]. However, this study recorded a large number of girls in the study group who had this problem, whereas the control group had a large number of boys with this problem, that being in accordance with the literature data [10]. It is important to stress that this research did not include testing of children's IQ since the speech development delay, according to earlier studies, is related with the intellectual disability as the significant cause of this problem [7, 8].

Nevertheless, it is hard to explain the differences in speech development delay by connecting it merely with physical illness because more than a half of children had an acute physical illness which, ac-

Table 4. Testing differences between the study and control group using chi-square test
Tabela 4. *Prikaz testiranja razlike između ispitivane i kontrolne grupe pomoću* χ^2 *testa*

Groups/*Grupe*	Observed number/*Posmatrani broj*	Expected number/*Očekivani broj*	Residual/*Ostatak*
Study/*Ispitivana*	14	9,5	4,5
Control/*Kontrolna*	5	9,5	-4,5
Total/*Ukupno*	19		

χ^2=0.039 df=1 p<0,05

cording to the diagnostic criteria, did not last long and often left no permanent consequences. In addition, speech development assessment test may not have been explicit enough for our environment because its standardization has not been done yet. Therefore, these results should be considered with more caution. Another explanation could be that, although these illnesses were acute, they required hospitalization due to their severe clinical manifestations, which is not the case with minor acute illnesses treated in outpatient departments. Besides, younger children often react to acute physical illness with transient regression which can be manifested in speech regression, so the testing and parent assessment covered this moment of speech regression. It would certainly be interesting to look into the causes of such results through further research by controlling variables that relate to the course of illness.

The main contribution is that this is the first study performed in our region so far that applied CBCL/1.5-5 questionnaire in children aged 18 to 36 months. Another contribution is the confirmation of association between physical illnesses and mental health problems of young children for the first time in our environment. In order to establish more precise association between certain physical illnesses and some mental health problems, further studies with more samples should be conducted.

Conclusion

Based on these results, it can be concluded that emotional problems and behavior problems are more pronounced in children (up to 3 years of age) with physical illnesses than in their healthy peers. In addition, children with physical illnesses have more pronounced problems associated with speech development delay.

Research results can have significant clinical implications in the form of sensitization and education of pediatricians helping them to recognize emotional and behavior problems in children with physical illnesses.

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ARTICULATION DISORDERS IN SERBIAN LANGUAGE IN CHILDREN WITH SPEECH PATHOLOGY

POREMEĆAJI ARTIKULACIJE U SRPSKOM JEZIKU KOD DECE SA PATOLOGIJOM GOVORA

Tanja DMITRIĆ[1], Mila VESELINOVIĆ [1,2] and Slobodan M. MITROVIĆ[1,2]

Summary

Introduction. Articulation is the result of speech organs and it means clean, clear and distinct pronunciation of voices in words. **Material and Methods.** A prospective study included 24 children between 5 and 15 years of age, of both sexes. All children were monolingual, Serbian being their native language. The quality of articulation was tested with Triage articulation test. **Results**. Neither omission nor distortion of plosives was observed in any of them, whereas substitution of plosives occurred in 12% of patients. Omission of affricates was not observed in any of the subjects, but substitution and distortion occurred in 29%, and 76% of subjects, respectively. Omission of fricatives was found in 29% subjects, substitution in 52%, and distortion in 82% of subjects. Omission and distortion of nasals was not recorded in any of the subjects, and substitution occurred in 6% of children. Omission of laterals was observed in 6%, substitution in 46% and distortion in 52% of subjects with articulation disorders. **Discussion and Conclusion**. Articulation disorders were observed not only in children diagnosed with dyslalia but in those with dysphasia and stuttering as well. Children with speech disorders articulate vowels best, then nasals and plosives. Articulation of fricatives and laterals was found to be most severely deviated, including all three disorders, i.e. substitution, omission and distortion. Spasms of speech muscles and vegetative reactions were also observed in this study, but only in children with stuttering.

Key words: Speech-Language Pathology; Child, Preschool; Adolescent; Child; Speech Articulation Tests; Speech Disorders; Stuttering; Age Factors; Sex Factors

Sažetak

Uvod. Izgovor glasova je rezultat aktivnosti govornih organa. Artikulacija podrazumeva čist, jasan i razgovetan izgovor svih govornih glasova u rečima. **Materijal i metode.** Rad je retrospektivno-prospektivna studija sprovedena na 24-oro dece uzrasta od pet do petnaest godina, oba pola. Deca su bila monolingvalana, svima je srpski jezik maternji. Kvalitet artikulacije ispitan je Trijažnim artikulacionim testom. **Rezultati.** Omisija i distorzija ploziva nije postojala ni kod jednog do njih, dok se supstitucija ploziva javljala kod 12% ispitanika. Omisija afrikata nije postojala ni kod jednog ispitanika, supstitucija kod 29%, a distorzija kod 76% ispitanika. Omisiju frikativa imalo je 29% ispitanika, kod 52% je postojala supstitucija, a kod 82% postojala je distorzija. Omisija i distorzija nazala nije postojala ni kod jednog ispitanika, a supstitucija se javila kod 6% ispitanika. Omisija laterala je postojala kod 6% ispitanika, supstitucija kod 46%, a 52% ispitanika sa poremećajem artikulacije imalo je distorziju laterala. **Diskusija i zaključak.** U ovom istraživanju poremećaj artikulacije, osim dece sa dijagnozom dislalije imala su i deca sa disfazijom i mucanjem. Deca sa govornim poremećajima najbolje izgovaraju vokale, nazale i plozive. Najteže oštećeni izgovor glasova je u grupi frikativa i laterala gde se javljaju sva tri oblika poremećaja, odnosno supstitucija, omisija i distorzija. Tokom ispitivanja, zapaženi su i spazmi govorne muskulature i vegetativne reakcije samo kod dece sa mucanjem.

Ključne reči: Patologija govora i jezika; Predškolsko dete; Adolescent; Dete; Artikulacioni testovi; Poremećaji govora; Mucanje; Uzrast; Pol

Introduction

Speech is a basic skill used almost effortlessly in many daily life activities. Despite this apparent simplicity, speech is made of a complex set of cognitive processes and a wide network of brain structures. Cognitive models of speech production generally include distinct processing levels. These allow use of semantic and linguistic information, as well as premotor and motor commands [1]. Speech production is a complex multistage process converting conceptual ideas into acoustic signals that can be understood by others. The stages include conceptualization of the intended message, word retrieval, selection of the appropriate morphological forms, sequencing of speech sounds, syllables, and words, phonetic encoding, initiation, and sequences coordination in the tongue, lips, and laryngeal muscles movements, which lead to vocal tract vibrating, and respiration control for vocal phonation and prosody [2].

Speech is the result of the speech organs activity. Speech organs correlation allows the pronunciation control and regulation. Therefore, speech represents a complete communication circle. Com-

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munication circle starts in the brain and uses efferent neural pathways to carry commands to the muscles of executive organs of speech. The senses notice the accomplished command of speech organs and use afferent neural pathways to inform the brain of it.

Articulation means clean, distinct and perspicuous pronunciation of all speech sounds in words. Sound articulation is made of three main factors: 1. the quality of pronounced speech sound; 2. the position occupied by speech organs during certain speech sound pronunciation; 3. the ability to recognize pathological speech sound and its differentiation from other speech sounds [4].

Distinctions in speech sounds articulation can be made by: 1. the place of speech sound articulation (bilabial, labiodental, dental, alveloar, palatal, mediopalatal, and velar), 2. the manner of speech sound articulation (vocals - when airflow passes freely, without obstacles and consonants - when there is an obstacle, an air column narrowing, or redistribution between the nose and mouth cavity), 3. speech sound resonance [5].

Articulation disorders are an irregularity or failure in pronouncing one or more speech sounds. The basic division of articulation disorders includes: absence of individual speech sounds (omission), replacing certain speech sounds with other speech sounds (substitution) and incorrect articulation of certain sounds (distortion). Causes of articulation disorders can be divided into organic and functional [6].

The aim of this study was to determine the status of children with articulation disorders (dyslalia), speech and communication development disorders (dysphasia) and fluency disorders (stuttering). The presence of tics, gestures and vegetative reactions was also included in the observation.

Material and Methods

This study was a retrospective – prospective study, which was conducted at the Department of Ear, Nose and Throat, Clinical Center of Vojvodina in Novi Sad in the period from May 1st, 2012 to June 1st, 2013. The study included 24 children of both sexes from 5 to 15 years of age. The children, whose native language is Serbian, are all monolingual.

A questionnaire was made based on the existing medical records, information given by parents and speech therapist, which provided data on the patients' age, their age when treatment was started, and the type of diagnosed speech disorders. Articulation quality was tested by a "Triage articulation test" [7].

Statistical analysis was performed by the software package Microsoft Excel 2007 and statistical package Statistica 5.5.

Results

The study sample consisted of 24 children, 7 girls (25%) and 17 boys (75%). The majority of children were 6 years old (17%). The average age was 10.5 years for the boys and 8.66 years for the girls (t-test did not show a statistically significant difference, p>0:05). According to the type of speech disorder, the majority of subjects (54%) had dyslalia, 25% had dysphasia, and stuttering was observed in 21%. At the moment when therapy started (that age did not match the age at which testing was done), the majority of children (11) were between 6 and 10 years of age (49%), 10 children were from 2 to 5 years of age (21%), while the lowest number of children (3) were from 11 to 14 years of age (10%). The average age when speech disorders therapy started was 6.41 years.

The results showed that 54% of the examinees had dyslalia, while 70% had disturbed articulation, and only 30% had a preserved and proper articulation. According to these data, it can be concluded that the subjects diagnosed with dysphasia and stuttering also had articulation disorders, which means that all the subjects from the group with dyslalia had disturbed articulation, as well as 7% of children

Table 1. Articulation and its characteristics by phoneme group
Tabela 1. *Artikulacija i njene karakteristike po grupama fonema*

		Omission *Omisija*	Substitution *Supstitucija*	Distortion *Distorzija*
Vowels/*Samoglasnici* (a, e, i, o, u)		/	/	/
Plosives/*Plozivi* (p, b, t, d, k)		/	12%	/
Affricates/*Afrikati* (c, č, ć, dž, đ)		/	29%	76%
Fricatives/*Frikativi* (f, v, s, z, š, ž, h, j, r)		29%	52%	82%
Nasals/*Nazali*		/	6%	/
Laterals/*Laterali*		6%	46%	52%
Articulation/*Artikulacija*	Normal/*Normalna*			30%
	Distortion/*Distorzija*			20%
	Substitution, omission and distortion *Supstitucija*, *omisija i distorzija*			16%
	Substitution and distortion/*Supstitucija i distorzija*			30%
	Substitution and omission/*Supstitucija i omisija*			4%

in the stuttering group and 9% of children in the dysphasia group had articulation disorders.

Table 1 shows the percentage of subjects with articulation disorders manifested as omission, substitution and distortion divided into phoneme groups (vowels, plosives, affricates, fricatives, nasals and laterals). It also shows the percentage of manifestation of these disorders alone or in combination with other articulation disorders. The table shows that subjects with articulation disorders preserved vowels articulation. None of them had omissions of plosives and distortions, while plosive substitutions occurred in 12% of subjects. None of the subjects had omissions of affricates, substitutions occurred in 29%, and distortions in 76% of the subjects. Omission of fricatives, substitutions and distortion of fricatives were found in 29%, 52% and 82% of subjects, respectively. None of them had omissions of nasals and distortions, and nasal substitutions occurred in 6% of subjects. Omissions of laterals occurred in 6% of subjects, substitutions in 46% of subjects and distortions in 52% of subjects with dyslalia.

The results of nasal resonance examination showed that the majority of subjects (96%) had balanced oral and nasal resonance. An open rhinolalia (*Rhinolalia aperta*) was found in 4% of subjects. One subject diagnosed with dyslalia had disturbed nasal resonance as well.

Speech muscle spasms were reported in 21% of subjects with stuttering diagnosis. They occurred as clonic in 12.5% and as tonic-clonic in 8.5% of subjects who had spasms. This research also monitored other speech phenomena, such as tics, gestures and vegetative reactions. The results showed that tics occurred in 13% of children, of whom 4% were diagnosed with dyslalia, and 9% were diagnosed with stuttering. Vegetative reactions occurred in 4%, only in children diagnosed with stuttering, while 83% of them did not exhibit any of the specified disorders.

Discussion

Dobrota [8] has stated that speech articulation disorders are the most common speech disorders. According to her research, good articulation was present in only 14% of children 4-5 years old, 24% of children 5-6 years old and 39% of children 6-7 years old. Vuletić [9] found articulation disorders in 30% of her study sample. Januzović-Žunić et al. (quote Dobrota) reported that 29.69% of preschool children had a certain articulation disorder. Veselinović et al. [4] conducted a study in Novi Sad which included 69 children from 6 to 10 years of age and found that 23.19% of them had articulation disorders. According to Kukić's research results on speech disorder frequency [10] in Middle Banat, articulation disorders occur in 41.03%. of children from 6 to 7 years of age. Stuttering was reported in 3.7% of subjects. In 1988 the Institute of Experimental Phonetic and Speech Pathology, Belgrade, published the fact that 10% of children had developmental dysphasia over a period of 10 years, but the latest data from the Institute suggest that this pathology has been increasing [11].

According to Guitar, stuttering occurs in about 5% of children [12]. The results of this study confirmed the findings of other authors. In the structure of children with speech disorders, the majority of children (54%) had an articulation disorder – dyslalia, 24% had dysphasia and 21% had stuttering. This study also showed a significantly higher percentage of articulation disorder frequency, as well as a higher percentage of stuttering and dysphasia compared to the results of the above mentioned authors.

Veselinović et al. [4] reported that articulation disorders were more common in boys (56%) than in girls (44%). Karbasi et al. conducted a study [13] on speech disorder frequency on a sample of 7,881 primary school children in the area of Yazd (Iran), and showed a higher frequency of stuttering in boys (16.7%) than in girls (12.7%). In this study, a higher frequency of examined disorder was also found in male subjects (75%) compared to the female subjects (25%), which was in accordance with the foregoing studies by other authors.

The number of cases diagnosed with stuttering is variable, but stuttering is most common among young children (approximately 5%), from 2 to 4 years of age [14]. In this study, stuttering was observed in children 5-15 years old. The authors of the previously mentioned articles also recorded the age in which speech disorders occurred. However, attention in this study was paid to the age of subjects when they were being tested and most of the children were 6 years old at that time.

Tung et al. [15] performed a study on a sample of 30 children, and reported that the age of their patients at which articulation disorder treatment started was from 3.5 to 6 years, whereas the age when dysarthria therapy started was 4 to 12 years as reported by Murray et al. [16] in their study which also included 30 subjects. Yairi [17] believes that the probability of curing stuttering is substantially reduced after 8 years of age. According to this study, the average age when therapy started was six years.

Golubović and Čolić [18] have found that articulation disorder manifests in 37.2% children 5.5 years old, 25.5% of children 6 years old and 19% of children 7 years old. In addition, all children from the study sample had normal articulation of vowels, plosives, and nasals. Omission was almost absent, substitutions were present, and phoneme distortions were most frequent. Frequently distorted phonemes were /č/, /c/, /š/, /ž/, /dž/, /r/, /đ/, /ć/, /s/, /l/, /lj/ [19].

Qualitative analysis of data obtained in Vuković and Ilić research [20] on articulation disorder developed in younger school age children has shown that disorders occur as distortion, substitution and omission of speech sounds, with distortion being the most common form.

The subjects from this study sample had correct vowel articulation, substitution of plosives and na-

sals, substitution of affricates and distortion, while substitution, omission and distortion occurred in the group of fricatives and laterals. This study also confirmed distortion to be the most common disorder, followed by substitution, and omission of speech sounds. Distortion alone occurred in 20% of patients. As previously said, disordered articulation was found in 70% of this study sample, which means that children diagnosed with dysphasia and stuttering also have incorrect articulation of certain phonemes, with different causes such as impaired attention or reduced phonological awareness. Incorrect speech sound pronunciation can be found in the definition of dysphasia although it is defined as a speech and communication disorder. It can also be seen in stuttering, which is defined as a disorder of speech fluency. As for dyslalia, irregular pronunciation of phonemes is at the level of the orofacial muscles without additional causes.

Aboul-Wafa et al. [21] found that all 36 subjects in their study sample had normal nasal resonance expect for two children aged 3 and 5 years, who had an abnormality of nasal resonance in the form of open rhinolalia. Nasal resonance was normal in 96% of subjects of the study sample. One child, having dyslalia as the leading diagnosis, was found to have a disorder of the nasal resonance in the form of open rhinolalia.

Stuttering is a speech disorder characterized by a disorder of fluency, rhythm and tempo of normal speech [10]. Fritzell [22] states that the main features of stuttering are spasms leading to speech flow interruption. According to Howell's [23] developmental stuttering investigations, involving 76 children aged between 8 and 12 years, clonic spasms usually occur (54%). In this study, speech muscle spasms occurred in 21% of children who had the diagnosis of stuttering. As for the type of spasm, clonic spasms occurred more often (12.5%) than tonic-clonic spasms (8.5%).

Prasse and Kikano [24] observed blinking, jaw twitching and involuntary head movements in children who stuttered. The same reactions were reported by Ashurstet al. [25]. The results of this study show that of all reactions that occurred in patients, tics occurred in 13% of cases, of which 9% in children diagnosed with stuttering and 4% in children diagnosed with dyslalia. Vegetative reactions occured in 4% of children, only in those with the stuttering diagnosis. None of the above reactions occurred in children diagnosed with dysphasia (26%). This leads to the conclusion that children with the stuttering diagnosis exhibit different reactions, and that compared to children from the other two groups, these reactions are most commonly manifested in children with stuttering diagnosis.

Conclusion

In this study, articulation pathology developed in children with dysphasia and stuttering as well as in children diagnosed with dyslalia. Children with speech pathology pronounce vowels, nasals and plosives best. The most severe corrupted articulation is in the group of fricatives and laterals, which show all three forms of the disorder such as substitution, omission and distortion. During examination, spasms of speech muscles and vegetative reactions were observed only in children with stuttering.

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CYSTATIN C – MORE THAN THE MARKER OF THE GLOMERULAR FILTRATION RATE

CISTATIN C – VIŠE OD MARKERA JAČINE GLOMERULSKE FILTRACIJE

Velibor ČABARKAPA

Summary

Introduction. Cystatin C is one of biomarkers that meet the conditions necessary for an endogenous substance to be a marker of the glomerular filtration rate. **Cystatin C – Properties.** Cystatin C is produced in the nucleated cells in a constant amount, and its serum concentration does not depend on muscle mass and protein intake. The catabolism of cystatin C is mostly done in the kidneys. **Determination of Cystatin C Level.** Cystatin C may be determined in the serum, plasma, capillary blood and urine. The laboratory methods which are mainly used to determine its level are nephelometric and turbidimetric immunoassays. **Cystatin C as a Marker of Glomerular Filtration Rate.** Cystatin C is superior to creatinine as a marker of kidney function, especially in the early stages of chronic kidney disease. Several formulas are available for calculating the glomerular filtration rate from serum cystatin C. **Cystatin C in Various Physiological/Pathophysiological Conditions.** The level of cystatin C should be interpreted carefully because there are factors that can affect its level regardless of the renal function (thyroid dysfunction, glucocorticoids use, malignancies etc.). Higher cystatin C concentrations in general population are associated with an increased cardiovascular risk, as well as with preeclampsia in pregnant women. **Conclusion**. The significant advantages of cystatin C as a kidney function marker are its use in the creatinine "blind" area, in pediatric and the elderly population. In addition, cystatin C could be used as a marker for cardiovascular risk assessment, in predicting and detecting preeclampsia, in patients with malignant diseases, etc.

Key words: Cystatin C; Glomerular Filtration Rate; Biological Markers; Immunoassay; Kidney Function Tests; Renal Insufficiency, Chronic

Sažetak

Uvod. Cistatin C je jedan od biomarkera koji zadovoljava uslove koje mora da ispuni neka endogena supstancija da bi bila marker jačine glomerulske filtracije. O**sobine cistatina C.** Produkuje se u ćelijama sa jedrom u konstantnoj količini. Njegova serumska koncentracija ne zavisi od mišićne mase i unosa proteina. Katabolizam cistatina C se uglavnom odvija u bubrezima. **Determinisanje nivoa cistatina C.** Može se određivati u serumu, plazmi, kapilarnoj krvi i urinu. Laboratorijske metode koje se najčešće primenjuju su nefelometrijski i turbidimetrijski imunoeseji. **Cistatin C kao marker jačine glomerulske filtracije.** Cistatin C je superiorniji marker bubrežne funkcije nego kreatinin, naročito u ranim stadijumima hronične bolesti bubrega. U upotrebi je više formula za izračunavanje jačine glomerulske filtracije iz serumskog cistatina C. **Cistatin C u različitim fiziološkim/patofiziološkim stanjima.** Nivo cistatina C je potrebno s pažnjom interpretirati zbog postojanja faktora koji nezavisno od bubrežne funkcije mogu uticati na njegov nivo (tiroidna disfunkcija, upotreba glikokortikoida, maligne bolesti i dr.). Više koncentracije cistatina C su u opštoj populaciji u vezi sa povećanim kardiovaskularnim rizikom, ali i sa pojavom preeklampsije kod trudnica. **Zaključak.** Jedna od značajnih prednosti cistatina C kao markera bubrežne funkcije je njegova upotreba u zoni „slepoj" za kreatnin, u pedijatrijskoj i starijoj populaciji. Osim toga, cistatin C bi se mogao korisiti i kao marker procene kardiovaskularnog rizika, u predikciji i detekciji preeklampsije, kod bolesnika sa malignitetom i dr.

Ključne reči: Cistatin C; Jačina glomerularne filtracije; Biomarkeri; Imunoesej; Testovi bubrežne funkcije; Hronična bubrežna insuficijencija

Introduction

The prevalence of kidney diseases, especially chronic kidney diseases (CKD), is constantly rising as a consequence of the increasing incidence of diabetes mellitus (DM) and hypertension, which represent the most common causes of CKD and end-stage renal disease (ESRD). A significantly higher number of patients are in the early stages of CKD [1]. Therefore, an accurate assessment of the renal

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Abbreviations

GFR – glomerular filtration rate
cysC – cystatin C
CKD – chronic kidney disease
ESRD – end stage renal disease
CV – cardiovascular
DTPA – diethylenetriamine pentaacetate
MDRD – Modicifaction of Diet in Renal Disease
CKD-EPI – The Chronic Kidney Disease Epidemiology Collaboration
Cre_{equ} – formulas for calculating the GFR from serum concentrations of creatinine
$CysC_{equ}$ – formulas for calculating the GFR from serum concentrations of cystatin C
PENIA – particle enhanced nephelometric immunoassay
PETIA – particle enhanced turbidimetric immunoassay
PE – preeclamspia
DM – diabetes mellitus
DN – diabetic nephropathy
CCIMT – intimo-medial complex of the common carotid artery

function for early detection of CKD and prompt therapy can largely prevent further progression of the renal disease and also reduce the risk of cardiovascular (CD) disease, which is significantly higher in patients with CKD.

The best indicator of the functional status of the kidneys is the glomerular filtration rate (GFR) [2]. There are different methods for calculating/measuring the GFR. In clinical practice, the most reliable methods for determining the GFR are radioisotopic methods with chromium-51 labeld ethylenediaminetetraacetic acid (^{51}Cr-EDTA), technetium-99mm diethylenetriamine pentaacetate (^{99m}Tc-DTPA) and ^{125}I-iothamalat radiotracers [3]. Their use is recommended for determining the GFR among potential kidney donors for transplantation or when evaluating the doses of toxic drugs [1], but the major drawback of these methods is that they can be used in highly specialized institutions only. Therefore, the most commonly used methods in everyday clinical practice are: calculating the GFR using predictive formulas derived from creatinine serum concentration (Cre_{equ}) - Cockroft-Gault's formula, Modicifaction of Diet in Renal Disease (MDRD), The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) in adults and the Schwartz's and Counahan-Barratt's formula in children, as well as the calculation of the creatinine clearance. However, each of these methods for estimating the GFR has limitations, which is why it was necessary to find new and more suitable GFR markers. One of these markers which seem ideal for assessing the GFR is cystatin C (cysC).

Cystatin C – Properties

Cystatin C is a protein of low molecular weight (about 13 kDa) which consists of about 120 amino acids. It belongs to the group of cysteine proteinase (lysosomal) inhibitors and it is probably one of the most potent inhibitors of those extracellular proteolytic enzymes [4]. Cystatin C also plays a role in the modulation of the immune system and has an antibacterial and antiviral effect (inhibition of viral replication) [5].

Cystatin C is produced in all of the nucleated cells in a constant amount. The isoelectric point of cysC is 9.3 which is why the protein is positively charged in the body fluids.

Unlike creatinine, serum concentration of cysC does not depend on muscle mass and protein intake, and the influence of gender is of little significance [6].

However, the level of cysC increases with age and in parallel with the decline in the GFR beginning in the third decade of life (average ~ 0.75 - 1 ml/min/year) [7], due to changes in the renal structure and the reduction in the number of the functioning nephrons.

The catabolism of cysC is mostly done in the kidneys, because after passing through the glomerular filter, which is facilitated due to the positive charge of the cysC molecule at a physiological pH and its low molecular weight, it is taken over by the proximal tubule cells and is almost completely metabolized (> 99%). Therefore, the urinary concentration of cysC is extremely low [8]. The extrarenal excretion of cysC is negligible.

Determination of Cystatin C Level

Determination of Cystatin C Blood Level

Cystatin C may be determined in the serum or plasma taken with anticoagulants such as lithium-heparin, sodium-heparin or potassium-ethylenediaminetetraacetic acid. As recommended by the majority of the manufacturers, cysC stability in serum/plasma is 7 days at 2-8°C, 3 months at -20°C if the sample is frozen up to 24 hours after the blood sampling, or at least 6 months at -80°C [9].

The laboratory methods which are mainly used to determine the level of cysC are PENIA (particle enhanced nephelometric immunoassay) and PETIA (particle enhanced turbidimetric immunoassay), whereby PENIA is more sensitive and is considered the method of choice [5]. However, high concentrations of the rheumatoid factor (RF) (values over 320 IU/mL) can lead to falsely elevated values of cysC in the blood. Besides, hypertriglyceridemia (and it is already on the concentration of 5.9 mmol/L) can affect the serum concentration of cysC. To overcome the impact of hypertriglyceridemia on cysC levels, a formula was derived for the correction of the cysC level:

$$CysC_{(mg/L)} = 0.963 \times CysC_{(mg/L)\ measured} + 0.043 \times triglycerides_{(mmol/L)}$$ [10]

In addition to the abovementioned methods, the enzyme-linked immunosorbent assay (ELISA test) has been developed as well, but it is not generally used in everyday clinical practice.

In addition to determining cysC levels in plasma and serum samples, studies done on healthy adult population have shown that the cysC concentration can be determined in samples of capillary blood by the immunonephelometric method.

Determination of Urinary Cystatin C Level

Determination of the urinary cysC level is associated with certain difficulties. In fact, cysC concentration is extremely low in the urine of healthy individuals and ranges from 0.03 to 0.3 mg/L i.e. 5.2 to 13.3 mg/mmol of creatinine [8], which significantly limits the use of this test in general everyday practice. Urinary cystatin C is stable (at pH≥5) for 48 hours at room temperature and for 7 days at -20°C to +4°C [11].

Urinary Cystatin C may appear in increased concentrations (up to 200 times) in case of tubular lesions independent from glomerular damage, then due to overcoming the threshold for reabsorption in tubulocytes or due to competitive inhibition in the case of massive proteinuria [12].

Cystatin C as a Marker of the GFR

Cystatin C is almost an ideal marker of the GFR because of its features such as: easy passage through the glomerular filter, absent tubular secretion and negligible/absent extrarenal excretion. A significant number of studies indicate that cysC is superior to creatinine as a marker of the GFR [13], especially in the early stages of CKD, i.e. in the creatinine "blind" area (in GFR between 60-90 ml/min/1.73 m^2) [14].

It is considered that the GFR calculated by the derived predictive equations using serum concentrations of certain endogenous substances is quite satisfactory and widely accepted estimation of the renal function [15]. Just as there are Cre_{equ}, there is a whole series of formulas for calculating the GFR from serum concentrations of cysC ($cysC_{equ}$). The existence of a large number of $cysC_{equ}$ is due to the existence of different unsynchronized methods which are used to determine the blood level of cysC, thus applying different mathematical models, as well as the variations present in the calibrators that are in use [16]. The equations which have been developed for the PENIA method cannot be used to calculate the GFR from a level of cysC estimated by the PETIA method because the difference in the calculated GFR range up to 10 ml/min/1.73 m^2 [17].

In most studies, the GFR calculated using $cysC_{equ}$ is slightly more correlated with the GFR values measured by nuclear-medical methods which are the referent methods, rather than the GFR calculated using Cre_{equ} [17]. Therefore, the $cysC_{equ}$ are more sensitive than the Cre_{equ} in detecting patients with CKD in which the GFR is 60-90 ml/min/1.73 m^2, also the application of $cysC_{equ}$ is very important in patients with GFR <60 ml/min/1.73 m^2 who are without other signs of kidney damage [18, 19]. In fact, if the GFR estimated using $cysC_{equ}$ is below 60 ml/min/1.73 m^2 it may be considered that the person has kidney hypofunction [15].

However, despite this, it is recommended not to use only one endogenous marker for the assessment of the renal function in clinical practice [15], that is both formulas, the $cysC_{equ}$ and Cre_{equ} sholud be used to calculate the GFR.

If the calculated GFR values are in accordance, then we calculate their middle value [20], but if not, it is necessary to estimate the impact of other factors on the calculated GFR, i.e. the level of creatinine and cysC in the serum [13]. In that case, it is more appropriate to use a formula derived from a substance which is not subjected to the impact of the identified interfering factors (e.g., thyroid dysfunction, the use of glucocorticoids on cysC or the muscle mass on creatinine level, etc.). If we cannot find an objective reason for the discrepancy in the calculated GFR values, it is preferable to measure the GFR by one of the reference methods [13] **(Table 1).**

Cystatin C in Various Physiological and Pathophysiological Conditions

There are factors in the general population contributing to an increased production or increased degradation of cysC that can affect its level, regardless of the renal function. These factors are age, elevated C-reactive protein levels, smoking, use of nephrotoxic drugs [24], as well as a variety of other physiological and pathophysiological conditions in particular. Therefore, the level of cysC should be interpreted carefully taking into consideration the impact of these so-called non-renal factors on the serum concentration of cysC.

Thyroid Dysfunction and Cystatin C

Cystatin C is in a significant positive correlation with the blood levels of the thyroid hormones, i.e. it is negatively correlated with the level of the thyroid stimulating hormone, which is why the calculated GFR using the serum concentrations of cysC is significantly lower in patients with thyroid gland hyperfunction than in the healthy population (when paired by gender and age), and vice versa in patients with thyroid gland hypofunction [25]. An increased level of cysC in patients with hyperthyroidism is most likely due to the increased metabolic activity in the organism, and vice versa in patients with hypothyroidism. For assessing the renal function in patients with thyroid dysfunction it is necessary to avoid the use of cysC until euthyroid state is achieved.

Pregnancy and Cystatin C

The level of cysC during the first and second trimester of pregnancy does not differ significantly from the level of cysC in non-pregnant women [26]. In the third trimester, an increase occurs in the cysC levels, even up to 29-39% when compared to the previous two trimesters [26].

A significant increase in the serum concentrations of cysC in pregnancy can be found in preeclampsia (PE). Moreover, the level of cysC is not only significantly higher in the pregnant women who develop PE when compared to the women with normal pregnancies, but the increased levels of cysC are also present a few weeks and/or months before the development of PE [27]. This increase is a re-

flection of the impaired renal function, and the increased placental production of cysC [28]. Therefore, cysC may be used as a marker of PE independently from other parameters, but it is recommended to use it in association with other markers in order to achieve better detection of PE [27, 29].

In addition, the level of cysC in the amniotic fluid is an indicator of the development and maturation of the fetal kidneys. It is especially suitable for testing and detecting the existence of a fetal obstructive uropathy when the level of cysC is significantly higher than in fetuses with normal renal function (cut-off: 0.97 mg/L with a diagnostic accuracy of 96%) [30].

Children, the Elderly and Cystatin C

Cystatin C is a more sensitive marker of GFR reduction in children when compared with the serum creatinine level, particularly in the early stages of CKD [31], then in children with low muscle mass [32], as well as in the detection of an acute kidney injury [33]. In fact, the serum creatinine level is in a significant positive correlation with the body height and mass in children [34], while the serum concentration of cysC after the first year of life and during the childhood is stable and is not subjected to these factors. The serum concentration of cysC is significantly higher in the first year of life than in older age [32]. Besides, cysC has advantages in comparison with the serum creatinine level because of its analytical performance, as there is lesser influence of hemolysis and hyperbilirubinemia on its level measuring, which is of particular importance in the pediatric population.

With the aging process there is a "physiological" decline in the GFR, and there is a reduction in the muscle mass with the consequent reduced creatinine production, which ultimately can give a false picture of a preserved functional status of the kidneys, that is if Cre_{equ} are used for estimating the GFR. Given that the serum level of cysC is not affected by the muscle mass, a reduction of the GFR in the elderly can be detected earlier by using the $cysC_{equ}$ than by using Cre_{equ} [35].

Malignant Disease and Cystatin C

Using cysC to estimate the GFR is limited in patients with certain malignancies because in malignant cells an overproduction of cysC could be found. Besides, in malignant diseases, due to the increased activity of the cysteine protease enzymes which contribute to the invasiveness of the tumor, there is probably a reactive increase in the production of cysC which is an inhibitor of these enzymes. This consequently leads to an increase in cysC circulating levels [36]. A dysfunction or a decreased activity of cysC is associated with higher metastatic ability of the tumor cells.

Studies indicate that there is an increase in the level of cysC in the following malignant diseases (in the absence of a renal impairment): leukemia, colorectal cancer, melanoma, hepatocellular carcinoma, prostate cancer, breast cancer, non-Hodgkin's lymphoma, particularly in its aggressive forms. In fact, some studies indicate that cysC could be a marker of progression or relapse in certain malignancies [37]. Therefore, cysC could be a therapeutic goal when applying the anticancer therapy.

Liver Disease and Cystatin C

In patients with chronic liver diseases, cysC should be measured in parallel with the serum creatinine as it is believed to contribute to a more accurate assessment of the renal function, which is very important, especially in the patients with liver cirrhosis who are being prepared for transplant. In addition, one of the serious complications of liver cirrhosis is the hepatorenal syndrome whose main characteristics are renal vasoconstriction, renal hypoperfusion and reduction of the GFR, so in these patients an early detection of the GFR reduction is of extreme importance.

In liver diseases, serum creatinine as a marker of the GFR has significant shortcomings. First of all, there is a negative analytical interference between hyperbilirubinemia and creatinine [38], and a reduction in the serum creatinine is associated with a characteristic reduction in muscle mass in chronic liver diseases. In a significant number of patients in advanced stages of liver cirrhosis, an increased level of cysC indicates a renal dysfunction, despite the fact that the serum creatinine concentration is within the reference range [39].

In addition, cysC could be used for monitoring the progression of liver dysfunction as studies indicate that chronic liver diseases, such as chronic hepatitis B and C, hepatocellular carcinoma and liver cirrhosis in particular are associated with higher levels of cysC when compared to healthy subjects [40].

Diabetes Mellitus and Cystatin C

Diabetic nephropathy (DN) is a chronic complication of DM, a disease that is characterized by a high rate of morbidity and mortality, as well as being the leading cause of ESRD. Although the results of the studies are contradictory, the majority of them indicate that cysC is a better marker of the GFR than creatinine in the patients with both type 1 and type 2 DM [41], especially in the early stages of DN [42, 43].

Although the glomerular damage is considered to be the main factor in the development and progression of DN, tubular damage may contribute to the progression of DN as well. Given the fact that elevated urinary levels of cysC indicate tubular kidney damage, this marker could be used in the prediction of renal dysfunction in patients with DM [44].

Cystatin C in Patients with Transplanted Kidneys

Monitoring renal function in kidney transplant patients is of crucial importance after transplantation. Some studies point to the advantages of cysC compared to creatinine [45], while others indicate similar diagnostic characteristics between $cysC_{equ}$ and Cre_{equ}

[46]. The use of cysC in these patients is limited largely due to the administration of corticosteroids. In fact, corticosteroids cause a dose-dependent increase in serum concentrations of cysC [46] since they lead to an increased expression of the genes that encode the synthesis of cysC. This increase in the cysC level happens 48-72 hours after a non-complicated transplantation, unlike the creatinine levels, which decrease after transplantation [47]. Therefore, in order to use the level of cysC as a marker of the GFR in patients with transplanted kidneys, it is necessary to establish new reference values for this marker.

Cardiovascular Diseases and Cystatin C

The serum concentrations of cysC are a predictor of CV disease, and all cause mortality, independent from the functional status of the kidneys [48]. In addition to being associated with an increased risk for progression of the renal dysfunction, the serum concentration of cysC ≥1.0 mg/L is also associated with an increased CV risk [49]. In fact, some studies indicate an association between the elevated serum concentrations of cysC and the thickness of the carotid intimo-medial complex of the common carotid artery (CCIMT) which is a surrogate marker for subclinical atherosclerosis [50]. When the serum concentration of cysC is ≥1.0 mg/L, the prevalence of patients with CCIMT >0.9 mm is increased. In addition, elevated levels of cysC, independent from the measured GFR, are associated with an increased stiffness of the arteries [51].

In addition, some studies indicate that cysC is a more sensitive predictor of CV morbidity than the measured GFR, as well as the calculated GFR using the MDRD formula. In fact, in a significant number of patients with preserved GFR estimated by the MDRD formula, the level of cysC was elevated [52]. This feature of cysC recognizing a subtle renal dysfunction that is not shown by the serum creatinine level and the GFR estimated by the Cre_{equ} may be an explanation for the greater sensitivity of cysC when compared with other markers of the renal function in the prediction of CV morbidity.

Although some studies indicate that inflammation has no impact on the level of cysC [24], other studies point to a significant correlation between the level of cysC and the level of C-reactive protein [53]. This fact suggests that inflammation, which is one of the unavoidable contributing factors for the development of early atherosclerosis, is a possible connection between cysC and the elevated CV risk. It is possible that the increase in serum concentrations of cysC during the development of atherosclerosis reflects the established new balance between the increased levels of the lysosomal cathepsins in different locations and the levels of cysC, which is an inhibitor of those enzymes, whose harmful effect is to stimulate the atherosclerotic plaque rupture [54].

Conclusions

Since it is still unreliable to asssess the renal function on the basis of an endogenous marker, cystatin C cannot completely replace creatinine. Therefore, in order to assess the functional status of the kidneys it is preferable to determine the levels of both markers simultaneously, and then to estimate the glomerular filtration rate using predictive formulas. In doing so, attention should be paid to the impact of non-renal factors on these markers. In the detection of chronic kidney disease it is especially of great importance to estimate one or both of the above markers repeatedly, and to follow their concentration changes in the serum over time.

Table 1. The most frequently used formulas to estimate GFR (ml/min/1.73 m^2) derived from serum concentrations of cystatin C

Tabela 1. *Najčešće upotrebljavane formule za izračunavanje JGF (ml/min/1,73 m^2) izvedene iz serumske koncentracije cistatina C*

Equation/*Formula*	Method, patients/*Metod, pacijenti*	Author/*Autor*
eGFR=77.239 x cysC (mg/L)$^{-1.2623}$ eJGF=77,239 x cisC (mg/L)$^{-1,2623}$	PENIA, adults/*odrasli*	Larsson et al. [21]
eGFR=86.7/cysC (mg/L)- 4.2 eJGF=86,7/cisC (mg/L)- 4,2	PENIA, diabetics/*dijabetičar*i	MacIsaac et al. [22]
eGFR=75.94/cysC (mg/L)$^{-1.17}$x1.2 (in case of renal transplant)/eJGF=75,94/cisC (mg/L)$^{-1,17}$x1,2 (*ako je pacijent sa transplantiranim bubregom*)	PENIA, children/*deca*	Zappitelli et al. [23]
eGFR=84.69 x cysC(mg/L)$^{-1.68}$x (1.384 if <14 years) eJGF=84,69 x cisC(mg/L)$^{-1,68}$x (1,384 ako je <14*godina*)	PETIA, adults, children/*odrasli, deca*	Grubb et al. [18]
eGFR=99.43 x cysC (mg/L)$^{-1.5837}$ eJGF=99,43 x cisC (mg/L)$^{-1,5837}$	PETIA, adults/*odrasli*	Larsson et al. [21]
Orebro-cyst (Gentian)/*Orebro-cist (Gencijan):* 100/CisC-14 Orebro-cyst (Dako)/*Orebro-cist (Dako):* 119/CisC-33	PETIA, adults/*odrasli*	Tidman et al. [20]

Legend: eGFR- estimated glomerular filtration rate; cysC- cystatin C

Legenda: eJGF − procenjena jačina glomerulske filtracije; cisC − cistatin C; PENIA- nefelometrijski imunoesej sa lateks česticama; PETIA − turbidimetrijski imunoesej sa lateks česticama

One of the significant advantages of cystatin C is its use in the pediatric and elderly population, while a significant disadvantage is its markedly higher price for its determination (up to 80 times higher) than the price for determining creatinine.

In addition, cystatin C could be used as a marker for cardiovascular risk assessment, in predicting and detecting preeclampsia, and it could also be used as a marker in patients with malignant diseases and other pathophysiological conditions, which still requires additional testing.

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FUNCTIONAL STATUS OF PATIENTS AFTER STROKE

FUNKCIONALNI STATUS PACIJENATA NAKON MOŽDANOG UDARA

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Summary

Introduction. Patients who have suffered from stroke become disabled and have specific problems due to the physical and mental disability that requires the implementation of rehabilitation and the creation of conditions for independent living, economic and social reintegration. The aim of this study was to evaluate the functional recovery of patients after ischemic stroke, during the subacute phase of medical rehabilitation. **Material and Methods.** The study was organized as a prospective study, which included 74 patients (44 men, 30 women) treated after stroke at the Department of Medical Rehabilitation, Clinical Center of Vojvodina during 2013. Motor recovery was assessed by Signe-Brunnstrom scale, and Barthel Index, Rivermead Mobility Index, and modified Rankin scale were applied to assess the function. **Results**. The average age of patients after stroke was 66.59 ± 9.607 years. The mean hospital stay was 34.35 days. The majority of patients in this study had right-hand hemiparesis 47 (63.5%), and 27 (36.5%) had left-hand hemiparesis. By analyzing the average value of motor recovery of the affected limb by S.Brunnstrom′s scale during rehabilitation at the Department of Medical Rehabilitation, it was found that the value at the end of subacute rehabilitation phase was significantly increased ($p<0.01$). The results of this testing showed a statistically significant improvement ($p<0.01$) in the average values of Barthel Index, Rivermead Mobility Index and modified Rankin scale during the rehabilitation treatment of stroke patients. **Conclusion**. The obtained results showed that the rehabilitation treatment resulted in better functional and motor recovery in the patients who had had ischemic stroke.

Key words: Stroke; Recovery of Function; Activities of Daily Living; Mobility Limitation; Disability Evaluation; Psychomotor Performance; Rehabilitation

Sažetak

Uvod. Pacijenti nakon moždanog udara postaju invalidne osobe sa specifičnim problemima uslovljenim fizičkom i mentalnom onesposobljenošću, koji zahtevaju sprovođenje rehabilitacije i stvaranje uslova za nezavisan život, ekonomsku i socijalnu reintegraciju. Cilj studije bio je ispitivanje funkcijskog oporavka pacijenata nakon ishemičnog moždanog udara u toku subakutne faze rehabilitacionog tretmana. **Materijal i metode.** Studija je koncipirana kao prospektivna studija, a obuhvatila je 74 pacijenta (44 muškaraca, 30 žena) stacionarno lečenih na Klinici za medicinsku rehabilitaciju, Kliničkog centra Vojvodine tokom 2013 godine. Procena motoričkog oporavka je vršena primenom Signe-Brunnstrom skale. Za procenu funkcijskih sposobnosti korišćen je Barthel Index, Rivermead Mobility Index, Modifikovane Rankin skale. **Rezultati**. Prosečna starost ispitanika je iznosila 66.59±9.61 godina, a prosečna dužina hospitalizacije je bila 34,35 dana. Najveći broj pacijenata /47(63.5%)/ u ovom istraživanju je imao desnostranu hemiparezu. Analizirajući prosečne vrednosti motoričkog oporavka zahvaćenih ekstremiteta po S.Brunnstrom-u na prijemu i otpustu sa Klinike za medicinsku rehabilitaciju, dobili smo statistički značajno poboljšanje vrednosti na kraju subakutne faze rehabilitacije ($p<0.01$). Rezultati ispitivanja funkcijskih sposobnosti su ukazali na visoko statistički značajno ($p< 0,001$) poboljšanje prosečnih vrednosti Barthel Index-a, Rivermead Mobility Index-a i Modifikovane Rankin skale na kraju rehabilitacionog tretmana bolesnika nakon moždanog udara. **Zaključak**. Dobijeni rezultati pokazuju da je u toku subakutne faze rehabilitacionog tretmana pacijenata nakon ishemičnog moždanog udara došlo do značajnog poboljšanja stepena motoričkog oporavka i funkcionalnosti.

Ključne reči: Moždani udar; Funkcionalni oporavak; Svakodnevne aktivnosti; Ograničenja pokretljivosti; Procena invaliditeta; Psihomotorni učinak; Rehabilitacija

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Abbreviations

SB – Signe-Brunnström
BI – Barthel Index
RMI – Rivermead Mobility Index
MRS – modified Rankin scale
ADL – activities of daily living

Introduction

Stroke impairs the functional status of an organism significantly and often results in disability in patients. It is estimated that 25-30% of patients remain permanently handicapped and in need of assistance and care [1,2]. The patient's recovery after stroke is monitored in everyday practice by standard clinical examinations, which is justified because of the incidence of complications, deficits, and the importance of their recovery [2,3]. Training of patients after stroke is a long and responsible process. In order to enable efficient motor re-education of a large number of patients with stroke, specific kinesiotherapeutical programs are used, such as proprioceptive facilitation-Kabat, Bobat and Signe-Brunnström. The choice of kinesitherapy method depends on the degree of functional disorders and the establishment of compensatory processes and motor control on account of the dynamic changes in the structure [4, 5]. The motor recovery of upper and lower extremities in patients after stroke is evaluated with Signe-Brunnström scale which includes six degrees. In the first degree, there are no movements, nor can they be caused, while in the sixth degree, isolated functional movements are present and spasticity is minimal [6]. Functional outcome of medical rehabilitation after ischemic stroke is determined by the specific scale for stroke: Barthel index (BI), Rivermead Mobility Index-a (RMI), Modified Rankin Scale (MRS), Signe-Brunnström (SB) scale. BI follows the functional independence before and after treatment, and indicates the level of disability [6]. Patients who have the maximum number of points (100) on this scale are content, capable of dressing and feeding themselves, walking for at least 100 m and climbing the stairs [7]. However, the maximum number of points does not mean full independence in all activities of daily living, because this index is estimated by instrumental activities. To assess the mobility of patients after stroke and with a head injury, the most commonly used index is RMI, which assesses the ability of patients to perform 15 tasks ranging from changing the position in the bed to even running without being helped. The total score on the scale ranges from 0-15, where 0 indicates the result of the complete inability to perform any function from activities included in the estimate [8, 9]. MRS is a simple and effective scale commonly used for evaluating patients after stroke. Rankin score 1 indicates the absence of significant disability, whereas score 5 indicates the most severe level of disability [10].

The aim of the study was to investigate the functional recovery of patients after ischemic stroke during the rehabilitation treatment depending on the laterality of the lesion, and the level of motor recovery.

Material and Methods

The prospective study included 74 patients (44 men, 30 women), their mean age being 66.59 ± 9.61 years, after stroke tested during the subacute phase of rehabilitation at the Department of Rehabilitation, Clinical Center of Vojvodina in Novi Sad 2013. The study group consisted of patients after ischemic stroke with lesions in the area of the middle cerebral artery. The data were obtained from medical history, physical examination, as well as from the available medical records of the patient. The length of in hospital treatment was recorded and the functional recovery during rehabilitation treatment was evaluated. We determined the motor recovery of the affected limb by SB scale, functional status of patients on the basis of scores of functionality in self-care activities: BI, RMI and MRS. All subjects were informed about anonymity and purposes of this study.

The data were analyzed using the statistical software package IBM SPSS Statistics 22.0 and utilities Word and Excel Microsoft Office Pro Plus 2013. Descriptive statistics was used for data processing. The results are presented in standard statistical measures of central tendency and range of results of mean values ($\bar{X}$), standard deviation (SD), interval values (maximum and minimum). The t-test for independent samples, Pearson's correlation coefficient was also used.

Results

The study included 74 patients (44 men, 30 women) who were treated after first ischemic stroke at the Department of Rehabilitation, Clinical Center of Vojvodina in Novi Sad during 2013. The highest percentage of patients in this study was older than 65 years (52.7%). Right-sided hemiparesis was present in 47 (63.5%) patients. The average length of hospitalization of patients after stroke amounted to 34.35 days (**Table 1**).

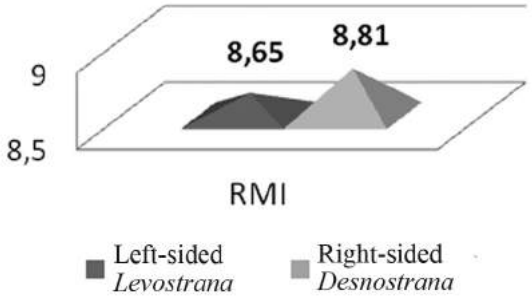
The results of testing the degree of motor recovery indicate that the patients, who had completed the rehabilitation treatment, had significantly higher scores on the SB scale in all segments of the locus extremities **(Table 2).**

The functional status of patients after ischemic stroke was evaluated from three aspects: independence in self-care activities using BI, RMI and total disability by using the MRS.

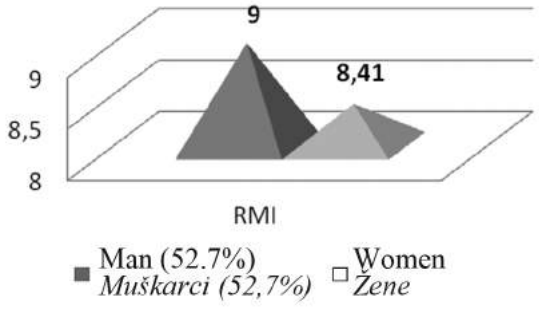
The average value of BI was 62.93 and 77.93 on admission and discharge, respectively (Table 3). According to the results obtained by testing the patients' mobility with RMI, the mean value at the beginning of rehabilitation treatment and on discharge was 6.72 and 8.75, respectively. The average value of MRS was 3.73 and 3.48 on admission and

Table 1. General characteristics of respondents
Tabela 1. *Opšte karakteristike ispitanika*

Patients' characteristics/*Karakteristike pacijenata*	N=74	
Age *Starost*	$\overline{X}\,\overline{X}$ ± SD Min-max	66.59 ± 9.607 31-89
Gender *Pol*	Men/*Muškarci* Women/*Žene*	40 (59%) 33 (41%)
Lateralization of lesion *Lateralizacija lezije*	Left-sided hemiparesis/*Levostrana hemipareza* Right-sided hemiparesis/*Desnostrana hemipareza*	27 (36.5%) 47 (63.5%)
Length of hospitalization *Dužina trajanja hospitalizacije*	$\overline{X}\,\overline{X}$±SD Min-max	34.35 ± 14.5 2-74



Graph 1. Average values of Rivermead Mobility Index in relation to the lateralization
Grafikon 1. *Prosečne vrednosti indeksa Rivermead Mobility u odnosu na lateralizaciju*



Graph 2. Average values Rivermead Mobility Index in relation to gender
Grafikon 2. *Prosečne vrednosti indeksa Rivermead Mobility u odnosu na pol*

discharge, respectively. The mean values obtained at the end of subacute rehabilitation phase for all three scales (RMI, BI and MRS) were statistically significantly increased ($p < 0.01$) **(Table 3).**

Each parameter was analyzed in relation to the outcome of rehabilitation which is defined in detail in this article, and represents the status after rehabilitation based on three criteria: BI, RMI, and MRS. BI ≥ 80 was reported in 56.8% of the patients, 13 16.2% of the patients had RMI ≥13 and 2.7% of patients had MRS ≤ 2, only one patient met all three criteria at the same time (**Table 4**).

The average values of RMI was estimated depending on the laterality of the lesion, gender and age. The average score on RMI was 8.65 and 8.81 in the patients with left-sided and right-sided hemiparesis, respectively. No statistically significant differences were found in the functional status of patients (RMI) in relation to lateralization (**Graph 1**).

The average values of RMI score were 9 and 8.41 for the men and the women, respectively. No statistically significant differences were found in the values of RMI regarding gender **(Graph 2)**

No statistically significant differences were found in the values of RMI score regarding age. The average value of RMI score was 8.93 and 8.62 for those under 65 and over 65 years of age, respectively **(Graph 3).**

Discussion

The outcome of medical rehabilitation of patients after stroke is usually assessed on the basis of independence in performing activities of daily living (ADL), the degree of patient's mobility, quality of life and level of social reintegration [11]. The

Table 2. Average values of motor recovery after Signe-Brunnström on admission and discharge.
Tabela 2. *Prosečne vrednosti motoričkog oporavka po Sajn-Brunstremu (Signe-Brunnström) na prijemu i otpustu*

Motor recovery/*Motorički oporavak*	Term/*Termin*	N/*N*	$\overline{X}\,\overline{X}$±SD
Proximal segment of the arm/*Proksimalni segment ruke*	Admission/*Prijem*	74	4,45±1.20
p< 0,01	Discharge/*Otpust*	74	4,80±1,21
Hand/*Ruka*	Admission/*Prijem*	74	4,25±1,27
p< 0,01	Discharge/*Otpust*	74	4,75±1,25
Leg/*Noga*	Admission/*Prijem*	74	4,35±1,08
p< 0,01	Discharge/*Otpust*	74	4,80±1,07

Table 3. Average values of RMI, BI and MRS on admission and discharge
Tabela 3. *Prosečne vrednosti RMI, BI i MRS na prijemu i otpustu*

Values on admission/*Vrednosti na prijemu*	Rehabilitation outcome/*Ishod rehabilitacije*	N	$\bar{X}$	SD
RMI p<0,01	Admission/*Prijem*	74	6.72	4.26
	Discharge/*Otpust*	74	8.75	377
BI p<0,01	Admission/*Prijem*	74	62.93	32.69
	Discharge/*Otpust*	74	77.93	25.49
MRS p<0,01	Admission/*Prijem*	74	3.73	1.17
	Discharge/*Otpust*	74	3.48	1.18

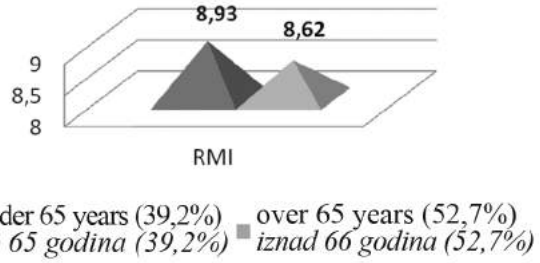
assessment of functional recovery of patients after medical rehabilitation can be defined as the absolute level of function at the time of discharge or changes in the degree of functional ability between admission and discharge.

Our study sample consisted of 44 men (59.5%) and 30 women (41%), which is consistent with the literature [12, 13]. The average age of patients in this study was 66.59 ± 9.61 years, with a higher prevalence of patients over 65 years of age (52.7%).

A number of authors [12, 13] have found in their studies that elderly people are predominant among those having had suffered stroke. Nakao et al. reported that in Japan the average age of patients with stroke was 73 years [14]. Literature data suggest that the age over 65 years is a limiting factor in the rehabilitation of patients after stroke, and older patients recover more slowly and achieve lower degree of independence in ADL [15, 16].

There were more patients with right-sided hemiparesis in this study (47) than those with left-sided hemiparesis (27). In his study, Mandic, found a larger number of patients with left-sided hemiparesis [12].

The results of our study show a statistically significant improvement in the value of motor recovery of affected extremities of patients after stroke at the end of subacute rehabilitation phase (p <0.01), which is in accordance with literature data [17]. The speed of motor recovery is used as an indicator of the outcome of functional recovery in the patients after stroke. The prognosis of motor recovery is better if during the first three weeks an initial movement in a certain segment occurs, which is then followed by movements in other segments of affected extremities. The highest degree of motor recovery occurs in the first three months after stroke [18]. Hashimoto et al. found in their study that the degree of motor recovery after Signe Brunnström was positively correlated with functional outcome of medical rehabilitation estimated on the basis of BI [19].



Graph 3. Average values of Rivermead Mobility Index in relation to age
Grafikon 3. *Prosečne vrednosti indeksa Rivermead Mobility u odnosu na starosno doba*

The functional status of patients after ischemic stroke was evaluated from the following three aspects: independence in everyday activities, mobility of patients after stroke and total disability, which were assessed using the BI, RMI and MRS, respectively. The success of rehabilitation was assessed according to the criteria defined according to literature data (values BI≥ 80, RMI ≥ 13, mRS ≤ 2) [20, 21].

The results of our study showed that the average value of BI was 62.93 and 77.93 on admission and discharge, respectively. Rehabilitation was successful in 42 patients (56.8%) after stroke, because their average values of BI was ≥ 80s.

According to the literature, the value of BI score of 61 and over indicates a good prognosis for functional recovery [14, 15, 22]. Nakao et al. reported that

Table 4. Criteria for the success of rehabilitation (RMI, BI and MRS)
Tabela 4. *Kriterijumi za uspeh rehabilitacije (RMI, BI i Modifikovane Rankin skale)*

Criteria/*Kriterijumi*	N/Number of patients/*N/Broj pacijenata*	% patients/*% pacijenata*
BI≥ 80	42	56.8
RMI≥13	12	16.2
MRS ≤2	2	2.7
All three criteria at the same time *Sva tri kriterijuma istovremeno*	1	1.35

the average value of BI in their stroke patients was 42.5 ± 37.4 and 57.9 ± 38.8 on admission and discharge, respectively, and 67.3 ± 37.2 six months after stroke. The patients with BI score ≥ 60 after the rehabilitation had better functional recovery than the patients with BI ≤ 60 (14). Similar results were obtained by Bassi et al. in their study on a sample of 126 patients with ischemic stroke, i.e. the average value of BI was 48.0 ± 19.9 and 74.0 ± 19.6 on admission and discharge, respectively [23].

Literature data indicate that the values of BI have predictive significance for the rehabilitation treatment of patients after stroke, higher than the level of damage, which is estimated by imaging methods [24].

To assess the ability of independent movement of patients after stroke, RMI is most commonly used because of its good reliability and sensitivity [25]. RMI values ≥ 4 in the acute phase of rehabilitation are favorable prognostic factor for the outcome of medical rehabilitation [25].

The results of our study showed that the average value of RMI was 6.72 and 8.75 on admission and discharge, respectively. The improvement of average values for RMI at the end of the subacute phase of rehabilitation treatment was highly statistically significant ($p < 0.001$). Twelve patients (16.2%) had the average values of RMI ≥ 13.

No statistically significant differences were found in the functional status of patients (RMI) regarding lateralization, gender and age.

Roorda et al. used RMI in order to assess the mobility of patients in their study. Before rehabilitation, 1.4% of patients could move independently after stroke, and after rehabilitation 80.5% of the patients were able to walk independently. The study has shown that patients have significant functional recovery in mobility after rehabilitation [26]. Similar results have been obtained by other authors who evaluated mobility of their patients using RMI [18, 19]. Literature data indicate worse functional recovery in females due to a larger number of associated diseases, poor premorbid functional status, as well as the constitutional characteristics [27, 28].

The results of our study show that two patients (2.7%) had the minimal disability after subacute phase of rehabilitation (MRS ≤ 2). The average value of MRS was 3.73 and 3.48 on admission and discharge, respectively. Highly statistically significant ($p < 0.001$) improvement in average values for MRS which was reported after rehabilitation treatment of patients after stroke is in accordance with literature data [29].

The MRS is used for rapid assessment of disability in patients after stroke [30]. Literature data suggest that the patients with values MRS ≤ 3 during the first week after stroke achieved good functional recovery after conducting the program of medical rehabilitation [31].

Conclusion

The degree of motor recovery of affected extremities evaluated by Signe-Brunnström scale and the ability to perform self-care activities according to Barthel Index was significantly higher at the end of the subacute phase of rehabilitation treatment. Functional status and mobility were significantly improved in all patients after ischemic stroke according to Rivermead Mobility Index, and disability of patients was significantly reduced during the rehabilitation treatment according to the modified Rankin scale. No statistically significant differences were found in functional status of patients after stroke (Rivermead Mobility Index) in relation to gender, age structure and lateralization of the lesion in. The data obtained in this way are of great importance for the evaluation of functional status of these patients.

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BACTERIAL INFECTIONS IN PATIENTS WITH LIVER CIRRHOSIS

BAKTERIJSKE INFEKCIJE KOD BOLESNIKA SA CIROZOM JETRE

Tomislav PREVEDEN

Summary

Introduction. Liver cirrhosis is characterized by a reduced defensive reaction to bacterial infections and patients with cirrhosis are at increased risk of developing infections, sepsis and death. The most common bacterial infections in these patients are spontaneous bacterial peritonitis, urinary tract infection, pneumonia, skin and soft tissue infection and bacteremia. The most common causes are Gram negative bacteria. The aim of this study was to determine the prevalence, localization and etiology of bacterial infections in hospitalized patients with liver cirrhosis. **Material and Methods.** This retrospective study included 401 patients with liver cirrhosis hospitalized at the Department of Infectious Diseases, Clinical Center of Vojvodina Novi Sad in the period from 2006 to 2010. Bacterial infection was diagnosed according to clinical examination, laboratory findings, radiological examination and bacterial positive culture. **Results.** The prevalence of bacterial infection was 38.15% (153/401). The most common infections were pneumonia (21.56%), urinary tract infection (20.91%), and spontaneous bacterial peritonitis (18.95%). Localization of infection remained undetermined in as many as 37 patients (24.18%). Bacterial cultures were positive in 32 patients (20.91%), Gram negative bacteria were commonly isolated, mostly Escherichia coli (71.87%). The mortality rate among patients with bacterial infections was 31.37% (48/153). **Conclusion.** Bacterial infections are often found in patients with liver cirrhosis, the most frequent being pneumonia, urinary tract infection and spontaneous bacterial peritonitis. Gram negative bacteria, especially Escherichia coli were predominant in the etiology. The extent to which bacterial infections are taken into consideration in cases with liver cirrhosis is rather high; however, they are not proved etiologically to the satisfactory level.

Key words: Liver Cirrhosis; Bacterial Infections; Risk Factors; Peritonitis; Urinary Tract Infections; Pneumonia; Escherichia coli

Sažetak

Uvod. Cirozu jetre karakteriše smanjena odbrambena reakcija organizma prema infekcijama, te pacijenti sa cirozom jetre imaju povećan rizik od bakterijskih infekcija koje mogu napredovati do sepse i završiti smrtnim ishodom. Bakterijske infekcije se kod ovih bolesnika najčešće manifestuju kao spontani bakterijski peritonitis, infekcije urinarnog i respiratornog sistema, infekcije kože i mekih tkiva, bakterijemije, a najčešći uzročnici su Gram-negativne bakterije. Cilja rada bio je da se utvrdi prevalencija, lokalizacija i etiologija bakterijskih infekcija kod hospitalizovanih bolesnika sa cirozom jetre. **Materijal i metode.** Retrospektivnom studijom je obuhvaćen 401 bolesnik sa cirozom jetre, hospitalizovan na Klinici za infektivne bolesti u Novom Sadu u periodu 2006−2010. godine. Dijagnoza bakterijske infekcije je postavljena na osnovu: kliničkog pregleda, laboratorijskih analiza, radioloških metoda dijagnostike i bakterioloških kultura krvi, urina, ascitesa i briseva kože. **Rezultati.** Prisustvo bakterijske infekcije utvrđeno je kod 153 bolesnika sa cirozom jetre (38,15%). Najčešći su bili pneumonija (21,56%), infekcija urinarnog trakta (20,91%) i spontani bakterijski peritonitis (18,95%). Kod 37 pacijenata sa bakterijskom infekcijom (24,18%), ishodište infekcije nije utvrđeno. Bakterijske kulture su bile pozitivne kod 32 bolesnika (20,91%) i najčešće su izolovane Gram-negativne bakterije, kod 25 bolesnika (78,12%) i to *Escherichia coli* kod 23 bolesnika (71,87%). Smrtni ishod bakterijskih infekcija je zabeležen kod 48 bolesnika (31,37%). **Zaključak.** Bakterijske infekcije su često prisutne kod bolesnika sa cirozom jetre i najčešće su lokalizovane na plućima, urinarnom traktu i u abdomenu kao spontani bakterijski peritonitis. U etilologiji dominiraju Gram-negativne bakterije, pre svega *Escherichia coli*. Kod bolesnika sa cirozom jetre na bakterijske infekcije dovoljno mislimo, ali ih nedovoljno etiološki dokazujemo.

Ključne reči: Ciroza jetre; Bakterijske infekcije; Faktori rizika; Peritonitis; Infekcije urinarnog trakta; Pneumonija; Escherichia coli

Introduction

Bacterial infections are often present in patients with liver cirrhosis, often leading to the progression of liver failure, occurrence of complications such as gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome and acute exacerbation of chronic liver failure. They are present on admission or develop during hospitalization in 30-40 % of patients with liver cirrhosis and are responsible for fatal outcome in 30-50 % of patients [1-3]. They result from immune dysfunction incurred during cirrhosis and the patients with cirrhosis are at increased risk of acquiring bacterial infection, deve-

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Abbreviations
SBP – spontaneous bacterial peritonitis
CRP – C-reactive protein
PCT – procalcitonin
ITU – infectio tractus urinarii

loping sepsis and the fatal outcome. The reasons for this are the transfer of bacteria from the intestinal lumen to the mesenteric lymph nodes, portal and systemic circulation and the existence of portosystemic shunts, damaged functions of reticuloendothelial system which lead to reduced removal of bacteria and endotoxins from the portal circulation [4, 5]. It is believed that bacterial infections are particularly likely to develop in patients with advanced liver cirrhosis (Child-Pugh high score), bleeding from esophageal varices, low levels of protein in ascites and those who had previous episodes of spontaneous bacterial peritonitis [6, 7]. Bacterial infections in these patients are enhanced by invasive diagnostic and therapeutic procedures such as esophagogastroscopy, placing of Blakemore probe to stop bleeding from esophageal varices, placement of urinary catheters, central venous or subclavian catheters, ascites paracentesis, alcoholism, malnutrition, immunosuppressive therapy, proton therapy inhibitors pumps and others.

Bacterial infections in patients with liver cirrhosis usually manifest as spontaneous bacterial peritonitis (SBP), urinary tract infections, and pneumonia. Together, they make up about two thirds of these infections while the remainder belong to infections of the skin and soft tissue infections, bacteremia and other infections [8, 9]. The most commonly isolated are Gram-negative bacteria, such as Escherichia coli, Klebsiella spp, Enterobacter spp. and Pseudomonas aeruginosa, as well as Staphylococcus aureus and Streptococcus pneumoniae being Gram -positive bacteria [10, 11]. Recently, there has been an increasing number of multidrug resistant strains of bacteria especially in hospital-acquired bacterial infections [6, 12, 13].

In order to achieve a more favorable treatment outcome of bacterial infections in cirrhotic patients it is very important to recognize the infection early and to introduce prompt and adequate treatment. As fever may be absent during infection in patients with advanced liver cirrhosis, the infection must be taken into consideration and proved in every patient with sudden decompensation of cirrhosis or exacerbation of disease. Clinical examination and determination of the acute phase inflammatory markers, such as C-reactive protein (CRP) and procalcitonin (PCT), may raise suspicion of the presence of a bacterial infection, which can be proved by taking bacterial cultures. Exacerbation of the disease and adverse outcome can be prevented by introducing adequate antibiotics as soon as possible [14]. In patients with liver cirrhosis who have had previous bleeding from esophageal varices, spontaneous bacterial peritonitis presence, or some other bacterial infection, it is recommended to apply prophylactic oral antibiotic treatment for seven days per month for the purpose of selective intestinal decontamination [15, 16].

The aim of this study was to determine the prevalence, localization and etiology of bacterial infections in hospitalized patients with liver cirrhosis.

Material and Methods

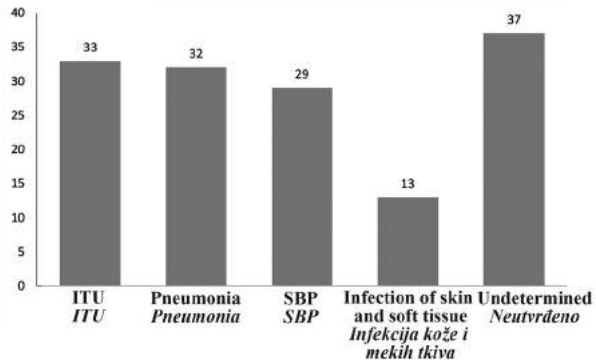
This retrospective study included 401 patients with liver cirrhosis hospitalized at the Department of Infectious Diseases, Clinical Center of Vojvodina Novi Sad during the period from 2006 to 2010. Diagnosis of bacterial infection was based on clinical examination (fever, visible infections of skin and soft tissue), laboratory findings such as elevated markers of acute phase inflammatory markers (CRP, PCT), bacterial positive culture of urine, blood, ascites and skin swabs. Diagnosis of SBP was based on diagnostic paracentesis and finding the absolute number of polymorphonuclears in ascitic liquid $\geq 250/mm^3$. Diagnosis of pneumonia was based on chest X-ray which verified the changes in the lung parenchyma corresponding to an inflammatory process. The data were analyzed by statistical package SPSS version 13.0, and the results are shown in graphs and tables created in Microsoft Office Excel 2007.

Results

Of 401 patients included in the study, 153 were found to have bacterial infection (38.15%). The most common infections were urinary tract infections, pneumonia and SBP, which were proved in 33/153 (21.56%), 32/153 (20.91%) and 29/153 patients (18.94%), respectively. Infections of skin and soft tissue were found in 13/153 patients (8.49%), while bacteremia was present in 9/153 patients (5.88%).

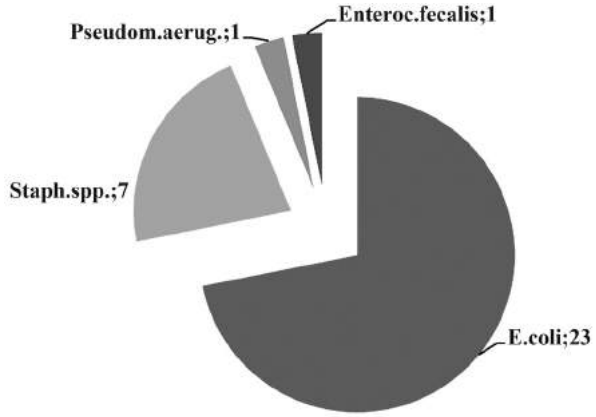
Table 1. Type of bacterial isolates taken for bacteriological cultures (N=32)
Tabela 1. *Vrsta bakterijskih izolata u odnosu na vrstu uzetog materijala (N = 32)*

	Escherichia coli	*Staphylococcus species*	*Pseudomonas aeruginosa*	*Enterococcus fecalis*	Total *Ukupno*
Urine culture/*Urinokultura*	19	0	1	1	21
Hemoculture/*Hemokultura*	4	5	0	0	9
Skin swab/*Bris kože*	0	2	0	0	2
Total/*Ukupno*	23	7	1	1	32



ITU (infectio tractus urinarii/*infectio tractus urinarii*); SBP (spontaneous bacterial peritonitis/*spontani bakterijski peritonitis)*

Graph 1. Identification of bacterial infection (n = 153)
Grafikon 1. *Lokalizacija bakterijske infekcije (n = 153)*



Graph 2. Types of bacterial isolates from samples of patients with liver cirrhosis (n = 32)
Grafikon 2. *Tipovi bakterijskih izolata iz uzoraka materijala kod bolesnika sa cirozom jetre (n = 32)*

The test performed failed to determine the localization of bacterial infections in 37/153 patients (24.18%).

Localization of bacterial infection in our patients is shown in **Graph 1**.

Positive bacterial culture confirmed the etiological diagnosis of bacterial infection in 32/153 patients (20.91%). These 32 positive bacterial cultures were as follows: 21 positive urine culture, 9 positive hemocultures and two positive swab cultures of skin taken from the site of infection. Of 33 patients with signs of bacterial infection of the urinary tract, positive urine culture was obtained in 32/33 (96.97%), all 9 patients with bacteremia had positive bacterial hemocultures (100%). Positive bacteriological culture swab provided bacteriological confirmation only in 2/13 (6.25%) patients with infection of skin and soft tissue. The diagnosis of SBP was based on the increased number of polymorphonuclear leukocytes in ascitic liquid (≥250 /mm³), while the bacterial culture sampled from the ascitic fluid remained sterile. Thirty two patients were diagnosed with pneumonia on the basis of changes in chest X-ray and elevated parameters of acute inflammation phase (CRP, PCT), which proved to be normalized after treatment with antibiotics on the check-up.

Of 32 patients, Gram-negative bacteria were isolated in 25 (78.12%), whereas Gram-positive bacteria were isolated in 7 patients (21.83%). Escherichia coli and Staphylococcus species were isolated in 23 (71.87%) and 7 patients (21.87%), respectively. One patient was found to have Pseudomonas aeruginosa (3.13%) and Enterococcus fecalis was also found in one patient (3.13%). Types of bacterial isolates in patients with liver cirrhosis and bacterial infection are shown in **Graph 2**.

Regarding the type of the material sample for bacteriological culture, Escherichia coli was isolated in 19 out of 21 bacteriologically positive urine culture, whereas Pseudomonas aeruginosa and Enterococcus fecalis was isolated in one sample, each. Of 9 positive blood cultures, Staphylococcus spp. was isolated in 5 samples and Escherichia coli in 4 samples. Staphylococcus spp. was isolated from both positive skin swab samples. The type of bacterial isolates taken for bacteriological culture is given in **Table 1.**

Lethal outcome of bacterial infections in patients with liver cirrhosis was reported in 31.37% of cases (48/153), while healing was achieved in 68.63% of patients (105/153).

Discussion

The results of this study indicate that bacterial infections often occur in patients with liver cirrhosis, in 38.15% of cases, which is consistent with the earlier studies. A similar prevalence of bacterial infection in patients with cirrhosis of 37.8% was reported by M. Drang et al., a group of Romanian authors, who stressed that the infection often passed without symptoms [17]. It is believed that the patients with liver cirrhosis and gastrointestinal bleeding are particularly prone to bacterial infections, which occur in about 45% of cases [7]. Having analyzed the occurrence of sepsis in patients with cirrhosis, Arvaniti V. et al. concluded that the occurrence of sepsis and multiorgan dysfunction in patients with terminal liver cirrhosis increased mortality four times [18]. Lethal outcome in 31.37% of patients with bacterial infection and cirrhosis in our study is consistent with the literature data.

According to the literature the most common types of bacterial infections in patients with liver cirrhosis are SBP, urinary tract infections and pneumonia, followed by infections of the skin and soft tissue infections, bacteremia and other infections [8, 9]. The distribution of types of bacterial infections in our study is consistent with the literature data since it has been found that the most commonly occurring infections are urinary tract infection (21.56%), pneumonia (20.91%), and SBP (18.94%).

Similar distribution of types of bacterial infections was found by Preda CM et al., a group of Romanian authors as well as by Fernandez J et al., a group of Spanish authors [19, 20]. What is worrying is the fact that the type of infection remained undetermined in ¼ (24.18%) of the patients in our study. The available literature does not offer such information because the studies only show the distribution of type or localization of infection without specifying whether there are undetermined types of infections. The group of patients with "undetermined type of infection" consisted of patients who had prolonged fever and elevated acute phase parameters, which disappeared after antibiotic treatment. It should be emphasized that this study was retrospective and data were not recorded precisely during hospitalization, CRP and PCT were not routinely taken in all patients, the patients did not undergo a detailed examination in order to confirm the presence of infection. In other words, more attention was paid to the treatment of liver cirrhosis and its decompensation than to the type of infection. Diagnostic paracentesis was not performed routinely in patients with ascites, and since it is known that SBP often goes asymptomatic, diagnostic paracentesis should be done in case of occurrence of ascites [21, 22].

The results of bacterial cultures in our study agree with literature data which also indicate that Gram-negative bacteria, especially Escherichia coli are predominant. According to recent data, approximately 65 % of bacterial infections in patients with liver cirrhosis are caused by Gram-negative bacteria, that being somewhat less than in our study where that participation was 78.12% [21]. It is important to emphasize that our study gave data on positive bacterial cultures in only 20.91% of the cases, which is not satisfactory because this percentage is much higher in the literature, ranging from 40-70% [2,19]. This small number of positive bacterial cultures in our study is unsatisfactory, but it should be taken into consideration that this was a retrospective study of hospitalized patients, whose samples for bacterial cultures were not taken routinely or frequently enough, that there may have been some inappropriate sampling, storage and transport of samples. In addition, a considerable number of patients had been taking antibiotics before sampling for bacteriological culture and the presence of a bacterial infection in hospitalized patients was not always taken into consideration.

Conclusion

Bacterial infections often occur in patients with liver cirrhosis. Therefore, they should be taken into consideration in patients with liver cirrhosis and acute exacerbation of the disease, i.e. decompensation in order to make the early etiological diagnosis and introduce antibiotics that cover the most common Gram-negative and Gram-positive bacteria as early as possible. A great number of positive bacterial cultures must be obtained in order to enhance the favorable outcome of bacterial infections in patients with liver cirrhosis. Even before receiving the results of bacterial cultures, biomarkers of acute phase of inflammation, such as C-reactive protein and procalcitonin, must be looked for because they raise suspicion of the presence of bacterial infection. A detailed clinical examination, sampling material for bacteriological culture, and paracentesis of ascites and chest X-ray may confirm the presence of bacterial infection, and thus appropriate antibiotic therapy can be introduced on time. It most often involves the application of third generation cephalosporins or quinolones for a period of 10-14 days. Consequently, if bacterial infections in patients with liver cirrhosis are taken into consideration, their influence on mortality can be decreased, the duration of treatment can be shortened and treatment costs can be reduced.

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RISK FACTORS FOR BILATERAL ANTERIOR CRUCIATE LIGAMENT INJURIES

FAKTORI RIZIKA ZA NASTANAK OBOSTRANE POVREDE PREDNJEG UKRŠTENOG LIGAMENTA

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Summary

Introduction. The aim of this study has been to identify which risk factors can influence bilateral anterior cruciate ligament injury. **Material and Methods**. Thirty-two operated patients took part in this survey during the period of ten years. There were 5 women and 27 men, with average age of 30.46 years (19-55). The respondents filled in the questionnaire by answering the questions regarding the time when getting injured and operated, mechanism of injuries, genetic and anthropometric data, characteristics of sports and every day activities. **Results**. The incidence of reconstructed bilateral injuries in relation to unilateral ones was 2.3% (50/2168). The age of respondents and side of the injured knee did not correlate significantly with the achieved subjective physical activity level after the second knee surgery. The average time from the first injury to operation was 10 months and 4.3 years since that moment up to the injury of the other knee. It took more than 9 months on average until the reconstruction of contralateral anterior cruciate ligament. The most of athletes were injured in football matches. Three-quarters of athletes returned to competition activities after the first operation, which caused the same injury of the contralateral knee. **Discussion and Conclusion**. Anterior cruciate ligament rupture of the contralateral knee most often occurs in young active athletes within the first four years after the initial reconstruction. Its frequency is not affected by sex, side of extremity, genetic predisposition, type of sport, concomitant injuries and the choice of graft. Returning to the same or higher level of sports activities after the first reconstruction is one of the preconditions for injuring the other knee in the same way.

Key words: Risk Factors; Anterior Cruciate Ligament; Knee Injuries; Questionnaires; Activities of Daily Living; Sports

Sažetak

Uvod. Cilj ovog rada predstavlja utvrđivanje koji faktori rizika pogoduju nastanku obostrane povrede prednjeg ukrštenog ligamenta. **Materijali i metode.** U istraživanju je učestvovalo 32 operativno lečena pacijenta, tokom desetogodišnjeg perioda. Među njima je bilo 5 žena i 27 muškaraca, prosečne starosti 30,46 godina (19−55). Anketirani pacijenti su dali odgovore na upitnik o: vremenu povređivanja i operacija, mehanizmu povrede, genetskim i antropometrijskim podacima, kao i karakteristikama sportskih i životnih aktivnosti. **Rezultati.** Incidencija rekonstruisanih obostranih povreda u odnosu na jednostrane iznosi 2,3% (50/2 168). Korelacija uzrasta ispitanika sa postignutim subjektivnim nivoom fizičke aktivnosti posle druge operacije kolena ne pokazuje značajnu statističku razliku, kao ni lateralnost (dominantnost ekstremiteta). Prosečno vreme od prve povrede do operacije iznosilo je 10 meseci. Od tada do povrede drugog kolena proteklo je još prosečno 4,3 godine. Potom je prošlo još prosečno 9 meseci do rekonstrukcije kontralateralnog prednjeg ukrštenog ligamenta. Najviše sportista povređeno je na fudbalskim utakmicama. Tri četvrtine sportista se nakon prve operacije vratilo takmičarskom aktivnostima, koje su bile uzrok iste povredu drugog kolena. **Diskusija i zaključak.** Povreda prednjeg ukrštenog ligamenta kontralateralnog kolena najčešće nastaje kod mladih aktivnih sportista u toku prve četiri godine nakon prvobitne rekonstrukcije. Na navedenu učestalost ne utiču: pol, strana povređenog ekstremiteta, genetska predispozicija, vrsta sporta, udružene povrede i izbor kalema. Povratak na isti ili viši nivo sportske aktivnosti posle rekonstrukcije prednjeg ukrštenog ligamenta kolena predstavlja jedan od preduslova za nastanak iste povrede drugog kolena.

Ključne reči: Prednji ukršteni ligament; Faktori rizika; Bilateralne povrede

Introduction

The annual incidence of unilateral anterior cruciate ligament injury (ACL rupture) in general population ranges between 0.01 and 0.08%, while it is significantly higher in sports active population, being 1.5-1.7% [1–5]. The frequency of nonsimultaneous bilateral ACL injuries ranges from 1.1% up to even 14% of the total number of ACL injuries [5–11]. Simultaneous ruptures are very rare, and they are reported in the literature only as individual cases [4, 12–15]. The risk of injuring the other knee is even greater than the risks for primary rupture, and the

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Abbreviations
ACL – anterior cruciate ligament injury
BMI – body mass index
BTB – bone-to-bone

second injury happens most often within the first three years after the first operation [6–9].

The causes of bilateral ACL injuries have not been explained sufficiently although there are various assumptions. Specific internal factors which are being intensively studied include: anthropometric, biomechanical, neuromuscular, anatomical, hormonal, and genetic risks [3, 16, 17]. Reduced width of femoral intercondylar notch, increased posterior tibial slope, bad neuromuscular control, ligament laxity, increased body mass index (BMI), female sex and the valgus position of the knee are linked with an increased risk of ACL injury [3, 16, 17].

This study has been aimed at analyzing possible causes of bilateral ACL ruptures and identifying risk factors on our specimen of patients, which should result in the prevention of bilateral injuries.

Material and Methods

Having been approved by the Ethics Committee of Clinical Center of Vojvodina, this retrospective study was performed at the Department of Orthopedic Surgery and Traumatology in Novi Sad. The study sample included 32 of 50 patients operated for bilateral ACL ruptures in the period from January 01, 2003 until December 31, 2012, who had given their consent to participate in this study. The average time of monitoring from the knee operations to the check-up was 4.9 years. The respondents were 5 women and 27 men, whose average age was 30.46 years (ranging from 19 to 55 years).

A questionnaire was designed and sent by e-mail to all patients, who were asked to provide data on the amount of time before the first and the second injury, between the injuries, between the injuries and surgical interventions, between the interventions and return to trainings and competitions. They also provided information on their sports activities and activities in their daily life.

The following parameters were included in the more detailed coverage of data for each patients: age structure, gender structure, family history of the same injury, height, body mass, amount of time spent on training before the injury, the amount of time between the first injury and operations, the amount of time between the first injury and return to training, the amount of time between the first operation and return to competition, the amount of time between the two injuries, the amount of time between the first operation and injuring the other knee, the amount of time between injuring the other knee and the second operation, the amount of time between injuring the other knee and return to training, the amount of time between injuring the other knee and return to competition, dominant leg, the achieved level of physical activities after the second operation.

The mean values, standard deviation, minimum and maximum were analyzed within descriptive statistics. The following statistical analyses were used: Spearman and Pearson's coefficient correlation and T-test for independent samples.

Results

During the study period lasting for ten years, 2168 unilateral ACL ruptures were operated. Fifty patients with reconstructed bilateral ruptures were among them, the incidence being 2.3%.

Out of 32 patients, 14 patients injured the right knee first and 16 patients injured first the left one, while both knees were simultaneously injured in two cases. The left leg was dominant in 19 patients (for jumping), and the right one was dominant in 13 patients. No statistically significant correlation was observed between the age of patients and their level of activity, nor the effect of the dominant leg on bilateral ACL injuries. The correlation of age and the activity level was $F(2.29)=1.59$, $p=.221$ ($p>.05$).

The periods between injuries and operations are shown in **Table 1.**

The injuries happened during the sports activities in all patients: 16 (75%) in competition, 8 during the training (25%) and 8 in recreational sporting activities (25%). The association between the type of sport and bilateral ACL rupture is shown in **Graph 1** and the competition level of sports activities of patients is given in **Graph 2**.

ACL and meniscus injuries during the first and contralateral knee injuries are shown in **Table 2**.

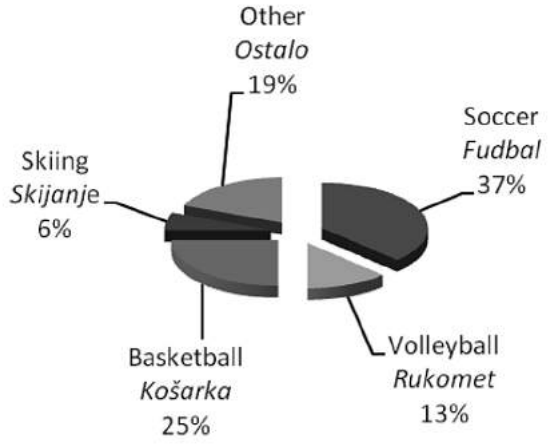
According to the answers in the questionnaire, 87.5% of respondents returned to trainings and 75% to competitions after the first operation. However, that percentage was lower after the second ACL

Table 1. Time of ACL injuries
Tabela 1. *Vreme povređivanja prednjeg ukrštenog ligamenta*

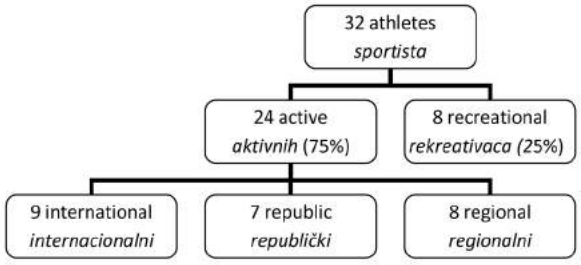
	Time/*Vreme*	Average/*Prosek*
1st injury – 1st operation *1. povreda – 1. operacija*	25 days – 7 years *25 dana −7 godina*	10.2 months *10,2 meseci*
1st injury – 2nd .injury *1. povreda − 2. povreda*	9 months – 15 years *9 meseci – 15 godina*	4.34 years *4,34 godine*
2nd injury – 2nd operation *2. povreda − 2. operacija*	5 days – 4 years *5 dana – 4 godine*	9.1 months *9,1 meseci*

Table 2. ACL and meniscus injuries during the first and contralateral knee injuries
Tabela 2. *Udružene povrede prilikom inicijalne i povrede prednjeg ukrštenog ligamenta kontralateralnog kolena*

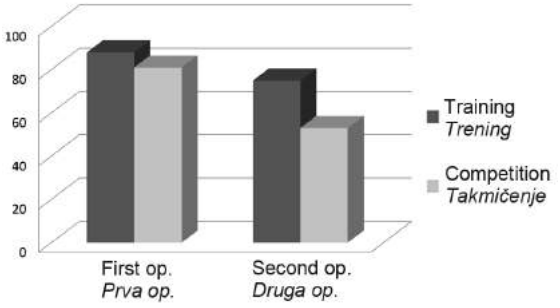
Injury *Povreda*	Isolated ACL/*Samo prednji ukršteni ligament*	Both menisci *Oba meniskusa*	Medial meniscus *Unutrašnji meniskus*	Lateral meniscus *Spoljašnji meniskus*
The first/*Prva*	15	3	6	3
The second/*Druga*	17	1	3	3



Graph 1. Sport that caused bilateral ACL rupture
Grafikon 1. *Vrsta sporta koja je dovela do obostrane povrede prednjeg ukrštenog ligamenta*



Graph 2. Sports activity and competition level of patients
Grafikon 2. *Nivo sportske aktivnosti i rang takmičenja pacijenata*



Graph 3. Return to trainings and competitions after the first and second ACL reconstruction
Grafikon 3. *Povratak treninzima i takmičenjima nakon prve i druge operacije prednjeg ukrštenog ligamenta*

reconstruction, being 81.2% and 53.1% of those who returned to trainings and to competitions (matches), respectively (**Graph 3**).

Discussion

While the risk factors, etiology and mechanisms of primary ACL injuries have been widely studied, reasons for ACL ruptures of the contralateral knee are not clearly defined, although those injuries are not rare. The most voluminous study was published by a Swedish group of authors [9] thanks to the National Register of Knee Ligaments Injuries [2]. Out of 9061 reconstructed ACL in the study sample, 270 bilateral reconstructions (3%) were done. Souryal et al. [10], Myklebust et al. [6] and Falstrom et al. [7] reported 4%, 9%, and 12% of bilateral injuries, respectively. The incidence increases with the length of the monitoring period of the patients, so in our sample it resembles the Swedish register and amounts to 2.3%.

While in some countries, such as Japan, bilateral ACL injuries are dominant in women [19], in Scandinavian countries sexes are almost equally represented [7, 9]. In our study, as well as in some others [10] men are most affected. The above mentioned does not suggest that men represent a group of athletes at risk, only that they are operated 2-8 times more often than women [19–22]. The group at highest risk for ACL injury is young, sports active population. Women are at 2-10 times greater risk than men, depending on the type of sport [3, 6, 18]. The reasons for epidemic appearance of ACL injuries among women in the world lie in the anatomic differences between gender: size of Q angle, increased valgus of knee joint, narrow intercondylar notch, wider pelvis, impact of estrogen hormone on ligaments during menstruation cycle, general laxity of ligaments and different time of contractions between anterior and posterior groups of thigh muscles [3, 6, 18].

Branch et al. [23] used robotics to measure and compare rotatory stability of knee joints without ACL rupture and with bilateral ruptures. The latter had significantly increased internal and decreased external rotation of tibia. Both internal and external rotation was increased in women compared to men. Rotatory instability may cause a simultaneous rupture of ACL, medial meniscus and medial colateral ligament because those injuries most often happen during forced valgus, moderate flexion and rotation of tibia [23].

According to our previous studies [20], the following factors did not significantly influence injur-

ing ACL in 450 operated patients: type of sport shoes, warming, genetic predisposition and taking daily therapy. Injuries occurred more often during competitions, at the end of matches, in activities without contact with other competitors, during landing or sudden change of direction, on dry surfaces, in athletes who had not prepared well.

Today, anatomic variations of knee joint are in the focus as risk factors, so we have found that patients with increased posterior tibial slope are at a greater risk of ACL rupture [25]. A narrow femoral intercondylar notch can also represent an anatomic risk factor for bilateral ACL rupture [10, 18].

Sward et al. [8] believe that the most prominent risk factor for a contralateral ACL injury is return to a high (competitive) level of physical activity. Our results are in agreement with the above mentioned because 75% of our operated patients returned to competition level of activities after the first operation, and then had another knee injury within the first 4 years after the primary operation. Most authors [5, 9, 25] confirm the above mentioned time frame, while Orchard et al. [26] found that the greatest risk factor for a contralateral ACL injury was a history of an ACL reconstruction in the previous 12 months.

Contralateral ACL rupture is most commonly associated with younger people, athletes under 20 years of age [9, 10]. We have observed, as Falstrom et al. did [7], that the second injury happened at somewhat older age, the average being 30.5 years of our patients and 29.1 years of theirs. Due to the fact that sports career is on the wane in those years, contralateral knee injury in the fourth decade may mean an end of career, while this happens less frequently in the second decade of life. In addition, every second active athlete has cartilage damage in the fourth decade [6], which can cause pain and lasting disruption of sports activities. Statistical analysis considering the correlation between the participants' age and the subjective level of physical activities which the respondents have achieved after the second knee surgery does not show a significant difference. The correlation is extremely low, so we can say that there is no connection between the age and activity level.

Family history may be considered a possible risk factor for bilateral ACL injuries according to some literature data. Although this issue is still being debated, no consensus has been reached. While some authors advocate this theory strongly [17, 27], the authors of this paper as well as others have not found the correlation [5, 10, 27]. Flynn et al. [28] found that patients having the history of ACL ruptures in their family: in the first generation (parent, brother or sister, child), the second (brothers and sisters of their parents) or in the third, are at a risk twice higher of injuring their ACL than general population without family history of injuries. Our study could not confirm this claim, because only four of our patients had ACL injuries in their family history (two fathers, a brother, and a sister), which is statistically insignificant representation.

Studies which have found a significant correlation between the side of the injured extremity and bilateral ACL injury are rare. Although there are some authors who believe that the reconstruction of nondominant limb is a potential predictor of contralateral ACL injury [29], we have not observed such a correlation.

The choice of graft can also be a risk factor. Leys and Sward et al. [8, 25] have concluded that reconstruction with bone-to-bone (BTB) graft carries a greater risk for bilateral ACL rupture (26%) than hamstring tendons (12%). Ardernord et al. [9] claim that graft harvesting of hamstring tendons from the contralateral unharmed knee significantly increased this risk. This probably weakens the function of the healthy knee resulting in it being injured later because the tendons cannot regenerate during a short period of time until the next rupture. However, the majority of studies [9, 21, 30] have proved that the choice of graft does not affect the bilateral ACL ruptures significantly. Our previous studies have also failed to find the correlation between the choice of graft and ACL re-ruptures [19, 21]. The cause may lie in the fact that ACL are reconstructed with BTB graft in professional athletes, while hamstrings tendons are usually applied in women and those who go in for recreational sporting activities, which impose less burden on the operated and uninjured knees.

The structure of sporting activities which the respondents were engaged in only confirmed our earlier epidemiological studies [20]. Intensive sports that involve movements of pivoting, forced valgus and anterior translation of tibia during one-leg landing represent activities of high risk for ACL rupture. The fact that in Vojvodina [20–22] 37-50% of patients get injured in football (soccer) only reflects sports preference of young population in Serbia due to the popularity of that sport among young professionals and recreational activities among the middle-aged population. Football is also the most prominent sport in this study, and the second and third place is taken by basketball and handball, respectively. In the study done by Souryal et al. [10], American football (rugby) was in the first place with 25.6%, followed by basketball (20.7%) and soccer (11%) This is in accordance with the findings of our studies. The difference is only in the fact that rugby is more popular sport in North America than soccer. Swedish authors [6] consider handball to be sport of a high risk due to rapid change of movement direction and pivoting, which says more about popularity of that sport in Scandinavian countries. Authors from Japan think that basketball and gymnastics are sports carrying the highest risks [18].

The most prominent risk factor for a contralateral ACL injury is returning to a high level of activity during intense trainings and competitions [7] which include sports with a lot of jumping, pivoting, leap aside and change in movement direction. This is in line with our results since only four participants (13%) did not return to training after the initial injury, and all the others resumed the previous

sporting activities at the level of training or competitions. According to earlier results, the most commonly injured athletes are those who are active in sports between 11 and 20 years of age, most often in competitive matches, and considerably less in friendly matches and during training. The parts of competition that have the highest risk are its middle part and end of match [20]. Competitive athletes, who train at least once a day most often for 90 minutes, are at a higher risk of injuring ACL. Our results showed that the patients who were at the competitive level of sports activities were mostly present in the structure of our participants (15 of them), while 8 of them were injured while training.

By correlating the associated injuries during the second knee injury and the reached level of physical activity in our study group, it has been proved that meniscus ruptures do not play a crucial role in restitution of activities. Statistical parameters do not show any statistically significant difference. The reason for such a result is again significant disproportions in the representation and associated absence of ruptures within the group, as well as the high percentage of those respondents who were not able to provide the information on associated knee injuries. Only 9.4% of the respondents had the rupture of medial meniscus, 9.4% had the lateral meniscus rupture, and 3.1% suffered from both menisci rupture simultaneously. As many as 25% of participants did not know if they had injury of menisci, while 53.1% of them had an isolated ACL rupture. Faltstrom et al. [7] found ruptures of medial meniscus in 15.4% of cases during initial injuries and 31.1% during the contralateral injuries [7]. Associated lateral meniscus injury was reported in 15.4% of initial ACL injuries and in 13.1% of contralateral ones. Both menisci got injured simultaneously during the initial rupture in 4.6% of cases and in 3.3% of cases during contralateral ACL rupture. Ardernord et al. [9] also concluded that the previous meniscal and chondral injuries were not predictors of future contralateral ACL reconstruction, although they noted significantly higher percentages than we did (40% menisci and 27.5% chondral lesions).

Since there are several aspects of doing physical activities, our study and similar ones need more detailed questionnaires to analyze the length of training before injuries, as well as the intensity and phases of sports activities (warming up, training, activity in other types of sports in relation to the primary one) in order to check the data obtained for that particular aspect of training-competitive process. Low statistical significance in the correlation between the associated initial and contralateral injuries with the reached level of physical activities after the second operations leads to the conclusion that it is necessary to study this issue on a sample greater than 32 patients, which is the main drawback of this study. The existence of a National Register, similar to the Swedish one, would certainly lead to a more comprehensive analysis.

Conclusion

Anterior cruciate ligament rupture of contraleteral knee occurs in young active athletes most often within the first four years after the initial reconstruction.

Sex, side of extremity, genetic predisposition, type of sport, concomitant injuries and choice of graft do not affect bilateral injury.

Returning to the same or higher level of sports activities after the first reconstruction is one of the preconditions for the appearance of the same injury of the second knee.

Determination of predisposing factors could help in preventing bilateral anterior cruciate ligament injuries.

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DEVELOPMENT OF PLASTIC SURGERY

RAZVOJ PLASTIČNE HIRURGIJE

Marija Đ. PEĆANAC

Summary

Introduction. Plastic surgery is a medical specialty dealing with corrections of defects, improvements in appearance and restoration of lost function. **Ancient Times.** The first recorded account of reconstructive plastic surgery was found in ancient Indian Sanskrit texts, which described reconstructive surgeries of the nose and ears. In ancient Greece and Rome, many medicine men performed simple plastic cosmetic surgeries to repair damaged parts of the body caused by war mutilation, punishment or humiliation. In the **Middle Ages,** the development of all medical braches, including plastic surgery was hindered. **New age.** The interest in surgical reconstruction of mutilated body parts was renewed in the XVIII century by a great number of enthusiastic and charismatic surgeons, who mastered surgical disciplines and became true artists that created new forms. **Modern Era.** In the XX century, plastic surgery developed as a modern branch in medicine including many types of reconstructive surgery, hand, head and neck surgery, microsurgery and replantation, treatment of burns and their sequelae, and esthetic surgery. Contemporary and future plastic surgery will continue to evolve and improve with regenerative medicine and tissue engineering resulting in a lot of benefits to be gained by patients in reconstruction after body trauma, oncology amputation, and for congenital disfigurement and dysfunction.

Key words: Surgery, Plastic; History of Medicine; Famous Persons

Sažetak

Uvod. Plastična hirurgija je hirurška grana koja se bavi korekcijom i rekonstrukcijom forme i funkcije. Prvi dokumenti nalaze se u indijskim tekstovima pisanim na sanskritu i detaljno svedoče o rekonstruktivnim operacijama nosa i ušiju. Medicina u staroj Grčkoj i Rimu nastavila je sa primenom intervencija radi modeliranja delova tela koji su bili povređeni u ratovima, drugim mehanizmima povređivanja ili bolestima. U **srednjem veku** nastaje zastoj u svim tadašnjim granama medicine do XVIII veka, kada ponovo počinju operativni zahvati rekonstrukcija delova tela. **Novi vek.** U plejadi vrsnih hirurga novog veka velik je broj entuzijasta i harizmatičnih likova koji se prihvataju hirurške discipline i postaju umetnici stvaranja nove forme. **Moderna era.** U XX veku stvorena je plastična hirurgija čije dimenzije postaju toliko obimne da se razvija nekoliko pravaca: rekonstrukcija deformiteta i defekata na telu, hirurgija šake, hirurgija glave i vrata, onkoplastika, mikrohirurgija, lečenje opekotina i njihovih posledica i estetska plastična hirurgija. U futurističkom razmišljanju, regenerativna medicina i tkivni inženjering sigurno će dati svoj doprinos i proširiti operativni program rekonstrukcija posle traume i onkoloških defekata kao i funkcionalno i estetsko rešavanje kongenitalnih malformacija.

Ključne reči: Plastična hirurgija; Istorija medicine; Poznate osobe

Introduction

Plastic surgery is a medical and surgical specialty which deals with corrections and reconstructions of body parts after injuries, birth or cosmetic defects. The basic idea is the achievement of satisfactory form and function. The name comes from the Greek word "plastikos" which means to shape, create or form. Plastic surgery today represents the art of surgical modeling [3].

This branch of medicine, which is applied to different parts of the body, with different roles, has developed in several directions, the latest being microsurgery. It was initially used in treatment of congenital anomalies or trauma, which later lead to replantation surgery and microsurgical free flap skin transfer. Another branch of this specialty is surgery of burns and its sequelae. Esthetic surgery was born as the culmination of art modeling, with a task to reconstruct the shape of the body altered by aging or unsatisfactory appearance.

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Figure 1. Drawing of nose reconstruction by Indian flap methode. Sushrura was the first who performed it in India. In the Middle Ages J. C. Carpue (Great Britain) performed it successfuly and published.
Slika 1. *Ilustracija rekonstrukcije nosa Indian flap metodom, koju je radio Sushruta u Indiji a uspešno izveo i objavio u Evropi Karpju (Carpue J.C.) (Velika Britanija)*

Ancient Times

The invention of writing and its application marked the beginning of Ancient Times. In all ancient civilizations there were people who offered help or healing to the sick and injured. Writing made it possible to record and transfer the knowledge and experience of educated people. Injuries of the nose and the way of its treatment, considered as the first descriptions of rhinoplasty, had been recorded in the medical papyrus dated from 1500-2000 BC, and was found by Edwin Smith in Egypt [4].

The first descriptions of surgery involving the reconstruction of body parts date from 800 BC and were written in Vedic medicine. The documentation about these works can be found in the written works of Sushruta, an Indian surgeon who is considered the father and founder of plastic surgery [5]. Sushruta and his contemporary Charak surgicaly treated patients and are well known for their nose and lip surgery (**Figure 1**). In India, the legal punishment at that time was cutting the nose so rhinoplasty was indeed necessary and it was performed as a method of reconstruction. In addition to these procedures, treatments of skin defects by rotational and pedicled lobes as well as methods of hemostasis were described in the notes. Sushruta Samhita records written in Sanskrit language are saved only in Arabic translation.

During the period of the Roman Empire, Aulus Cornelius Celsus (the first century AD) (**Figure 2)** wrote „De Medicina“, where the surgical reconstruction of ear, nose and lips was recorded [6]. There is a preserved text of breast reduction in men, as well as the reconstruction of defects with advancement flaps. In the fourth century AD, the famous Byzantine physician Oribasius wrote the encyclopedia „Synagogue Medicae“ which consisted of 70 volumes. In the book 42, chapter 25 and 26, a detailed description of reconstruction of facial defects (the eyebrows, forehead, cheeks, nose and ears) can be found [7].

Middle Ages

With the fall of the Roman Empire and spreading of Christianity, the time of mysticism and religion began, and surgery in all its forms became neglected. The period of the early Middle Ages represents hindered development of all surgical disciplines except the minor progress in surgery of cleft palate.

According to the recorded data from the XV century, the Branca family from Sicily developed some reconstructive methods. A father and his son from the family Branca, who were barbers, used the flap taken from the upper arm to reconstruct the nose or the face. The flap remained tied for twenty days and then was separated from the donor region [10] (**Figure 3**). The method had to be hidden and passed down as a family secret (the method was not published to avoid prosecution by the Church).

Al-Rhazi (865-925), an Arab physician and Avicenna, the Latin name for the Persian physician Ibn Sina (980-1037) (**Figure 2**), gave the description and emphasized the importance of the first aid in injuries caused by fire. They used cold water and greasy coatings later in the treatment [8].

During the Renaissance period, when science and art were flourishing, surgical disciplines developed as well. In the XV century Serafeddin Sabuncuoglu (1385-1468) wrote the article “Imperial Surgery” and described the material for maxillofacial surgery, intervention on the eyelids, as well as the protocol for the treatment of gynecomastia which is believed to represent the foundation for the development of modern breast reduction surgery [9].

New Age

The new age began with remarkable discoveries in the fields of science, art, technology and economy. Surgery developed into science which became a field of great interest of eminent doctors educated at medical faculties of universities throughout Europe.

The most famous name of Italian plastic surgery in the XVI century, today still considered as “the

Figure 2. *Photos of plastic surgeons from the new age and modern era (photos are arranged from the left to the right in rows).
Slika 2. **Plastični hirurzi nove i savremene ere (fotografije sleva nadesno, redovi odgore prema dole)*
First row/*Prvi red:*
Karl Ferdinand fon Grafe (Karl Ferdinand von Graefe); Johan Fridrih Difenbah (Johann Friedrich Dieffenbach); Baron Gijom Dipietren (Baron Guillaume Dupuytren); Bernard fon Langenbek (Bernhard von Langenbeck); Karl Tirš (Carl Thiersch)
Second row/*Drugi red*:
Aleksis Karel (Alexis Carrel); Ser Harold Gilis (Sir Harold Gillies); Ser Arčibald Makindo) Sir Archibald McIndoe Sterling Banel (Sterling Bunell); Aleksandar A. Limberg (Aleksandar A. Limberg)
Third row/*Treći red*:
Sofi Spic (Sophie Spitz); Harold E. Klajnert (Harold E. Kleinert); Zora Janjžeković; Volas H. Klark (Wallace H. Clark); Aleksander Breslov (Alexander Breslow)
Fourth row/*Četvrti red*
Heri Banke (Harry Buncke); Foad Nahai (Foad Nahai); Marko Godina; Stefan J. Mates (Stephen J. Mathes); Bernar Devušel (Bernard Devauchelle)

Figure 3. Drawing of Tagliacozzi's nose recontruction method
***Slika 3**. Ilustracija Taljakocijeve (Tagliacozzi) metode rekonstrukcije nosa*

father of modern plastic surgery" by some historians, was Gasparo Tagliacozzi (1545-1599) (**Figure 2**). In 1597, he published the book "De Chirurgia Curtorum Per Insitionem" which marks the beginning of modern plastic surgery. Tagliacozzi's main interest was the reconstruction of defects of nose and other parts of the body, resulting either from injuries or diseases. Tagliacozzi also reconstructed the nose using the skin of the upper arm (**Figure 3**) [6]. Despite the success of his procedures this great surgeon was condemned by the church, which considered these procedures contrary to Christian laws. The nose reconstruction did not become a regular practice in Europe before 1816, when the English surgeon Joseph Constantine Carpue (1764-1846) successfully conducted such an operation after years of working experience in India [10].

Karl Ferdinand Von Graefe * (1787-1840), who was a professor of surgery with extensive experience as a war surgeon, started nose reconstruction in war injuries using the Tagliacozzo's method in 1817 in Berlin. The expression "plastic" was mentioned for the first time in a book he published [6]. He advocated the establishment of separate departments in hospitals, which would perform experimental and applied reconstructive surgery.

Johann Friedrich Dieffenbach*(1792-1847), Von Graeff's student, was the first who routinely performed reconstructive surgery of the nose, lips and other reconstructive methods in tendons and skin in Berlin in 1829. His postulates of the esthetic and functional secondary rhinoplasty apply even nowadays [6].

In Paris in 1834, Baron Guillaume Dupuytren * (1777-1835) described the basics of anatomy and surgical treatment of palmar fibromatosis, which was later called Dupuytren's contracture after him [11]. At the same time in Berlin, Bernhard von Langenbeck * (1810-1882) was the first to describe a transposition flap used for the lower lip defects and gave a description of cheilognathopalatoschisis reconstruction [12].

In 1838 Eduard Zeis (1807-1868) published a plastic surgery handbook and described everything known in plastic and reconstructive surgery at that moment [13]. Victor von Bruns (1812-1883) published an atlas of reconstruction of the nose, lips, heilognathopalatoschisis and head and neck defects in 1857 [14]. In 1862 John Wood described the inguinal flap and its function in covering hand defects. It was also the first axial stalk lobe described [15].

Jacques Joseph is a name of German surgery of that time and remembered to this day in surgery of the head and neck: (1865-1934). He became famous for his otopostasis procedures and surgery of the nose [16].

Jacques Louis Reverdin (1842-1929) introduced the use of skin grafts in 1869. He removed them with a scalpel and transferred to the area with granulation tissue, that being the first skin transplantation in history [17].* Carl Thiersch (1822-1895) introduced the application of thin skin grafts with larger surface area for a successful resolution of major defects of the skin in 1874 [18]. In 1895, Vincenz Czerny (1842-1916) described a breast reconstruction using transplanted lipoma from a hip to fill in the defect after extirpation of fibroadenoma [19].

The end of XIX and beginning of XX century is important because the surgeon William Halsted's (1852-1922), Baltimore (USA) gave grounds for radical mastectomy and radical excision of melanoma [20].

Modern Era

The Modern Era is the period of time continuing into the present moment without interruption, and represents modern history, which means that is present in "living memory". The beginning of the XX century, which is considered the beginning of the modern era, witnessed a number of large-scale wars, which inevitably led to numerous injuries not only in soldiers but in civilians as well. All that imposed the need for reconstructive surgical procedures, but plastic surgery had not been promoted as a separate branch of medicine before the First World War, when the rapid course of many creative innovations in reconstructive surgery began:

In 1902, Alexis Carrel* (1873-1944) described the triangular suture of blood vessel and won the Nobel Prize in 1912.

Suzanne Noël (1878-1954) was the first female plastic surgeon. She gave the instructions for facial rejuvenation by cutting strips of the frontal region near hair in 1911. In 1914 [21] during the First World War, many surgeons became famous after their reconstructions of defects and scars after wound healing, such as Sir Harold Gillies* (1892-1960) and Archibald McIndoe from Great Britain, Hippolyte Morestin (1869-1919) from France, Erich Lexer from Germany, Johannes Fredericus Esser from the Netherlands (1877-1946), and so on.

In 1918 a Dutch surgeon Fredericus Johannes Esser described "biological flap" which involved lifting more tissue in one artery lobe. He was the founder of rotation lobe on the face and neck used for large defects. In 1920, Kirschner described temporal lobe of superficial temporal artery and Blair used thicker grafts for reconstruction of skin defects in 1921 [22].

At the same time, in 1936, Paget developed a cylindrical dermatome technique, which enabled the removal of larger grafts of different thicknesses.

Allen B. Kanavel (1874-1938), Sterling Bunell* (1884-1957) and others were the pillars of hand surgery in the period between the two world wars and they put all their knowledge and experience into the book published in 1942 explaining the treatment of injuries, tumors and deformities of the hand [23].

In spite of being a general surgeon, Sterling Bunell introduced many principles in plastic and vascular surgery and orthopedics. He wrote a book "Surgery of the Hand" which was published in 1944.

During World War II, Dr Edward Delos Churchill (1895-1971) [24] introduced the term of delayed primary closure of wounds after early debridement and control of war wound contamination. In 1946, Alexander Aleksandrovich Limberg* (1894-1974), a Soviet military surgeon and dentist, performed reconstructions of defects using diamond-shaped transpositional flap, as well as numerous maxillofacial surgeries.

The next few decades were marked in the annals of plastic surgery by the rapid development of several important sub-groups of specialties: implantation surgery, microsurgery and esthetic surgery.

During the mid-century, malignant skin tumors represented significant oncologic clinical pathology. Sophie Spitz* (1910-1956), an American histopatholgist, gave a great contribution to diagnosis of these tumors in 1948. She proposed the classification of melanocytic nevi, describing juvenile melanoma, today known as Spitz nevi [25].

In 1960, Strömbeck introduced a new method of breast reduction with deepitelization of a pedicle [26]. Ivo Pitanguy, a plastic surgeon from Brazil, introduced the term dermolipectomy and used methods of "dry liposuction" [27]. That same year, Jacobson and Suarez experimented on sutures of blood vessels under the microscope and introduced the microsurgical technique in plastic and reconstructive surgery. In 1961, Thomas Cronin and Frank Gerow, Houston, USA, introduced the silicone breast prosthesis implantation [28]. Harold E. Kleinert* (1921-2013) and Mort Kasdan performed the first successful revascularization of the thumb in 1964 [29].

In 1968 in Maribor, Dr Zora Janžeković* (1918), introduced tangential excision of the necrotic tissue as a method of early treatment for patients with burns. This contributed to better survival and gave remarkable results in treating patients with extensive burns. This method is still the best solution for the treatment of burn wounds [30]. American histopathologist Wallace H.CLARKE* (1924-1997), classified melanoma according to their histological invasiveness of the skin in 1969 and in 1970 Alexander Breslow* (1928-1980), also an American pathologist, described micrometer thickness of histological invasiveness of skin melanoma. These classifications are still used to grade skin melanoma [31].

Mr. John Cobbett performed the first successful transplantation of the big toe to the hand to reconstruct the thumb in 1968, and Harry J. Buncke* (1922-2008), the father of microsurgery in the USA, did it in 1972 [32]. They were followed by many others.

Doctor Marko Godina*(1943-1986), the great name of plastic surgery and microsurgery, presented his results of defects reconstruction using latissimus dorsi muscle free flaps in 1978 [33].

John F. Burke (1922-2011) from Harvard used artificial skin (Integra) for the reconstruction of defects after necrectomy in patients with burns in 1981 [34]. In the same year, Stephen J. Mathes* (1943-2007) and Foad Nahai* published the first classification of microsurgical flaps [35].

Abraham George Thomas carried out the first face and scalp transplant in a 9-year old girl in India in 1994 [36].

Then the era of allotransplantation began. Longtime experimental works were completed when the first entire hand transplantation was carried out successfully in Lyon in 1998. Dubernard and his team performed the transplantation of the hand successfully in a 48-year old man [37].

In 1998 Milomir Ninković, as a member of a surgical team in Innsbruck, promoted the method of functional reconstruction of the urinary bladder using a free latissmus dorsi muscle flap [38].

In 2005, Bernard Devauchelle*, a maxillofacial surgeon, and his team successfully performed the first transplantation of middle part of the face (nose, chin, cheeks, lips) [39].

Sir Harold Gillies (1892-1960), a great name in the English surgery, helped to establish the department of plastic surgery and burns at the MMA (Military Medical Academy) in Belgrade, in 1945. The head of the department was Prof. Dr. Vinko Arneri, the founder of plastic surgery in this region.

Prof. Dr Branislav Bogdanov founded the Ward for Plastic Reconstructive Surgery of the Provincial Gen-

eral Hospital in Novi Sad in 1964. Enthusiastic young surgeons started to treat severe tissue defects, congenital anomalies as well as burns and their sequelae.

In 1986, the Ward for Children and Youth Plastic and Reconstructive Surgery was founded within the Department of Children's Surgery of the Institute for Child and Youth Health Care in Novi Sad, whose main field of activity is treatment of congenital anomalies and burns in children.

As for the future of plastic surgery, regenerative medicine and tissue engineering will certainly contribute to and expand the possibilities of surgical reconstruction after trauma and oncology defects, as well as better functional and cosmetic results in solving complex congenital malformations.

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DR AVRAM JOZEF VINAVER (1862-1915) – PIONEER OF RADIOLOGY IN SERBIA

DOKTOR AVRAM JOSIF VINAVER (1862−1915) − PIONIR SRPSKE RADIOLOGIJE

Rade Radomir BABIĆ[1] and Gordana STANKOVIĆ BABIĆ[2]

Summary

Introduction. Dr Abraham Joseph Vinaver (1862-1915), a Jew from Poland, was a pioneer of radiology in Serbia. He graduated from the Faculty of Medicine in Warsaw (1887), but lived and worked in Šabac (the Kingdom of Serbia) since 1890. **Dr Abraham Joseph Vinarev - Career Development.** He procured the first X-ray machine and developed radiological service in Šabac five years after the discovery of X-rays. These were the beginnings of radiology in Serbia. He introduced the application of artesian wells. **Dr Abraham Joseph Vinarev – a Participant at the First Congress of Serbian Physicians and Naturalists, Belgrade 1904.** "The diagnostic importance of X-rays in lung disease, especially in initial tuberculosis" and "Five Years of Treatment by X-Ray Machines" were the first works in the field of radiology in Serbia by this author. **Dr Abraham Joseph Vinaver - Reserve Medical Officer in the Serbian Army.** During the Balkan Wars, he was a volunteer with the rank of major engaged in military corps and he participated in the First World War as well. He died of malaria in 1915 in Gevgelija. **"Dr Avram Vinaver"- Stanislav Vinarev.** His dedication to work during the typhus epidemics was put into verses of a poem by his son Stanislav Vinarev. **Conclusion.** Dr Avram Vinaver Joseph was a noble man with a great heart, who selflessly sacrificed himself for the Serbian people and Serbia. He gave his contribution to the development of health services in Serbia, both in peacetime and wartime conditions. Dr Abraham Joseph Vinaver laid the foundations for today's radiology in Serbia.

Key words: History of Medicine: Famous Persons; History, 19th Century; History, 20th Century; Radiology; Radiotherapy; X-Rays; Water Wells; Serbia

Sažetak

Uvod. Doktor Avram Josif Vinaver (1862−1915), Jevrejin iz Poljske, bio je pionir srpske radiologije. Diplomirao je na Medicinskom fakultetu u Varšavi (1887). Od 1890. godine živeo je i radio u Šapcu (Kraljevina Srbija). **Dr Avram Josif Vinaver − kretanje u službi.** Nabavio je prvi rendgenski aparat i razvio radiološku službu u Šapcu, pet godina po otkriću X-zraka. Bili su to počeci radiologije u Srbiji. Uveo je u primenu arterške bunare. **Dr Avram Josif Vinaver − učesnik Prvog kongresa srpskih lekara i prirodnjaka, Beograd 1904. godine.** „Dijagnostička važnost Rentgenovih zrakova kod bolesti pluća, naročito kod početne tuberkuloze" i „Pet godina lečenja Rentgenovim zracima" bila su prva saopštenja iz oblasti radiologije u Srbiji ovog autora. **Dr Avram Josif Vinaver − rezervni sanitetski major srpske vojske.** Za vreme Balkanskih ratova bio je dobrovoljac sa činom majora angažovan u vojnom sanitetu. Učesnik je i I svetskog rata. Umro je od malarije 1915. godine u Đevđeliji. **„Dr Avram Vinaver" − Stanislav Vinaver.** O požrtvovanom radu dr Avrama Josifa Vinavera u vreme epidemije pegavog tifusa u Srbiji svedoči i pesma njegovog sina Stanislava Vinavera. **Zaključak.** Doktor Avram Josif Vinaver je bio čovek plemenitog srca koji se nesebično žrtvovao za srpski narod i Srbiju. Dao je doprinos razvoju zdravstvene zaštite stanovništva Srbije podjednako i u mirnodopskim i u ratnim uslovima. Doktor Avram Vinaver je postavio temelje današnje radiologije u Srbiji.

Ključne reči: Istorija medicine; Poznate osobe; Istorija 19. veka; Istorija 20. veka; radiologija; Radioterapija; X-zraci; Arterski bunari; Srbija

Introduction

Dr Avram Jozef Vinaver (1862, Warsaw - 1915, Gevgelia), a pioneer of radiology in Serbia, was a Polish Jew. He contributed to the development of health services in Serbia, especially Šabac, the region of Mačva and other regions, both in peacetime and wartime conditions (**Figure 1**) [1–6].

He received his primary and secondary education in his hometown, where he graduated from the Faculty of Medicine in 1887. Having acquired the academic title, Dr Avram J. Vinaver settled in Šabac in 1890, in the former Kingdom of Serbia, where he worked and lived with his wife Rosa (1871, Krakow -1942, Belgrade). They had two children, a son and a daughter. The son, named Stanislav, (March 1,1891, Šabac, the Kingdom of Serbia - August 1, 1955, Niska Banja, the Federal People's Republic of Yugoslavia) was a writer, translator and erudite. Their daughter Mjećeslava, whose nickname was Mjeća, died at an early age (1898-1910).

Dr Vinaver spoke Hebrew, German, French, Polish, Russian and Serbian language. He participated in the Balkan Wars and World War II. After the victory of the Serbian army at Cer and the Battle of Kolubara, Dr Avram Jozef Vinaver arrived in Gevgelia with his

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Abbreviations
TBC – tuberculosis

unit (Serbia, Former Yugoslav Republic of Macedonia today), where, exhausted by myocardial typhus fever that he had suffered earlier, he contracted malaria and died in 1915. He was buried in a common grave according to his own free will.

Dr Avram Jozef Vinaver - Career Development

Having graduated from the Faculty of Medicine, Dr Avram J. Vinarev became the first assistant to Professor Johann Freiherr von Mikulicz-Radecki (May 16, 1850, Czernowitz – June, 14, 1905, Breslau), and then to Professor Christian Albert Theodor Billroth (April 26, 1829, Bergen auf Rügen - February 6, 1894, Abbazia). Upon his arrival in Serbia, on the 2nd of March 1889, Dr Vinaver was first appointed to the position of the secondary physician of the General State Hospital of Belgrade. After eight months of work, he was transferred to the General Hospital in Šabac, where he worked under contract as an ordinarius since he was a foreigner. Soon afterwards, he opened a private doctor's office and became the first physician with private medical practice in Šabac (1889).

Dr Avram Jozef Vinaver contributed to the development of health services in Šabac, the region of Mačva, Serbia and other regions. He introduced the application of artesian wells. In 1900, only five years after the discovery of X-rays, he had an X-ray machine transported to Šabac and thus laid the foundation of today's radiology in Serbia. At that time, many developed countries did not have an X-ray machine. It was an X-ray machine with gas (ion) tubes, bought in Vienna, assembled in a building that was located next to the apartment of Dr Avram. Thus, Dr Avram Jozef Vinarev developed a radiological service there and Šabac became the first city in the Kingdom of Serbia which had an X-ray machine [1, 2, 4, 6, 7]. However, it is necessary to point out that in 1897 the Serbian Army already purchased an X-ray machine for the needs of the Military Hospital in Belgrade.

Dr Vinarev contributed to the fight against tuberculosis (TBC). He procured Koch's lymph for the treatment of tuberculosis patients from Berlin (1891). This medicine was the forerunner of tuberculin, the today's Bacillus Calmette–Guérin (BCG) vaccine [1, 2, 4, 6].

Dr Avram Jozef Vinarev – a Participant at the First Congress of Serbian Physicians and Naturalists, Belgrade, 1904

Dr. Vinaver wrote about his experience in working with X-rays, diagnostic and therapeutic possibilities of X-rays in his first papers, which were presented at the First Congress of Serbian Physicians and Naturalists held in Belgrade from the 5th to 7th of

Figure 1. Dr Avram Jozef Vinaver (1862-1915)
Slika 1. *Dr Avram Jozef Vinaver (1862-1915)*

September 1904, under the highest protection of His Majesty King Peter I [1, 6, 9–12]. The titles of the papers presented by Dr Vinarev were: *Diagnostic Importance of X-Rays in the Treatment of Lung Diseases, Particularly in the Initial Stage of Tuberculosis*, *Five Years of X-ray Treatment* and *Several Considerations Addressing the Issue of Whether Syphilis Can Be Inhered from the Father* [10–12]. The presented papers were published in the Proceedings of the First Congress of Serbian Physicians and Naturalists under the highest protection of his Majesty King Peter I in Belgrade on the 5th, 6th and 7th of September 1904, and printed in the state printing house of the Kingdom of Serbia 1905 "[9].

The works by Dr Vinarev - *Diagnostic Importance of X-Rays in the Treatment of Lung Diseases, Particularly in the Initial Stage of Tuberculosis* [10] and *Five Years of X-Ray Treatment* [11] – were the first papers in the field of radiology in Serbia, and among the first publications of this type in the world.

In his work *Diagnostic Importance of X-Rays in the Treatment of Lung Diseases, Particularly in the Initial Stage of Tuberculosis* [10] Dr Vinaver wrote: "X-rays have been destined to make a difference in this field and to ensure the success of these efforts. However, although the early uncertainty and roaming in the dark when making a diagnosis disappear as the time passes, and although we assure ourselves that "roentgenology is a valuable supporting device", Roentgen rays have not been given their true right of the citizenship which they deserve". Dr Vinaver continues: "X-rays can be applied in two ways:

1) Roentgenoscopy i.e. observing the objects by means of a fluorescent shield or screen because our eyes cannot see X-rays, and

2) Radiography, which is founded on the fact that the Roentgen rays act upon silver salts in the same way as ordinary light rays do, and therefore we can use them to get the same image as by ordinary photos. However, there is a huge difference between these images..... by means of radiography we get the image which is an algebraic sum of all dark and clear places through which Roentgen rays have passed."

In this work Dr Vinaver gave the axiom of the overall radiological diagnosis: "It is not the X-rays but the intellect of a doctor that establishes a diagnosis."

When discussing the future of X-rays and the application of X-ray diagnostics, Dr. Avram Vinaver, like a prophet, emphasized ".... no doubt that this method is the method of the future." At the same time, independently of Dr Vinaver, Nikola Tesla, our outstanding scientist, came to the same conclusion on the other side of the world [10, 13].

Dr Vinaver continued writing about the importance of chest X-rays: "The importance of chest X-rays in pneumonia is that they the central infiltrates inaccessible to physical methods. Variot and Chicotot first drew attention to the diagnosis of such latent pneumonia. Lichteim also emphasized the same importance of X-rays. In my practice, I have had a case of a so-called central pneumonia in a five-year old child, without any physical symptoms, and chest X-rays revealed an intense shadow in the left lower lobe. Chest X-rays also indicate that the shadow still exists in resolution of pneumonia, where symptoms of auscultation are not present any more... X-ray devices are also used to give an accurate diagnosis and prognosis of sclerosis, emphysema, pneumonia..... In case of abscess and gangrene, which I am going to talk about, X-rays provide a topical diagnosis and thus enable a surgeon to treat his patient "Les rayons de Röntgen guident sa main"."

Further on, Dr A.J.Vinaver wrote: "We find foreign bodies in bronchi: the flora and fauna and mineral kingdom have their representatives here. ..... So far, in my career, I have found foreign bodies in my patients three times..... Roentgen rays enable us to make a timely diagnosis, which we have not been able to do so far.....And the position of Echinococcus in the lungs can be accurately diagnosed, as demonstrated by Rosenfeld Levy-Dorn..... The French were the first to apply the X- rays to diagnose pleura. Bouchard, Guilleminot, and Beclere enhanced the diagnosis of pleura by means of analyzing many radiographic symptoms and explained many pathologic developments which have been problematic so far.... X-rays provide the basis for selecting the patients for surgical treatments and thus ensure the success of surgery undertaken; on the other hand, we will use the X-rays to solve many questions related to the mechanics of pneumothorax."

Dr Vinaver wrote the following about tuberculosis: "In order to assess the importance of X-rays in tuberculosis, it is best to review the results of previous methods critically. The earlier methods encompass: percussion and auscultation, TBC bacillus sputum smear, tuberculin shots..... The comparison of chest X – Radioscopy/ Radiography with physical methods which were applied to diagnose phthisis created both excessive enthusiasm and excessive skepticism at the beginning of the application of X-rays. ..... Radioscopy is a completely different thing. It detects injuries deep inside in a special way. ... By means of radioscopy, Kelsch and Boinon found 73 cases of latent tuberculosis in 124 young soldiers." In summary, Dr Vinaver said: ".... there should be no lung surgery without using Roentgen rays."

Figure 2. A charity stamp with the image of Dr Avram Jozef Vinarev

Slika 2. *Doplatna poštanska martka sa likom dr Avrama Jozefa Vinavera*

In his work *Five Years of X-ray Treatment* [11] dr Vinaver presented the therapeutic possibilities of X-rays on a sample of 62 treated patients and said: "Most radiotherapists use soft pipes, in which the fluorescent light is intensely yellow, and which is capable of illuminating the chest of an adult at a distance of 1 to 2 meters, has a low power of 2.3 amperes, with the interruption of 15 to 20 per second, whereby the distance between the tube and the skin is 15 to 20 centimeters, while the duration of exposure ranges from 5 to 15 minutes."

In his paper, Dr Vinaver quoted professor Holckneht from Vienna, one of the most prominent world radiologists of the time. In honor of professor Holckneht, the application of Holckneht's chronoradiometer and Freund's device used for a more precise measurement of the radiation dose (they used a fea-

ture of some salts of halogen elements to change the color under the influence of X-rays) was introduced.

Dr Vinaver further wrote ..."nowadays it is possible to treat favus in only 1 to 2 hours instead of months because those instruments for measuring doses of X-ray radiation enable the exposure to radiation without interruption after every 10 to 20 minutes of exposure in order to avoid overexposure of the patient.

Having analyzed the results of the treatment of their patients with X-rays, Dr Vinaver emphasized

- that he had achieved the complete success in all treated non-malignant diseases, except in chronic scrotal eczema. One out of two cancer patients was cured, while the other (Ca Labia inf. Cum meta gl. submandibularis contralateralis) suffered a partial regression of cancer;
- that the cancer cells were more sensitive to X-rays than the healthy cells which they stem from;
- that the greater the reaction of healthy tissues (skin erythema, dry and moist desquamation, necrosis etc.), the greater the effect of X-rays on pathological processes was achieved;
- that the applied dose of X-radiation was determined on the basis of the reactions of healthy tissues (erythema dose - erythema on the skin; there were early and late post-radiation reactions of healthy tissues).

At the end of the paper Dr Avram Vinaver concluded: " we will commit an unforgivable sin against our patients if we remain indifferent to the treatment by means of X-rays and do not make it possible to them to be treated and cured using X- rays."

In his third work *Several Considerations Addressing the Issue of Whether Syphilis Can Be Inhered from the Father* [12] Dr Vinaver spoke of "the existence of the spermatic inheritance of syphilis", illustrating his claim by several cases from his medical practice.

In his paper Dr Vinaver said: "I have no intention to argue with advocates of the germinative theory, and, therefore, I am not going to criticize arguments and counter-arguments related to this theory, the infectiousness of sperm itself, the analogy with other infectious diseases, etc." .... He also added: "I am convinced that until the contagium of syphilis is determined, no theory will be able to explain all phenomena to us." .... Finally, the author concluded: "My intention was just to prove that all theories about hereditary syphilis which rule out the possibility of mother-child transmission often conflict with the facts of life. "Pas de syphilis herditaire sans infection de la mère".

Dr Avram Jozef Vinarev - A Reserve Medical Major of the Serbian Army

During the Balkan Wars, Dr Vinaver was a volunteer with the rank of major, and did his service in military medical corps. During the Balkan War I, Dr Avram Vinaver was the head of the military hospital in Kursumlija and Vranje and during the Balkan War II, he was the head of the Military Hospital in Valjevo, where the World War I caught him [1, 2, 5, 6].

During the World War I, Dr Vinaver held the post of a warden of Valjevo hospital as a medical major. Dr Avram Jozef Vinarev was captured during a violent raid of the occupying Austrian army, and sentenced to death (Valjevo, 17 November 1914). However, the regrouping and advancing of the Serbian army after the Battle of Kolubara (Suvoborska battle, 16th of November -15th of December 1914) forced the enemy to retreat in panic. There was no time to execute the death penalty, so Dr Avram Vinaver survived.

In October 1914, the region of Valjevo was affected by a spotted fever. Austro-Hungarian soldiers brought typhus to Serbia. By December 1914, the disease reached epidemic proportions and spread to the rest of Serbia [14,15]. In the winter of 1914, Dr Avram Vinaver contracted the disease in Valjevo, but survived:

"He knew .....

Since he was shaking because of the recurrent fever

For many days ..... " This is an excerpt from the poem *Dr Avram Vinaver* written by his son Stanislav [16].

According to the academic Koča Todorović, this vicious disease affected about 600,000 persons (about 15% of the population) in Serbia and the number of casualties rose to 135,000 [15].

No history of warfare has shown evidence that an army started the war with such a small number of doctors as Serbia did (450 doctors per around 4.5 million inhabitants) [14, 15, 17]. The Serbian medical corps, together with the help of foreign medical missions from Russia, Great Britain, the United States of America, France, Greece, Canada, the Netherlands, Denmark and many other countries that responded to the desperate pleas of the Serbian government, which was powerless in the face of the humanitarian disaster, successfully defeated epidemic typhus in Serbia by the end of August in 1915.

However, in August 1915, a new trouble struck our nation. An increase in the number of cases of typhoid fever due to water pollution was noticed. Dr Richard Strong, a Harvard University professor, was in Niš at that time and oversaw the quality of water from artesian wells in Valjevo and the environment [8].

Dr Vinaver introduced artesian wells into use and this represents his contribution to the development of the health protection services in Serbia.

Already exhausted from myocardial typhus fever, Dr Avram Jozef Vinaver contracted malaria and died in Gevgelia.

"Dr Avram Vinaver" - Stanislav Vinarev

During World War I, Stanislav Vinaver, the son of Dr Avram Vinaver, left his studies in Paris and

started volunteering in the Serbian army. He was sent to the non-commissioned officer military school in Skopje, to the famous unit "1,300 corporals" [1, 2, 6].

In these difficult times, Dr Avram Vinaver´s wife Rosa published a book of patriotic texts titled "From Vranje to Thessaloniki" [1, 2, 6].

After the Great War, Rosa and their Stanislav settled in Belgrade.

During the World War II, Rosa Vinaver, being a Jew, was sent to the concentration camp at Sajmiste in Zemun where she tragically lost her life in the gas chamber (1942).

Between the two world wars, Stanislav Vinaver was a journalist and worked in the diplomatic service of the Kingdom of Yugoslavia. He married "a German from Banat", with whom he had two sons, Vuk and Konstantin. The Second World War caught Stanislav and his family in Berlin, where he was working for the Yugoslav Embassy and was a correspondent for a Belgrade newspaper. Wartime conditions and patriotic education made Stanislav Vinaver return to Yugoslavia and respond to the military summons. Stanislav Vinaver was captured and taken to a camp in Osnabrück (Germany) during the attack of the German army against the Kingdom of Yugoslavia. He managed to survive in the camp. After the end of the World War II, Stanislav returned to his homeland. He worked as a journalist. He died in Niska Banja in 1955 and was buried at the New Cemetery in Belgrade [1,6].

A disturbing poem *Dr Avram Vinaver*, written by Avram's son Stanislav, testifies to Avram's dedication to his work [16]. The poem belongs to the poetic cycle *War comrades*, published by the Publishing and bookstore company *Geca Kon AD* Belgrade in 1939 [16].

"..... Dr. Avram Vinaver
Medical Major
The warden of the Fifth Reserve Hospitals
Walked with difficulty leaning on the stick,
Gaunt from illness and worries,
Visited the sick patients day and night
He observed their bewildered glance
Judging it, he knew where one was
On the path of life and death ..... "

In the continuation of the poem, Stanislav Vinaver describes hellish scenes during the typhus epidemic:

"..... They are ranting
Our whole country is ranting with them during typhus fevers.
The sick can be found in camps,
Trains drive the sick,
Homes are full of them.
In the villages, on small huts
On outbuildings
In plum orchards
Black flags are flaunting
The plague darkens the world ..... ".

The poem took place in Valjevo, a region near the front and the biggest focus of infection. History has recorded that at that time the typhoid epidemic took its toll on the Serbian army and Serbian population.

Serbia has not forgotten Dr Avram Jozef Vinaver. In October 2008 the Post of Serbia put a charity stamp with the image of Dr Avram Jozef Vinarev into circulation. The following text, written in the Cyrillic letter, is inscribed: Dr Avram Jozef Vinarev, the year of birth and death: (1862 - 1915); the nominal value of the stamp: 10.00. The text: "Cancer is curable" is inscribed in red letters; the name of the country of origin – Serbia is written in white letters, just like the logo: Serbian Anti-Cancer Society **(Figure 2)**. The circulation of 1,200,000 pieces significantly contributed to funding the anti-cancer institutions of Serbia [7].

Conclusion

Dr Avram Jozef Vinarev was a noble man with a great heart who selflessly sacrificed himself for the Serbian people and Serbia, but he left no grave to his family and the homeland of Serbia. Dr Avram Jozef Vinarev greatly contributed to the development of health care of the Serbian population in peacetime and wartime conditions. He introduced the application of artesian wells. He had an X-ray machine transported to Šabac, Serbia, and developed the radiological service. He wrote about his rich experience in working with X-rays, diagnostic and therapeutic possibilities of X-rays in his first papers, which were presented at the First Congress of Serbian Physicians and Naturalists held in Belgrade from the 5th to the 7th of September 1904, under the highest protection of His Majesty King Peter I. His works titled *Diagnostic Importance of X-Rays in the Treatment of Lung Diseases, Particularly in the Initial Stage of Tuberculosis* and *Five Years of X-Ray Treatment* represent the first publications in the field of radiology in Serbia. Dr Avram Jozef Vinaver laid the foundations of today's radiology in Serbia.

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LETTERS TO EDITORIAL BOARD
PISMA UREDNIŠTVU

Banjari I. A maternal bond the story of the infinite loop of iron deficiency anemia (*Veza za majkom - priča o beskajnom krugu anemije zbog nedostatka gvožđa*).

The article by Milankov et al. [1] reminded us about the forgotten or better to say neglected link between iron deficiency anemia (IDA) in pregnant women and IDA in infants. IDA is the most common nutritional deficiency around the globe, with an immense public health significance and cost burden. It has a complex etiology that includes iron stores, digestion, iron content and bioavailability in foods, and iron distribution in the body through different stages in the lifecycle (e.g. adolescence, pregnancy) [2, 3]. The prolonged imbalance in any of the above mentioned items leads a person into the infinite loop of IDA.

Its severity is measured by a number and intensity of symptoms following iron depletion and gradual development of IDA. Risk groups include infants, children, adolescents (especially girls), women of reproductive age and pregnant women [2,3]. It is important to note that a large proportion of women of reproductive age enter pregnancy with depleted iron stores [3]; for example, in the United States more than 1/3 of women of reproductive age have deprived iron stores [2]. The reasons for such iron status among women include genitourinary tract bleeding, a common fad dieting practice, and the low consumption (and preference) of iron rich foods [3]. Pregnancy as the "critical window" in fetal programming [3] should be given a higher attention in relation to IDA in infants since studies have shown that the infant's iron endowment reflects the mother's iron status during pregnancy, and even before pregnancy [4]. Due to a number of adverse effects which IDA has on developing fetus and pregnancy outcomes [3, 4], supplementation with iron or iron-folic acid has been widely recommended and practiced [3, 4]. Still, findings from clinical trials on how different supplementation formulations affect iron status during pregnancy and pregnancy outcomes (i.e. time of delivery, birth weight) are equivocal. For example, West et al. [5] conducted a cluster randomized, double-masked trial enrolling more than 44.000 pregnant women from rural Bangladesh who were provided with supplements containing 15 micronutrients or iron-folic acid alone. Multiple micronutrients supplementation group had a statistically significant reduction in preterm delivery (RR 0.85, P=0.02) and low birth weight (RR 0.88, P<0.001) as compared to iron-folic acid supplementation group [5]. This contradicts earlier findings from a double-masked randomized controlled community trial conducted on pregnant women from rural Nepal [6]. The study results showed that supplementation with iron-folic acid had increased hemoglobin and had a 54% reduction in IDA; the combination of folic acid, zinc and iron had a 48% reduction, while the combination of folic acid, zinc, iron and 11 other micronutrients had a 36% reduction; whereas supplementation with folic acid alone had no influence on IDA [6].

Besides mother's iron status before and during pregnancy, additional important factors to be considered when discussing IDA in children include the impact of environment, socio-economic factors, habits in the family, especially the ones related to the mother, certain individual characteristics (gender, time and way of delivery, birth weight and associated diseases) as well as the child's diet [1, 2, 4, 7]. A child's diet depends solely on mother, her health condition after the birth, her attitudes, perception, cultural and health education [1,7]. Breastfeeding is the best choice for an infant. It influences the short-, medium and long-term health of children and women. Strong evidence supports findings that in both low- and high-income settings not breastfeeding contributes to infant mortality, hospitalization for preventable disease such as gastroenteritis and respiratory disease, increased rates of childhood diabetes and obesity, and adult disease such as celiac and cardiovascular disease [7]. Breastfeeding affects *intelligence quotient* (IQ), and educational and behavioral outcomes of the child. Importantly, a dose response relationship was found, with the greatest benefit resulting from breastfeeding exclusively, with no added food or fluids for approximately 6 months [7], which has been recommended by the World Health Organization (WHO) [8].

According to the WHO statistics, the numbers of children breastfed for less than 6 months in the ex-Yu countries are still quite high [8]; in Serbia 38.5%, in Bosnia and Herzegovina 41.2%, in Montenegro 45.1%, and 23.5% in Croatia. Race and income are major predictors of whether a woman will exclusively breastfeed for 6 months. The highest rate of breastfeeding is among wealthy whites [7,8]. Prolonged breastfeeding serves as a protecting agent from IDA. A retrospective study conducted by Milankov et al. [1] has shown that breastfeeding rates in Vojvodina increased from 65.68% in Study I (1988 – 1995) to 71.03% in Study II (2010 – 2011), and the longer the period of breastfeeding was, the milder IDA was manifested in the infant. Interestingly, the WHO data show that in Vojvodina 48.3% of infants are breastfed for less than 6 months, which is the highest in all regions in Serbia [8] (for example, in Belgrade this percentage is 27.2%). These findings can possibly be attributed to low socio-economic status in Vojvodina with an average income lower than the average in the republic (60.923 RSD/year vs. 61.963 RSD/year) [9]. High

poverty rates need to be considered as well. The current unemployment rate in the Republic of Serbia is 16.8%, being the highest unemployment in Vojvodina, i.e. 18.7%. Importantly, women are more affected with unemployment than men (17.3% vs. 16.4%) [9]. Women with low incomes are often financially compelled to quickly return to the workforce [10], and for them formula is a convenience. The use of complementary foods changed for better, according to Milankov et al. [1]. They have found that industrial milk formulas are used more often (28.4% in Study I, 50.0% in Study II) while a common practice of giving cow's milk (diluted or undiluted) during the 80s is slowly being forgotten (34.52% in Study I vs. 25.64% in Study II) [1].

The impact of economic poverty is immense. High unemployment rates and low incomes affect diet of the whole family. Iron rich foods are often expensive (e.g. red meat) and in the case of limited finances these foods are the first ones to be crossed out on the shopping list or sporadically consumed [10]. This form of food deprivation leads to a low nutritional intake of iron, causing a high risk for IDA development. The risk of developing IDA increases in a pregnant woman or an infant coming from a family which is experiencing economic insecurity.

Infant formulas are fortified with iron which lowers the risk of IDA in infants that are not breastfed. For such children, prolonged economic poverty could lead to worsening dietary patterns, and even returning to earlier practice of giving cow's milk. Feeding children with cow's milk worsens symptoms of IDA; Milankov et al. [1] confirmed that the highest percentage of severely anemic children was fed with cow's milk (56.52% in Study I, 64.30% in Study II).

Pregnancy should serve as a starting point for implementation of IDA prevention strategies. These strategies should be continued after birth, and include promotion of breastfeeding. The changes caused after the implementation of such strategies have a broad-spectrum and long-lasting impact on the overall health of population, with the potential to improve life chances, health and wellbeing [7]. This, however, asks for the economic stability, which has been endangered. By tackling the economic poverty and promoting the above health patterns, the maternal bond will deepen well beyond emotional.

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Propratno pismo

– Mora da sadrži svedočanstvo autora da rad predstavlja originalno delo, kao i da nije objavljivan u drugim časopisima, niti se razmatra za objavljivanje u drugim časopisima.

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– Navesti u koju kategoriju spada rad koji se šalje (originalni naučni rad, pregledni članak, prethodno saopštenje, stručni članak, prikaz slučaja, istorija medicine).

Rukopis

Za pisanje teksta koristiti *Microsoft Word for Windows*. Tekst treba otkucati koristeći font *Times New Roman*, na stranici formata A4, proredom od 1,5 (i u tabelama), sa marginama od 2,5 cm i veličinom slova od 12 pt. Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana. Naslovna strana treba da sadrži kratak i jasan naslov rada, bez skraćenica, zatim kratki naslov (do 40 karaktera), puna imena i prezimena autora (najviše 6 autora) indeksirana brojkama koje odgovaraju onima kojim se u zaglavlju navode uz pun naziv i mesta ustanova u kojima autori rade. Na dnu ove stranice navesti titulu, punu adresu, e-mail i broj telefona ili faksa autora zaduženog za korespondenciju.

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– Koristiti mere metričkog sistema prema Internacionalnom sistemu mera (*International System Units – SI*). Temperaturu izražavati u Celzijusovim stepenima (°C), a pritisak u milimetrima živinog stuba (mmHg).

– Ne navoditi imena bolesnika, inicijale ili brojeve istorija bolesti.

Uvod sadrži precizno definisan problem kojim se bavi studija (njegova priroda i značaj), uz navođenje relevantne literature i sa jasno definisanim ciljem istraživanja i hipotezom.

Materijal i metode treba da sadrže podatke o načinu dizajniranja studije (prospektivna/retrospektivna, kriterijumi za uključivanje i isključivanje, trajanje, demografski podaci, dužina praćenja). Statističke metode koje se koriste treba da budu jasne i detaljno opisane.

Rezultati predstavljaju detaljan prikaz podataka dobijenih tokom studije. Sve tabele, grafikoni, sheme i slike moraju da budu citirani u tekstu, a njihova

numeracija treba da odgovara redosledu pominjanja u tekstu.

Diskusija treba da bude koncizna i jasna, sa interpretacijom osnovnih nalaza studije u poređenju sa rezultatima relevantnih studija publikovanim u svetskoj i *domaćoj* literaturi. Navesti da li je hipoteza istraživanja potvrđena ili opovrgnuta. Izneti prednosti i ograničenja studije.

Zaključak u kratkim crtama mora da odbaci ili potvrdi pogled na problem koji je naveden u Uvodu. Zaključci treba da proizilaze samo iz vlastitih rezultata i da ih čvrsto podržavaju. Uzdržati se uopštenih i nepotrebnih zaključivanja. Zaključci u tekstu moraju suštinski odgovarati onima u Sažetku.

5. Literatura. Literatura se u tekstu označava arapskim brojevima u uglastim zagradama, prema redosledu pojavljivanja. Izbegavati veliki broj citata u tekstu. Za naslove koristiti skraćenice prema *Index Medicus*-u (http:// www.nlm.nih.gov/tsd/serials/lji.html). U popisu citirane literature koristiti Vankuverska pravila koja precizno određuju redosled podataka i znake interpunkcije kojima se oni odvajaju, kako je u nastavku dato pojedinim primerima. Navode se svi autori, a ukoliko ih je preko šest, navesti prvih šest i dodati et al.

Članci u časopisima:

∗ *Standardni članak*

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

∗ *Organizacija kao autor*

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

∗ *Nisu navedena imena autora*

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

∗ *Volumen sa suplementom*

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

∗ *Sveska sa suplementom*

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

∗ *Sažetak u Časopisu*

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

Knjige i druge monografije:

∗ *Jedan ili više autora*

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

∗ *Urednik(ci) kao autor*

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

∗ *Poglavlje u knjizi*

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

∗ *Rad u zborniku radova*

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

∗ *Disertacije i teze*

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

Elektronski materijal

∗ *Članak u Časopisu u elektronskoj formi*

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

∗ *Monografije u elektronskoj formi*

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

∗ *Kompjuterski dokument (file)*

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

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Dozvoljeno je najviše šest priloga!

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– Svi prilozi biće štampani u crno-beloj tehnici. Ukoliko autori žele štampanje u boji potrebno je da snose troškove štampe.

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Ukoliko autor i svi koautori nisu uplatili članarinu za Medicinski pregled, rad neće biti štampan. Radovi koji nisu napisani u skladu sa pravilima Medicinskog pregleda, neće biti razmatrani. Recenzija će biti obavljena najkasnije u roku od 6 nedelja od prijema rada. Uredništvo zadržava pravo da i pored pozitivne recenzije donese odluku o štampanju rada u skladu sa politikom Medicinskog pregleda. Za sva dodatna obaveštenja obratiti se tehničkom sekretaru:

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Tel. 021/521 096; 063/81 33 875
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INFORMATION FOR AUTHORS

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

– review papers should have the introduction, subtitles corresponding to those in the paper and conclusion. It is to be followed by up to 10 Key Words from the list of Medical Subject Headings, MeSH of the American National Medical Library.

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

Material and methods should contain data on design of the study (prospective/retrospective, eligibili-

ty and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

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Articles in journals

∗ *A standard article*

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

∗ *An organisation as the author*

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