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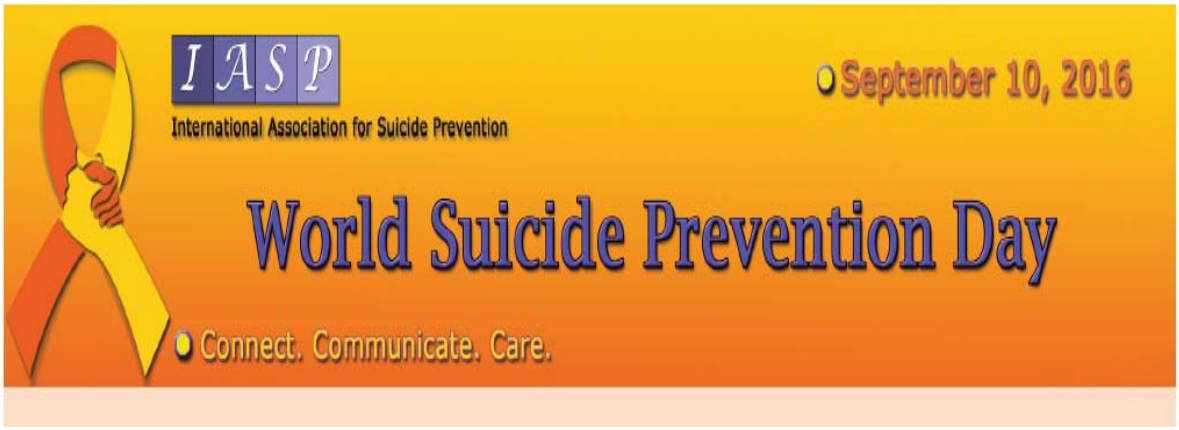

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Since 2003 the World Suicide Prevention Day marks on September 10th each year with the aim to focus public attention on the unacceptable global burden and costs of suicidal behavior, promote understanding about suicide and highlight the significance of effective prevention activities. On the occasion of this year's World Suicide Prevention Day, the Editorial Board of the Vojnosanitetski Pregled invites all its collaborators to participate in activities to increase the awareness of the public health significance of suicide and effective ways of its prevention (see Editorial, p. 799–802).

Od 2003. godine, 10. septembra obeležava se Svetski dan prevencije samoubistava sa ciljem da se usmeri pažnja javnosti na neprihvatljiv, globalni porast samoubistava i troškove koji ih prate, da promoviše razumevanje suicidnog ponašanja i istakne značaj aktivnosti za njegovu efikasnu prevenciju. Povodom ovogodišnjeg Svetskog dana prevencije samoubistava Uredništvo Vojnosanitetskog pregleda poziva sve svoje saradnike da se uključe u aktivnosti čiji je cilj podizanje svesti o javnozdravstvenom značaju suicida i efikasnim načinima njegove prevencije (vidi Uvodnik, str. 799–802).

E D I T O R I A L

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World suicide prevention day

Svetski dan prevencije samoubistava

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Introduction

The first World Suicide Prevention Day was held in 2003 as an initiative of the International Association for Suicide Prevention (IASP) and the World Health Organization (WHO). Since then, World Suicide Prevention Day has taken place on 10th September each year.

"Connect, communicate, care" is the theme of the 2016 World Suicide Prevention Day. Fostering connections with those who have lost a loved one to suicide or have been suicidal themselves is crucial to furthering suicide prevention efforts. People need to discuss suicide as they would any other public health issue if people are to dispel myths about it and reduce the stigma surrounding it. Clinicians and other service providers need to care enough about people at risk to commit suicide and need to make suicide prevention as their core business. Communities need to care enough about people at risk to commit suicide, and to be able to identify and support those who may be at heightened risk. Most of all, people need to care about themselves [1].

Statistics

The WHO estimates that over 800,000 people die by suicide every year. This roughly corresponds to one death every 40 seconds. Up to 25 times as many again make a suicide attempt. The tragic ripple effect means that there are many more people who have been bereaved by suicide or have been close to someone who has tried to take his or her own life.

In 2012, in the world suicide was the fifth leading cause of death among people between 30 and 49 years of age, and the second one in people between 15 and 29 years of age.

Although traditionally suicide rates is highest among older men, suicide among young people is on the rise and makes the group with the highest risk in developing countries and in the third of the economically developed countries.

According to the WHO in all European countries, suicide is more common among men, while suicide attempts are more frequent among women [1]. These differences can be explained by pronounced impulsiveness in men when they more often choose the more efficient (more lethal) methods of suicide. As well, there is the fact that the significant role in suicidal behavior have a different cultural expectations of men and women, when suicide becomes an option that they think, because when men are in suicidal crisis, they rarely seek help [2].

In 2012, the average suicide rate (number of suicides per 100,000 inhabitants) in the world was 16. The highest suicide rate in the world is in Guyana (44.2), followed by South Korea (28.1) and Sri Lanka (28.8). The lowest suicide rates in the world are in Saudi Arabia, Syria, Kuwait and Lebanon, where the suicide rate is less than 1 *per* 100,000 inhabitants.

The suicide rate in Europe is the highest in Lithuania (28.2) and Kazakhstan (23.8), followed by 10 countries of the former Soviet Republics [1].

Suicide rate in the world for the last 50 years has increased by 60%. Since 1953 a growing trend of suicide rate has also been observed in Serbia. The lowest rates of suicide were registered at the beginning of the 50s of the XX century, about 12 to 100,000 and the maximum in 1992 and 1997 with the rate of 20.9 *per* 100,000. The rate of suicide in Serbia has been decreasing since 2000 [3–5].

According to data obtained from the Statistical Office of the Republic of Serbia (Department for Demography) in a 10-year period, from 2006 to 2015, in Serbia, about 1,200 people committed suicide on the average *per* year. In the observed period, the suicide rate decreased from 19.43 in 2006 to 15.0 in 2015. Men 2.5 to 3.2 times more likely commit suicide than women (Table 1).

Suicide is most often performed by individuals with secondary education, pensioners and married persons. The most common method of suicide among men and women are hanging and drowning, the second most common method in males is by firearm and poisoning with solid or liquid substances in females. In the period 2011–2015, the highest number of suicides was performed by individuals older than

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Table 1

Annual suicide rate (*per* 100,000) in Serbia within the period 2006–2015

Year of suicide	Total	Males (M)	Females (F)	M/F ratio
2006	19.4	28.3	11.1	2.56
2007	18.3	26.9	10.2	2.63
2008	17.5	25.3	10.2	2.46
2009	18.8	28.1	9.9	2.81
2010	16.6	25.5	8.1	3.14
2011	17.4	25.8	9.3	2.77
2012	17.3	26.6	8.4	3.17
2013	16.7	25.9	8.1	3.20
2014	15.9	24.7	7.6	3.26
2015	15.0	23.0	7.4	3.11

75 years (23.4%), among them 40% suicide committers were people older than 65 years [2].

Analysis of committed suicides in the Serbian Armed Forces within the period 2001–2010 was carried out on the basis of data obtained by psychological suicide autopsy. In the observed period, 61 members committed suicide, that is, 50.82% of the military personnel of the Serbian Armed Forces (11.48% officers, 27.86% of noncommissioned officers, 11.48% of contract soldiers) and 49.18% of soldiers during their military service. The most common motive of suicide in officers is negative life achievement; in contract soldiers and noncommissioned officers problematic relationship with the emotional partner is the most common and in soldiers exhausted adaptational capacity for military service [6–11].

The etiology of suicide

The risk of suicide-related behavior is supposed to be determined by a complex simultaneous interplay of sociocultural factors, psychiatric history, personality traits and genetics as well as neurobiological vulnerability. A recent neurobiological research, particularly studies on families with suicide, as well as studies on twins and adopted children suggest that genetic factors play a significant role in the predisposition to suicidal behavior. Gen-specific suicide has not been found, but research suggests the association between suicide, aggression and impulsiveness. This view is supported by adoption and family studies indicating that suicidal acts have a genetic contribution that is independent of the heritability of Axis I and II psychopathology. The heritability for serious suicide attempts was estimated to be 55%. Further understanding of the genetics and pathophysiology of suicidal behavior is therefore very important [1, 6].

According to sociological theories, suicide is the result of impaired balance and damaged relations between individuals and social institutions (marriage, family, professional organizations, cultural and moral norms) which is supported by the fact that the suicide rate in traditional societies is considerably lower.

In the psychodynamics of suicide, currently there are 3 psychoanalytic theories. According to the first theory (Freud), suicide is the result of moving the murderous impulses. A suicidal person wishes death, which was originally targeted towards another person, turned toward oneself. According to the second theory (Karl Meninger) a person who has committed suicide, focuses suicidal intentions on the destruction of life of survivors. According to the third theory (Fenihel) there is a desire for union with the beloved object, often a figure of the mother, in suicides. In this sense we can see a correlation between suicide and the day of the anniversary of the death of a parent or with some other significant dates in the life of suicidal person [6, 12].

Suicide risk factors

Risk groups to carry out suicide are young, persecuted, imprisoned, refugees, migrants, the elderly and seriously ill, depressed and lonely (single and unmarried) people. Very important factors are: addiction to alcohol and drugs, raped and sexually abused in childhood, abused by peers in the adolescent period, mentally ill, persons prone to self-mutilation and suicide attempts, emphasized aggressive and impulsive persons, persons with family, marital or relationship problems, unemployment, rapid depletion and socially miserable, people prone to risk and danger, self-sacrificing, excessive moralists, adventurers tend risks, dangers and challenges. According to religion, suicide is more common among Protestants than among Catholics and Jews, among Christians than among Muslims, as well as in white than in black patients.

An important role is played by identification (identification with a model) and imitation of lifestyle role models and idols, so-called Werther syndrome. It is well-known that many public figures are a copycat model for young people to commit suicide (Marilyn Monroe, Ernest Hemingway, Yesenin, etc.).

The modern form of suicide is a so-called cyber suicide, the term used when the victim publicly, in front of the webcam, attempts or commits suicide. At specialized sites and forums suicidal person speaks about his/her plans for suicide. Also through sites and forums one can get detailed instructions how to commit suicide. There are also internet sites and chat rooms where suicidal people can meet each others and arrange to commit suicide together.

Protective factors against suicide are moral and religious considerations [6].

Most common motives for suicide are separation problems (abandonment by partners), the problem of loneliness in old people, problems with parents in youths. There are also a so-called balance of suicide when a person, faced with illness, difficult living conditions, especially with difficult financial situation, decides to kill him/her self [13, 14].

Presuicidal syndrome

In response to threats from the environment, people in crisis exert psychological, somatic and behavioral symptoms. Depression accompanying feelings of helplessness, and then the feeling of hopelessness, as a prelude to presuicidal syndrome. Overflowing anxiety and depression, people in crisis are hard to bear, and have a desire to ''escape'' from intolerable situation, when in order to reduce tensions begin to think about suicide, evaluate the possibility to choose lethal means which are then taken (tablets, rope, rifle, etc). The ultimate outcome is the suicidal act.

In people with presuicidal syndrome changes in physical appearance and behavior can be observed: neglect of external appearance, changed facial expression (sad), decline in general hygiene, change in dress style, exhaustion, bodily harm (consequences of self-harm), then changed behavior (withdrawal, hypersensitivity, nervousness, fatigue, indecision, apathy or rather agitation and hyperactivity, mood variability, mood inability to relax), loss of interest (interrupting contact with the social environment, lack of participation in joint activities (so-called. "social rituals"), change in habits (excessive cigarette smoking, alcohol consumption – narcotics), loss of interest in sex, hobbies, even in activities that were previously enjoyed, long sleep or insomnia, waking up very early in the morning, have nightmares, night get up, walk around the room, striking change in body weight, lack of appetite and weak or too eating (loss, rarely weight gain, increased abuse of psychoactive substances or alcohol; they finish their affairs, pay debts, say good-bye to their friends and relatives, and give back valuable personal belongings. One must pay attention to the statements made by the suicidal person, their ideas, statements, plans, earlier suicide attempts [6, 12].

Therapy

In accordance with the guidelines of the WHO general practitioners have a significant role in the prevention of suicide and in early detection of the first signs of presuicidal syndrome. Studies show that 60–70% of people who have intention to kill themselves are examined by a general practicaniors one month before they attempted or committed suicide. If life crisis is not recognized, it could be the motive for suicide attempt, and, also, the risk factor for repeated suicide attempts [1].

The application of psychotherapeutic crisis intervention help people to recognize their feelings and thoughts that lead them to crisis, all of which have relevance for the prevention of suicide attempts. People who have come through an episode of extreme suicidal thinking often say that sensitively-managed conversations with others helped them on their course to recovery [12, 15].

Suicide prevention program in Serbia

The fact is, suicide is preventable.

The plan of the WHO in sucide prevention is reduction of suicide rates in the world by 10% till 2020. In this context, there is the planned program of education for the population in order to reduce stigma (labeling) of people asking psychiatrist for help when in crisis and to reduce discrimination against people suffering from psychiatric disorders. The media also have an important role to play in suicide prevention [1].

Suicide prevention program in Serbia should just be focused on the male population that is a more vulnerable population group than the female population. The explanation of this phenomenon can be that women are characterized by some features which contribute to the protection of suicide. These are primarily established mutual relations with other persons, that women feel more willing to freely exchange views, to consult with others when they have problems and to accept help from a friend. Women are more likely to see a doctor in connection with problems related to mental health, easier to verbalize problems and are willing to share their emotional experiences with others, which facilitates detection and treatment of psychiatric disorders when they are in crisis and thus contribute to reducing the risk of suicide.

On the other hand, men in relation to its social role are more exposed to occupational stress, which, along with frequent substance abuse, especially alcohol, are significant risk factors for suicide. Culturally, men highly value independence and determination, and avoid seeking professional help when they find themselves in crisis. So, it is necessary to work on health education in order to improve the motivation of the population, especially the males to seek professional help which would contribute to reduce risks of suicide [2].

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ORIGINAL ARTICLES

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Assessment and self-assessment of the pharmacists' competencies using the Global Competency Framework (GbCF) in Serbia

Ocena i samoocena kompetencija farmaceuta u Srbiji korišćenjem Globalnog okvira kompetencija

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Abstract

Background/Aim. Pharmacists' competence represents a dynamic framework of knowledge, skills and abilities to carry out tasks, and it reflects on improving the quality of life and on patients' health. One of the documents for the Evaluation and Competency Development of Pharmacists is the Global Competency Framework (GbCF). The aim of this study was to implement the GBCF document into Serbian pharmacies, to perform assessment and self assessment of the competencies. **Methods.** The assessment and self-assessment of pharmacists' competencies were performed during the period 2012−13 year in eight community pharmacy chains, in seven cities in Serbia. For assessment and self-assessment of pharmacists competencies the GbCF model was applied, which was adjusted to pharmaceutical practice and legislation in Serbia. External assessment was conducted by teams of pharmacists using the structured observation of the work of pharmacists during regular working hours. Evaluated pharmacists filled out the questionnaire about demographic indicators about the pharmacist and the pharmacy where they work. **Results.** A total of 123 pharmacists were evaluated. Pharmacists' Professional Competency Cluster (KK1) had the lowest score (average value 2.98), while the cluster Management and Organizational Competency (KK2) had the highest score (average value 3.15). The competence Recognition of the Diagnosis and Patient Counseling (K8), which belonged to the cluster KK1, had the lowest score (average value for assessment and self-assessment were 2.09, and 2.34, respectively) among the all evaluated competencies. **Conclusion.** GbCF might be considered as an instrument for the competencies' evaluation/self-evaluation and their improvement, accordingly.

Key words:
pharmaceutics; pharmacies; community pharmacy services; serbia; professional role; questionnaires; patient satisfaction; quality of life.

Apstrakt

Uvod/Cilj. Kompetencije farmaceuta predstavljaju dinamični okvir i obuhvataju znanja, veštine i sposobnosti da se izvrše zadaci sa ciljem unapređenja kvaliteta života i zdravlja bolesnika. Jedan od dokumenata za ocenu i razvoj kompetencija farmaceuta je globalni okvir stručnosti − *Global Competence Framework* (GbCF). Cilj ovog rada bio je primena GbCF u apotekama u Srbiji i ocena i samoocena kompetencije farmaceuta. **Metode.** U periodu 2012−2013. godine izvršena je ocena i samoocena kompetencije farmaceuta u osam apotekarskih lanaca iz sedam gradova u Srbiji. Za ocenu i samoocenu stručnosti farmaceuta primenjen je model GbCF, prilagođen praksi i zakonodavstvu u Srbiji. Eksternu ocenu izvršili su timovi farmaceuta kroz strukturiranu opservaciju (upotrebom GbCF dokumenta) kompetencija farmaceuta tokom radnog vremena. Ocenjivani farmaceuti su popunili i upitnik o demografskim pokazateljima koji su se odnosili na podatke o samom farmaceutu i apoteci u kojoj radi. **Rezultati.** Ocenjena su ukupno 123 farmaceuta. Najviša ocena kompetencija farmaceuta zabeležena je za skup „Upravljanje i organizacija" (KK2) (srednja vrednost 3,15), dok je skup „Stručno znanje" (KK1) (srednja vrednost 2,98) ocenjen najnižom ocenom. Kompetencija K8 – „Prepoznavanje dijagnoze i savetovanje bolesnika", koje pripadaju skupu KK1, imale su najniži skor (srednja vrednost u proceni i samoproceni iznosila je 2,09 i 2,34, respektivno) posmatrajući sve, kompetencije. **Zaključak.** Dokument za ocenu i razvoj kompetencija farmaceuta GbCF može služiti kao instrument za ocenu/samoocenu kompetencije, a samim tim i za njihovo poboljšanje.

Ključne reči:
farmaceuti; apoteke; farmaceutske službe, javne; srbija; profesionalna uloga; upitnici; bolesnik, zadovoljstvo; kvalitet života.

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Introduction

The imperative facing health workers of today is competence. Competence represents a dynamic framework of knowledge, skills and abilities to carry out tasks, and it reflects on improving the quality of life and on patients' health[1, 2].

Pharmacists' competencies have been a lasting subject of consideration and research of the professionals as well as the professional bodies [3–8] who strive for working out adequate tools for assessing and developing the competencies of pharmacists [9–12].

One of the most popular benchmarks, the General Level Framework (GLF) [12], developed by the Competency Development and Evaluation Group (CoDEG), has found its application in the assessment, and self-assessment of pharmacists, hospitals and public pharmacists across several continents [13-18], thereby showing a significant progress in the development of competencies. The development of the global policy framework (GbCF) might lead to a harmonization of the pharmaceutical profession globally. Although the differences between various education systems and teaching techniques often exist, pharmacists do share a common goal in professional practice – that is improving patients' health. In order to reach this goal, one must strive for achieving competence in his/her work, regardless work conditions, country or culture [7].

Striving for the formulation of the global level competency framework (by expert health authorities and associations) has resulted in the creation of the Action Plan for the Period 2006−2010, following many years of work [3, 4, 7]. In addition, it has resulted in the Draft Document for the Evaluation and Competency Development in Pharmacists [19], which has been tested in dozens of countries, under the title of the GbCF. The document was created by testing it in practice and by developing of the existing forms, primarily the GLF document.

The GbCF document and the competency evaluation methodology allow for the option of external assessment and self-assessment of competencies, as well as for setting forth of the individual and systemic objectives towards pharmacists' performance improvement. However dominant the external assessment as a way of evaluating the knowledge and work performance is, one may not rule out the value of the self-assessment. It has been proven that the self-assessment is an important skill necessary for the on-going development of health workers [13−15, 17]. Self-assessments complement other types of teaching in order to enhance the knowledge, skills, and other professional qualities; they actually develop the ability to manage one's self-improvement [19]. Even though some legitimate reservations about the objectivity of the self-assessments do exist [20], they provide a good basis for altering the everyday practice and for setting of the personal goals related to professional development, and they may also help boost self-confidence about one's own professional values [21].

Unlike the GLF, the GbCF document recognizes the need for the harmonization of pharmaceutical care, and so one of its aims is therefore establishing equal access to the pharmaceutical care, as well as the equal quality of it on a global level. Application of GbCF contributes to competence development and application the framework of competencies on global level would enable harmonization of competencies and their standardized development and improvement the work of pharmacists [22].

The implementation of the framework in Serbia

According to the Health Care Law of the Republic of Serbia [23], every health professional, who provides health care to citizens, is required to have a work license. The Pharmaceutical Chamber of Serbia [24], as the licensing authority, in issuing Health Care Work Licenses to pharmacists in Serbia has not dealt with the evaluation of the pharmacists' competencies so far.

The first evaluation of pharmacists' competencies in Serbia was carried out at the pharmacy Subotica, using the GLF document (2011−12) [25]. At that time, professional competencies of pharmacists were assessed, following the example of neighboring Croatia [16, 18]. An intervention for improving some less developed skills was performed (based on the evaluation results). The GLF was assessed as an effective tool for evaluating and developing competencies, and so a broader scientific community became intrigued by the project. In 2012, a Development of Pharmacists' Competencies Convention brought interested pharmacists and representatives of the professional bodies together in Subotica, and facilitated work of an Expert Panel regarding validation of the GbCF document. The validation of the document was then performed. The document was implemented previously in Croatia, and later in Macedonia (both neighboring countries to Serbia, with similar pharmacy practices, legislature and education, and with common cultural, linguistic and traditional backgrounds). After the validation, the document was implemented in several pharmacy chains in Vojvodina.

The aim of this study was to implement the GbCF document into Serbian pharmacies as well as to perform assessment and self assessment of the pharmacists' competencies.

Methods

Before the implementation (from July to September of 2012), participation in the research with GbCF document was offered to all 43 pharmacy chains in the region of Vojvodina. All the pharmacists from pharmacy chains interested to participate in this research gave their written consents for participation in the project. Prior to the implementation of the assessment, all pharmacists were informed about the document, its contents, objectives and methodology. No one of the surveyed pharmacists declined to participate in the project. Each of the pharmacists performed self-assessment of the competencies and than their competencies were assessed by external assessors.

External assessments of pharmacists were performed by 8 teams of pharmacists (each consisting of three pharmacists from each pharmacy chain). The external assessors were selected by convenient sampling from the pharmacists working in the chains where evaluation was performed, and they assessed their peers individually reaching the final decision by consensus of three. Each team member had pharmacy work

experience of more than five years and completed an appropriate training to ensure the consistency and uniform criteria of the assessments. The training covered an introduction to the document and experiences from the practice, as well as a hands-on part: joined assessments together with experienced evaluators of the pharmacists' competencies.

Assessing teams conducted structured observations of the pharmacists' work in pharmacies for several hours during the course of regular business hours. Several hours of observation (3−5 h) were dedicated to evaluating of each pharmacist, pending the number of patients, the events during practice, and other circumstances.

GbCF comprises the areas of pharmacists' work performed in pharmacies. Areas were divided into four clusters: pharmaceutical public health competencies, pharmaceutical care competencies, organization and management competencies and professional / personal competencies. These clusters include twenty competencies (K1-K20). Each competency was measured by specific indicators (SP) − behavioral statements (SP1-SP100) and was related to the professional performance of pharmacists.

A 2010 version of the partially modified and validated GbCF was used for the assessment and self-assessment of pharmacists' competencies; the version had been adjusted to the common practices and the legislation in Serbia. The document consists of several clusters of several individual competencies described by few specific indicators. The Serbian version of the GbCF contains three clusters (competency groups): pharmacists' professional competencies (KK1: K1-K8 Competencies), management and organizational competencies (KK2: K9-K14 Competencies) and Personal and Professional Competencies (KK3: K15-K20 Competencies). The number of clusters has undergone changes since the original version of the GbCF document, which contained four clusters, following the cultural adaptation of this document geared for the wider region of The Balkans (including the Republic of Croatia and the Republic of Macedonia). However this influenced only reorganization of the number and the kind of competencies without omitting any. This allows a simpler and more efficient use of the document which is more suitable for the Serbian population of the pharmacists. All work activities of pharmacists were included in the measurement. Therefore, the total number of competencies has remained the same (20 in total), while the number of specific indicators has been 101. Specific indicators (SP 1-101) provide a detailed description of the behavior features of a competent pharmacist. In assessing the level of the individual pharmacist competency in the particular field, and in assessing how well pharmacist's knowledge, skills and attitudes reflected the requirements of the document, the assessors applied a structured competency assessment document, based on the GbCF document, and used a Likert scale, as well the description of the contents of specific behavioral indicators. In the applied 1−4 Likert scale, number 1 indicates that the assessment does not meet the expected standard, while number 4 indicates that the expected standard practice is always displayed, with only the sporadic errors. Ratings were determined by consensus of the team members, and each assessed pharmacist was informed about the rating results afterwards. In addition, each participant filled out a questionnaire with demographic indicators pertaining to the pharmacist him/herself, and the pharmacy where he/she worked.

National pharmaceutical associations supported the research: The Pharmaceutical Chamber of Serbia and the Alliance of the Pharmaceutical Associations of Serbia. In addition, each institution involved in the study gave an official approval.

For data analysis we performed several statistical tests: analysis of variance (ANOVA), and univariate tests of significance. Statistical significance was assessed for the $p < 0.05$. All analyses were conducted using the *Statistika* (version 12).

Results

Descriptive analysis

The pharmacists from the 8 out of 43 pharmacy chains accepted to participate. Accordingly, the study involved 123 pharmacists. The main characteristics of the participating pharmacists are shown in the Table 1.

Table 1

Demographic characteristics of pharmacists (n = 123)

Characteristics	Participants, n (%)
Gender, n (%)	
female	119 (96.75)
male	4 (3.25)
Age (years), $\bar{x} \pm SD$	42.07 ± 10.48
Work experience (years), $\bar{x} \pm SD$	15.88 ± 10.93
Education, n (%)	
master degree-level pharmacists	107 (86.99)
master degree-level pharmacists with the additional one postgraduate year	16 (13.01)
Position, n (%)	
pharmacy manager (units)	59 (47.97)
pharmacist	64 (52.03)
Location of relevant pharmacies, n (%)	
city centre	98 (79.67)
periphery, suburban / rural area	25 (20.33)

$\bar{x}$ – mean value; SD – standard deviation.

Assessment results of the external assessors sorted by competency clusters

Assessing the competencies according to clusters the areas of measured competencies were quite uniform, with the highest average score recorded for the cluster KK2 = 3.15, then the cluster KK3 = 3.04 and at the end for the KK1 = 2.98. Table 2 shows the mean and standard deviations for each of the competencies.

The lowest values were recorded in K19 − *quality assurance and research in the work place*.

Summarized scores for each competency cross analyzed with sociodemographic results

There were statistically significant differences observed in clusters of competencies KK1 (F = 3.73, $p = 0.02$), KK2 (F = 6.58, $p = 0.01$) and KK3 (F = 5.76, $p = 0.004$) between

Table 2

Characteristics of competencies in relationship to the assessment type

Competency code	Competency name	External assessment	Self-assessments
		$\bar{x} \pm SD$	
KK1 − Pharmaceutical professional competencies			
K1	Health promotion	3.32 ± 0.70	3.12 ± 0.60
K2	Medicines information and advice	3.30 ±0.69	3.24 ± 0.60
K3	Access to medicines	2.91 ± 0.55	2.96 ± 0.61
K4	Compounding medicines	3.19 ± 0.72	3.07 ± 0.85
K5	Dispensing of drugs and medical devices	3.11 ± 0.47	3.20 ± 0.47
K6	Pharmacotherapy	3.27 ± 0.62	3.28 ± 0.56
K7	Drug therapy follow-up	2.66 ± 0.70	2.63 ± 0.70
K8	Recognition of diagnosis and patient counseling	2.09 ± 0.48	2.34 ± 0.67
KK2 Management competencies and organizational			
K9	Finance and accountable management	3.38 ± 0.61	3.20 ± 0.63
K10	Teamwork and human resources management	2.90 ± 0.65	2.98 ± 0.67
K11	Improvement of the service quality	2.56 ± 0.71	2.55 ± 0.79
K12	Procurement	3.21 ± 0.54	3.05 ± 0.73
K13	Effective inventory control	3.36 ± 0.53	3.22 ± 0.65
K14	Work place management	3.47 ± 0.60	3.37 ± 0.51
KK3 Personal competencies and professional			
K15	Communication skills	3.06 ± 0.58	3.11 ± 0.56
K16	Professional development and competency improvement	2.94 ± 0.66	3.00 ± 0.61
K17	Legislation and regulations	2.91 ± 0.65	2.96 ± 0.66
K18	Professional and ethical practice	3.40 ± 0.55	3.47 ± 0.53
K19	Quality assurance and research in the work place	2.62 ± 0.50	2.83 ± 0.61
K20	Self-management	3.30 ± 0.60	3.32 ± 0.50

$\bar{x}$ − mean value; SD − standard deviation.

Pharmacists recorded the highest competency scores in the following competencies: K14 – *work place management*, K18 − *professional and ethical practice*, and K9 − *finance and accountable management*, and the lowest average values for the competence K8 − *recognition of diagnosis and patient counseling*, K11 − *improvement of the service quality*, and K19 − q*uality assurance and research in the work place*.

Among the pharmacists' professional competencies, the highest level of competence is shown in K1 − *health promotion*, and the lowest in K8 − *recognition of diagnosis and patient counseling*.

Regarding competencies of the organization and management, the highest level of competence the pharmacists showed in K14 − *work place management*, while the lowest values in K11 − *improvement of the service quality*.

Professional and personal competencies had the highest values in K18 − *professional and ethical practice*.

the different age groups of pharmacists (group A − below the age of 35, group B − 36 to 50 years of age, and group C − from 51 to 65 years of age) using ANOVA. The highest level of competencies was observed in the B group, then the C group, and the lowest in the A group. Based on the *post hoc* Tukey honest significant difference (HSD) test, it was concluded that there were significant differences between the clusters of KK1, KK2 and KK3 competencies among the pharmacists from the age groups below 35, and from 36 to 50 years of age ($p = 0.02$ for KK1, $p = 0.001$ for KK2, $p < 0.05$ respectively for KK3).

The ANOVA test showed that there were no significant statistical differences between: the Length of Pharmacists' Work Experience and the Pharmacists' Professional Competency Cluster KK1 ($p > 0.05$ F = 2.56); whereas significant statistical differences were observed between the four groups of length of pharmacists' work experience (less than

10 years, from 10 to 20 years, from 20 to 30 years and from 30 to 40 years) and KK2 ($p < 0.05$, F = 5.11), as well as KK3 Cluster ($p < 0.05$, F = 4.67).

In regards to the competency clusters KK1, KK2 and KK3, the *t*-test showed that there were statistically significant differences between the groups of pharmacists with postgraduate education and pharmacists with a university degree ($t = -2.83$, $p < 0.05$ for KK1, $t = -2, 53$, $p = 0.01$ for KK2, $t = -2.14$, $p = 0.03$ for KK3), where the specialists showed a higher level of competence. Use of the *t*-test showed statistically significant differences related to the type of the working place held: the Head of the pharmacy *vs.* the Pharmacist, where the heads have shown a higher score in the KK2 ($t = -2.83$, $p < 0.05$), while in the other two clusters of competencies (KK1, KK3) the working place did not show significant effects (KK1, $t = -0.19$; $p > 0.05$, KK3, $t = -1.65$, $p > 0.05$).

Differences in the mean competency values between the pharmacists, grouped by pharmacy location, size and area (rural *vs*. urban) were not statistically significant. When we analyze the data in all eight pharmacy chains, in 75% of pharmacy chains the largest value of competency clusters had the cluster KK2, and in 50% of pharmacy chains the lowest value of competency clusters had the KK1.

Analysis of the external assessors' assessment in relation to the self-assessment of pharmacists

The results obtained by self-assessments of competencies by the pharmacists themselves confirmed the results of external assessors partially (Table 2). It was noted that the assessment by external assessors contained higher score values than the pharmacists' self-assessments for next competencies: Health promotion, Medicines information and advice, Compounding medicines, Drug therapy follow-up, Finance and accountable management, Improvement of the service quality, Procurement, Effective inventory control and Work place management.

Application of the *t*-test showed that there were no statistically significant differences in the scores of external assessors and self-assessments of pharmacists in clusters KK1 pharmacists' professional competencies ($t = 0.14$, $p = 0.88$) and cluster KK3 ($t = -1, 56$, $p = 0.12$). When it comes to cluster KK2, statistically significant differences between the rating of external assessors and assessment of the pharmacists themselves were found ($t = 2.00$, $p = 0.04$).

The analysis of individual competencies showed a high correlation between the scores assigned by the external assessors and the self-assessment scores of the pharmacists (the Pearson's correlation coefficients were in range from r = 0.37 to r = 0.61, and all correlations were statistically significant for the level of $p < 0.05$). The results of the *t*-test emphasized the statistically significant differences in the following competencies: K1 ($t = 3.42$, $p < 0.05$), K8 ($t = -4.03$, $p < 0.05$), K9 ($t = 3.51$, $p < 0.001$), K12 ($t = 3.04$, $p < 0.05$), K13 ($t = 2.87$, $p < 0.05$), K14 ($t = 2.08$, $p < 0.05$), and K19 ($t = -3.66$, $p < 0.001$).

The assessment scores were noticeably lower than the self-assessment ones in K8, K9 and K19, whereas in the other competencies, the assessment scores had higher values than the self-assessed scores.

Discussion

This study is among the first studies in the South Eastern Europe, focusing on the pharmacists' level of competencies with the help of a global-level assessment tool. Competencies of the pharmacists were assessed using external assessors and the pharmacists themselves, confirming the intelligibility and validity of the model applied. The document demonstrated a wide framework that allowed assessments and self-assessments of pharmacists' competencies within public pharmacies of Serbia. By cross analyzing of competencies' scores with the demographic data, the study showed a correlation between the certain demographic indicators and the competencies of pharmacists.

An analysis of the demographic data revealed that the study used a cross section of pharmacists, as their age, gender and educational structure reflected the larger pharmacist population from the Northern Serbia (Vojvodina Branch of the Pharmaceutical Chamber of Serbia) [24].

Further analysis of our data showed that there was a high degree of interdependence of the areas of competency. According to McRobbie et al. [1], pharmacists with a higher level of the certain competency demonstrated the competency in the rest of the areas, thereby proving that competence meant in fact the whole dynamics of knowledge, skills and experience of pharmacists.

By cross analyzing the respondents' demographic data, we determined that the levels of the pharmacists' competencies were related to the theoretical knowledge as well as experience. The specialist pharmacists have a higher level of pharmacists' professional competencies. The pharmacists of different ages differed more in professional competencies. The professional and life experience greatly affected the following competencies: Organization and Management, Professional and Personal. Research conducted in the UK, which applied a similar instrument [21] showed that the self-assessed competencies were affected by age in a positive way, whereas the categories: Activity recording and Postgraduate education were more prevalent in younger pharmacists. Gender, status/working place in a pharmacy and the pharmacy type also influenced the study's self-assessment part, while our study pointed out the importance of the work place and the level of education. Interestingly enough, the specialist pharmacists showed a higher level of self-criticism in both studies, rating themselves lower as compared to the pharmacists without an additional education/training.

The evaluation of pharmacists' competencies provided an insight into the areas, where pharmacists' skills were developed, and where the specific indicators attained higher levels (Promotion of health, Work place management, Professional and ethical practice). More significantly, however, the evaluation also identified the areas in need of improvement

(Recognition of diagnosis, Improvement of the service quality, Quality assurance and Research in the work place).

The role of pharmacists in promoting health in Serbia has been developing for the last ten years through research in the social pharmacy area at Faculties of Pharmacy, and since the Health Care Law has made provisions for it [23]. For the pharmacists, it has also represented a new area of activities, where they have recognized their role and place. Acceptance and implementation of the publicly promoted activities reflected also on the results of a similar research conducted in the region, where pharmacists from Serbia achieved a higher level of the competence Promotion of health in relation to colleagues from Croatia was investigated, too [18, 26]. However, the acceptance of that kind of pharmacist' role is quite uneven globally. A research conducted in Nigeria [27] showed that pharmacists believed that they could carry out health promotion activities successfully. A study in Sweden [28] demonstrated that pharmacists were active in modifying their role within public health, however they were in need of the support of the system in order to develop it. Whereas the pharmacists in Scotland (about 1/3 of participants) [29] felt a lack of competence in the promotion and protection of public health or in encouraging behavior changes. A study conducted in Moldova [30] suggested that pharmacists did not give great importance to health promotion activities and preventive screening. They evaluated them as the lowest in relation to other activities of professional work, as well as their own competence in these areas: self-assessments were between 3.2 and 4.4 [on a scale from 0 (low competence) to 5 (high competence)].

According to the Good Pharmaceutical Educational Practice document [31] (by the International Pharmaceutical Federation), one of the seven "starring roles" of a pharmacist is also being a manager. Pharmacists as managers are aware of the importance of knowing the basics of finance and the accountable management, taking part responsibly in creation and achievement of the financial plans, payment collections for goods and services, transparency of financial operations, as well as the concerns about the cost and tangible assets. All these are the specific indicators of this competency, where the respondents demonstrated a higher level of competence.

The competency Professional and ethical practice is among the best rated, and includes specific indicators related to demonstrating the professional attitude and belonging to the profession, as well as the respect for ethical principles in pharmaceutical practice. High average grades in this competency group suggest respect for the importance of rational thinking, critical approach and resolving of ethical dilemmas, which are important for positive treatment outcomes [32].

Recognition of diagnosis, which is included in the patient consultation and diagnosis competency, is neither sufficiently accepted, nor developed in Serbia by the pharmacists. A research, that has been conducted in Serbia [25] and Croatia earlier [18, 26] with the help of a similar instrument (GLF), has suggested that those activities have not yet been accepted as part of the routine work of pharmacists. One possible explanation may lie in the fact, that they were not an integral part of the regular Pharmacy University curriculum, either in Serbia or in some other, more advanced country [33] until a few years ago. This reflects on pharmacists, avoiding to provide those services. On the other hand, the younger pharmacists, who have acquired theoretical knowledge, did not have enough experience to demonstrate them in their own practice.

Low assessment values of the Improvement of the service quality competency were affected by its specific indicators: Design and implementation of new services and Innovations and resolution, prevention and follow-up of the DRPs. These specific indicators required a very creative and thorough approach to work (high above average, as in other professions), and they can be found only in sporadic pharmacists. Studies conducted around the world confirm that for the innovations in pharmacists' practice there is a lengthy adjusting and accepting period required, not only by the patients but also by the pharmacists (usually explained by the lack of competence) [28–30]. The aforementioned is true for the "introduction of new services and new design", where pharmacists showed a lower level of competencies. Lower values of competencies in the area of Quality assurance and research in the work place suggest a lack of routine practice of establishing and complying with the standards, the pharmacovigilance routines, as well as the research of the pharmaceutical practice. Pharmacy practice studies are carried out globally at an increased rate. They focus on various issues, from the studies on knowledge and attitudes of patients [33–35] to the ones on pharmacists' opinions or their behavior assessment [36–38]. Although these research is important for competence improvement and development, the competency scores suggest that the pharmacists in Serbia are not familiar nor involved in research studies. This might be explained by the lack of interests and small number of studies conducted at the moment.

Self-assessment vs. assessment

The results obtained through self-assessments of pharmacists' competencies confirmed the assessors' results partially, indicating well-established and accepted standards and assessment methodologies. Poor correspondence between self-assessment and assessment scores may be due to inconsistencies, uncoordinated criteria or a poor methodology [39]. If the correlation is high, self-assessment is regarded as good, and *vice versa* [40]. Sixty-five per cent of the previous studies approximately demonstrated lacking proper correspondence between the assessment scores and self-assessments. Customarily, the most self-confident participants prove the least competent, and the ones of mediocre competence tend to award themselves the most realistic and objective scores [41–43]. In our study though, it is the opposite: in four (out of twenty) competencies, self-assessments are lower than ratings of the external assessors. They involve a promotion of health competency and a competence in the cluster of organization and management. That may indicate a lack of objectivity and coordination of criteria, or increased self-criticism by the evaluated pharmacists. All these represent the potential weaknesses of the methodology. The

pharmacists' perception of the lack of competence in the area of public health was also observed in the studies in Scotland [29] and Moldova [30]. Nevertheless, pharmacists in Nigeria [27] considered themselves as being competent. Although some studies did not find a proper correlation between self-assessments and external assessments [20, 39–43], the results obtained in our study indicate a relatively high coordination of criteria between the assessors and the pharmacists and satisfactory objectivity by both sides.

Conclusion

The paper represents the first implementation of the global assessment document related to competencies in Serbian public pharmacies in the north of the country, thereby proving feasibility of implementing the global competency framework model in Serbia. Assessing the competencies according to clusters the areas of measured competencies were quite uniform, with the lowest average score recorded for the Pharmacists' Professional Competency Cluster (KK1) and highest for the Management and Organizational Competency (KK2). Although there was no statistical difference between the scores of self-assessment and assessment of Pharmacists' Professional Competency Cluster, this cluster was also the one with the competence of the lowest individual average score (Recognition of diagnosis and patient counseling). Therefore, the global competency framework might be considered as an instrument which could point out the cluster that needs to be improved at the community pharmacy settings. Positive experiences in the use of the instrument represent a good basis for the development of competencies and improving the quality and efficiency of education of the pharmacists.

In the future, when pharmacists' personal initiative and support by the system assume the vital role, the application of the global competency framework might upgrade the pharmaceutical health care in Serbia to a higher level.

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Translation and validation of the Croatian version of the Oral Impacts on Daily Performances (OIDP) scale

Prevođenje i valjanost hrvatske verzije Upitnika o uticaju oralnog zdravlja na dnevne aktivnosti

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Abstract

Background/Aim. Among numerous sociodental indicators the Oral Impacts on Daily Performance (OIPD) is one of the most broadly applied. The aim of this study was to develop and test psychometric properties of a Croatian version of OIDP scale. **Methods.** The OIDP instrument was translated from English to Croatian in a forward-backward method. The Croatian version was tested for reliability, construct validity and responsiveness on a sample of 702 participants (255 men), aged 18–86 years. **Results.** Internal consistency of Croatian version of the OIDP was acceptable (alpha = 0.80) and 69.4% of the examinees had oral impacts relating to one or several performances. The most frequently affected performance was eating (53.7%). The test-retest reliability was high (r = 0.99; 95% CI: 0.97–0.99), the mean difference between the OIDP summary scores in two-week interval was not statistically significant. In construct validity testing there was statistically significant correlation between OIDP and self-assessed general and oral health, somatisation, depression and Oral Health Impact Profile ranging from 0.157 to 0.516. Responsiveness was confirmed by a significant reduction of oral impacts on daily performances in subjects before and after treatment of acute dental pain ($p < 0.001$). **Conclusion.** The Croatian OIDP index showed good psychometric properties in terms of construct validity, internal consistency, test-retest reliability and responsiveness confirming its appropriateness for use among Croatian population.

Key words:
oral health; attitude to health; quality of life; questionnaires; croatia.

Apstrakt

Uvod/Cilj. Među mnogobrojnim sociodentalnim pokazateljima Upitnik o uticaju oralnog zdravlja na dnevne aktivnosti (OIDP) najšire se primenjuje. Cilj istraživanja bio je da se razviju i testiraju psihometrijske karakteristike hrvatske verzije OIDP. **Metode.** Upitnik OIDP preveden je s engleskog na hrvatski jezik metodom napred-natrag. Proverena je pouzdanost, verodostojnost i osetljivost hrvatske verzije na uzorku od 702 ispitanika (255 muškaraca), starih od 18 do 86 godina. **Rezultati.** Interna konzistencija hrvatske verzije OIDP upitnika bila je prihvatljiva (alpha = 0,80) i 69,4% ispitanika imalo je oralni uticaj na jednu ili više aktivnosti, s tim da je uticaj bio najviše ispoljen na jedenje hrane (53,7%). Test-retest pouzdanost bila je vrlo visoka (r = 0.99; 95% CI: 0.97–0.99), a glavna razlika između OIDP zbirnih rezultata u dvonedeljnom intervalu nije bila statistički značajna. U ispitivanju valjanosti upitnika (prevoda upitnika) postojala je statistički značajna povezanost između OIDP i samoprocene opšteg i oralnog zdravlja, somatizacije, depresije i profila uticaja oralnog zdravlja u rasponu od 0,157 do 0,516. Osetljivost upitnika potvrđena je značajnim sniženjem uticaja oralnih činilaca na izvođenje svakodnevnih aktivnosti pre i nakon tretmana akutnog dentalnog bola ($p < 0,001$). **Zaključak.** Hrvatska verzija OIDP pokazala je dobre psihometrijske karakteristike u smislu valjanosti izrade upitnika, interne konzistencije, test-retest pouzdanosti i osjetljivosti, potvrđujući njegovu prikladnost za upotrebu među domaćim stanovništvom.

Ključne reči:
usta, zdravlje; stav prema zdravlju; kvalitet života; upitnici; hrvatska.

Introduction

Oral health related quality of life (OHRQoL) has been recognized as a multidimensional construct containing not only physical but also psychosocial issues [1–3]. A professional can diagnose physical state, but not psychological or social wellbeing, which can only be assessed through indicators of oral impacts on daily performances and quality of life [1]. Their use provides important information on functional and social dimensions of oral conditions. This information reflects

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the self-perceived oral health needs. So far many OHRQoL measures are developed, validated and used: Oral Health and the Sickness Impact Profile; The Dental Impact Profile, The Oral Health Impact Profile, The Dental Impact on Daily Living, Subjective Oral Health Status Indicators, etc [1].

Among numerous sociodental indicators the Oral Impacts on Daily Performance (OIDP) is one of the most broadly applied. It uses a theoretical concept modified from International Classification of Impairments, Disabilities and Handicaps of World Health Organization which has three levels: oral status and impairments, intermediate impacts (pain, discomfort, functional limitations and dissatisfaction with appearance), and ultimate impacts (psychosocial and physical disability and handicap) [1]. While the majority of OHRQoL instruments focus on measuring the second level, the OIDP puts emphasis on the third level in order to determine oral impacts on the ability to perform everyday activities. Its simplicity, short form and good psychometric characteristics make it easy to use in a wide range of age groups and cohorts [4–7].

The OIDP is a generic instrument, used in many studies to assess the impact of oral health on quality of life before and after different dental treatment [8–12]. The results showed that the impact of oral health on quality of life decreased with time after treatment, indicating improvement in QoL, although these effects may be better traced by condition-specific instruments.

In this study, the English version of OIDP was translated into Croatian and validated, in order to provide the basis for further application on Croatian population.

Methods

The translated instrument was tested on a sample of 702 participants (255 men and 447 women) aged 18–86 years (mean age 41.2 ± 19.6). Sampling procedure included convenient sample: students, workers, subjects at regular annual check-ups at the Institute for Public Health Rijeka, consecutive voluntary blood donors at the Department of Transfusion, Medicine University Hospital Rijeka and patients of the University Dental Clinic, during the year 2011. All the participants gave written informed consent to the survey procedures, approved by the Institutional Review Board of the Rijeka University School of Medicine. The questionnaire was self-administrated.

The OIDP index measures oral impacts on eight performances, *ie* eating, speaking, cleaning teeth/denture, sleeping and relaxing, emotional stability, smiling, carrying out main role/everyday activities, social contacts. The development of the Croatian OIDP demanded a cross-cultural adaptation. Linguistic validation comprised forward translation of the English OIDP instrument into Croatian, followed by backward translation of the draft Croatian version into English. OIDP was first translated into Croatian independently by two dentists who were experts in quality of life measures and proficient in English and Croatian. After a panel discussion of four dental specialists, the first draft of translation was formed. To check the clearness of the items in a Croatian linguistic and cultural context, 20 subjects (students and patients) administrated the questionnaire, and according to their remarks few linguistic modifications were thereafter done. Croatian version was then translated back into English independently by a dental postgraduate student and an English major student. After the back translation, a native speaker and a dentist fluently in English checked the meaning of items of original instrument and back-translated Croatian version resulting in a final version approved by the panel.

For each dimension performance score was calculated as a product of severity and frequency score. The OIDP score was calculated by the formula: OIDP score = sum of performance scores / maximum possible score X 100. Respondents also graded the impact for the following oral problems on their daily activities: toothache, sensitive tooth, tooth decay, tooth space due to non-erupted permanent tooth, fractured tooth, tooth colour, tooth shape or size, position of tooth, bleeding gum, swollen gum, calculus, oral ulcers, bad breath, deformity of mouth or face, eruption of permanent tooth, missing permanent tooth. The Likert scale was used ranging from 0 = not at all to 5 = a great deal. The questionnaire also included questions referring to the self-reported general health as well as oral health (based on a five-point Likert scale ranging from 1 = excellent to 5 = poor). Oral Health Impact Profile (OHIP)-14 CRO [2], and somatisation and depression domains of the Brief Symptom Inventory (BSI) were also administrated [13, 14]. It was assumed that respondents with higher OIDP score would have lower self-reported general and oral health, higher level of somatisation and depression, and higher OHIP. OHIP-14 CRO was used as a gold standard for OHRQoL assessment, since it showed good psychometric characteristics in Croatian population [2].

The internal consistency and the test-retest reliability were used as a measure of instrument's reliability. The internal consistency was assessed by calculating the average inter-item correlation and the Cronbach's alpha for the OIDP subscales and summary score. The test-retest reliability was calculated by intra-class correlation coefficients (ICC) using summary OIDP scores from the repeated administration of the questionnaire. The same instrument was administered by 41 subjects twice within a two-week period by respondents who were not provided by any oral or dental treatment, assuming that the OHRQoL would not change during that period.

Construct validity was evaluated by assessing association between the OIDP summary score and OHIP-14 CRO, self-reported general and oral health, and somatisation and depression levels by using the Spearman rank correlation and ANOVA.

The responsiveness of the OIDP was tested on 34 patients suffering from toothache who completed the OIDP questionnaires before the treatment and one month later. It was predicted that the OHRQoL would improve within that period. The significance of the difference in the OIDP score was assessed by using paired samples *t*-test, the standardized response mean and the effect size.

Results

The prevalence of oral impacts on daily performances was high and 69.4% of respondents experienced at least one impact in the last six months, with speaking being the least frequently

affected and eating the most (Table 1). Sensitive teeth were the most frequently reported oral problem (61.5%; impact 1.0 ± 1.0), followed by tooth position (54.6%; impact 1.1 ± 1.2), and mouth /face deformity was the least (4.6; 0.1 ± 0.7; Table 2).

Internal consistency of the Croatian version of OIDP was acceptable, which was shown in standardized Cronbach's alpha of 0.80. None of the items would substantially affect reliability of the OIDP if they were deleted (Table 3). All correlations between OHIP domains were positive, average inter-item correlation was 0.33 and ranged from 0.18 (speaking and social contacts) to 0.81 (smiling and social contacts).

The test-retest reliability was high (r = 0.99; 95% confindence interval (CI): 0.97–0.99), the mean difference between the OIDP summary scores in two-week interval was -0.53 (95% CI: -1.20–0.14) and was not statistically significant.

Regarding construct validity, there was a statistically significant correlation between OIDP and self-assessed general and oral health, somatisation, depression and OHIP, ran-

Table 1

Prevalence of oral impacts on daily performances

Performance	Prevalence (≥ 1), %
Eating (jelo i uživanje u hrani)	53.7
Speaking (govor i jasno izgovaranje)	23.4
Cleaning teeth/denture (čišćenje zubi ili proteza)	39.8
Sleeping and relaxing (spavanje i odmaranje)	32
Emotional stability (održavanje emocionalnog stanja bez razdražljivosti)	30
Smiling (smijanje i pokazivanje zubi bez srama)	40.8
Carrying out main role/everyday activities (izvođenje svakodnevnih aktivnosti)	26.8
Social contact (uživanje u kontaktima s drugim ljudima)	32.1
Any impact	69.4

Table 2

Prevalence of self-reported oral conditions and their impacts on daily activities

Oral conditions	Prevalence (≥ 1), %	Impact	
		mean	SD
Toothache (zubobolja)	45.9	0.8	1.1
Sensitive tooth (osjetljivi zubi)	61.5	1.0	1.0
Tooth decay (pokvareni zub)	36.0	0.7	1.2
Tooth space due to non-erupted permanent tooth (prazno mjesto za zub (jer nije niknuo trajni zub))	9.7	0.2	0.7
Fractured tooth (slomljen trajni zub)	15.8	0.4	1.0
Tooth colour (boja zuba)	38.6	0.7	1.1
Tooth shape or size (oblik ili veličina zuba)	28.0	0.5	0.9
Position of tooth (položaj zuba (npr. krivi / zbijeni ili izbočeni / stršeći, razmaknuti / razdvojeni))	54.6	1.1	1.2
Bleeding gum (krvarenje desni)	44.7	0.8	1.0
Swollen gum (otečene desni)	33.5	0.6	1.0
Calculus (kamenac)	31.3	0.5	0.9
Oral ulcers (ranice u ustima)	41.9	0.8	1.1
Bad breath (zadah)	44.6	0.8	1.1
Deformity of mouth or face (deformitet usta ili lica (npr. rascjep usne ili nepca))	4.6	0.1	0.7
Eruption of permanent tooth (nicanje trajnog zuba)	26.9	0.6	1.1
Missing permanent tooth (nedostaje trajni zub)	10.1	0.2	0.8

SD – standard deviation.

Table 3

Internal consistency of Croatian version of Oral Impacts on Daily Performance (OIDP) questionnaire

Parameter	Corrected item-total correlation	Cronbach's alpha if item deleted
Eating	0.50	0.74
Speaking	0.40	0.76
Cleaning teeth/denture	0.41	0.76
Sleeping and relaxing	0.49	0.75
Emotional stability	0.46	0.75
Smiling	0.54	0.74
Carrying out main role/everyday activities	0.56	0.75
Social contact	0.61	0.72

Alpha: 0.77; Standardised item alpha: 0.80.

ging from 0.157 for general health to 0.516 for OHIP (Table 4). There was an evident tendency for increasing OIDP with increasing level of self-perceived dental treatment need, somatisation and depression, and decreasing self-perceived oral health (Table 5).

A significant difference between the mean OIDP score in subjects before and after treatment of acute dental pain confirmed responsiveness ($p < 0.001$) (Table 6).

Table 4

Construct validity of Oral Impacts on Daily Performance (OIDP) questionnaire assessed by Spearman's rank correlation

Parameter		OIDP
Self-perceived general health	*r*	0.157
	p	0.044
Self-perceived oral health	*r*	0.356
	p	< 0.001
Self-perceived dental treatment need	*r*	0.446
	p	< 0.001
Somatisation	*r*	0.318
	p	< 0.001
Depression	*r*	0.273
	p	0.002
OHIP	*r*	0.516
	p	< 0.001

OHIP – Oral Health Impact Profile.

Table 5

Construct validity of Oral Impacts Daily Performance (OIDP) questionnaire assessed by ANOVA

Parameter	Mean	SD	*p*
Self-perceived dental treatment need			
not at all	0.78	2.05	
a little	2.57	3.24	
to some extent	3.60	3.87	
considerably	11.48	15.12	
very much	30.92	26.52	< 0.001
Self-perceived oral health			
excellent	0.80	1.57	
very good	3.57	3.80	
good	4.10	5.49	
fair or poor	7.01	14.44	0.023
Somatisation			
normal (< 0.535)	2.19	4.51	
moderate (0.535–1.105)	2.65	3.51	
severe (> 1.105)	6.48	8.15	0.005
Depression			
normal (< 0.428)	2.23	4.57	
moderate (0.428–0.857)	2.60	3.70	
severe (> 0.857)	7.22	8.27	0.002

SD – standard deviation.

Table 6

Responsiveness testing of Croatian Oral Impacts Daily Performance (OIDP) questionnaire

n	Mean baseline score–mean follow-up score	95% CI for mean difference	Standardized effect size	Standardized response mean	*p*
34	9.21–3.78	3.43–7.44	0.66	0.95	< 0.001

n – number of examinees; CI – confidence interval.

Discussion

This is the first study in which the OIDP index was adapted in Croatian and tested its validity on Croatian population. The development of the Croatian version of the OIDP was performed by following established procedures and the methodology from similar studies [4, 15, 16]. The professionals fluent in both English and Croatian carried out the forward-backward translation process. There are several translation categories usually operating (forward-only translation, forward translation with testing, back-translation, back translation and monolingual test, back translation and bilingual test, back translation and monolingual and bilingual tests) each method presenting some advantages and disadvantages with the last quoted being the most powerful [17]. Inclusion of several translators, panel of professionals and examinees of various groups show significant exertions made into the cross-cultural adaptation of the instrument. The present survey demonstrated that the Croatian version of the OIDP instrument is reliable and valid for use among subjects in

Croatia. Its psychometric attributes in terms of content, criterion and construct validity as well as internal and test-retest reliability underwent successful testing and empirical verification.

Inter-item correlation, corrected item-total correlation, and Cronbach's alpha indicated that this index has excellent internal consistency. All item-total correlations were above the threshold of 0.20, as suggested [18] for including an item in a scale, which implies the homogeneity of the items. Alpha values were above than the recommended limits, and even higher than in other studies [1, 19]. The above mentioned implies that the items of Croatian OIDP instrument are well and positively intercorrelated, therefore appropriate to constitute an unidimensional instrument.

The Croatian OIDP is a generic OHRQoL instrument, measuring a construct most similar to unidimensional short form OHIP-14. Many generic and condition-specific instruments have been developed so far in dental medicine to express how an individual perceives oral pain or discomfort (Graded Chronic Pain Scale, OHIP), jaw function limitations (Jaw Functional Limitation Scale, Mandibular Function Impairment Questionnaire), or his/her dental appearance [Psychosocial Impact of Dental Aesthetics Questionnaire (PIDAQ), Orofacial Esthetic Scale (OES)], etc. [18–23]. Instruments measuring OHRQoL can be unidimensional (like OES), while the majority are multidimensional (such as PIDAQ).

The Croatian version of OIDP has good construct validity. It is capable to discriminate levels of self-perceived dental treatment need, self-perceived oral health, somatisation and depression. The correlation was poor for self-perceived general health, somatisation and depression, moderate for self-perceived oral health and dental treatment need, and good for OHIP. All the tested relationships between OIDP score and subjective oral health measures demonstrated a trend in the assumed direction. It is logical and expected that OHIP and OIDP are very well correlated because they measure similar construct. It is understandable that the correlation was moderated for self-perceived oral health and dental treatment need because the participants do not connect impaired quality of life with treatment need (they got used to that condition, and probably do not want changes). Also, in Croatia people avoid oral healthcare, thereby reflecting low socioeconomic status. It was not surprising that a correlation was poor for self-perceived general health because they are two kinds of health that participants differentiate. We expected higher correlation with somatisation and depression, but in our sample there were no patients primary with acute or chronic health conditions, such as toothache, that could produce significant psychosomatic symptomatology. And for depression probably in Croatian cultural context people are less aware of their teeth and dental appearance and they do not tend to significantly suffer because of it. All correlations between OIDP domains were positive, average inter-item correlation was 0.33 and ranged from 0.18 (speaking and social contacts) to 0.81 (smiling and social contacts).

The frequency of oral impacts on daily performances was high, which was similar to other researches [5, 6, 16], or even higher [1, 6, 7]. The reason of differences in prevalence may be related to cultural differences. Eating was the most prevalent performance affected by oral impacts among the ten items, and speaking being the least frequently affected, which is consistent with the other research [5–7, 19, 22–24].

The OIDP and OHIP-14 are proved to be valid questionnaires to assess the impacts of oral conditions on quality of life. Both established on the model of oral health which claims that diseases lead to impairment and functional limitation at the level of the organ, and consequently to one's disability, death or social deprivation [3]. The OHIP-14 may be preferred due to its easier administration and somewhat higher reliability [22]. However, OHIP-14 measures the second level of consequences, and OIDP focuses on measuring the third level, still encompasses all of the consequences of the second level impacts in performing daily activities. Specificity of OIDP feature is that it provides a percentual measurement scale [1].

Beside Croatian, the OIDP was cross-culturally adapted from English into many languages [4, 5, 16, 25–31] and also showed good psychometric properties. Its version for children (Child-OIDP) was developed in 2004 [32]. Heretofore several cross-cultural adaptation and validation of Child-OIDP are presented [33–35], and it is one of the most widely used OHRQoL instruments in children.

Future studies should focus on development of Croatian version of the Child-OIDP version.

Conclusion

The Croatian OIDP demonstrated good psychometric properties, establishing itself as appropriate instrument to measure the OHRQoL of Croatian population.

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Prevalence of *Borrelia burgdorferi sensu lato* in *Ixodes ricinus* ticks and assessment of entomological risk index at localities in Belgrade

Prevalencija *Borrelia burgdorferi sensu lato* kod krpelja *Ixodes ricinus* i procena entomološkog indeksa rizika na lokalitetima Beograda

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Abstract

Background/Aim. The first case of human Lyme borreliosis (LB) in Serbia was recorded in 1987. The number of reported LB cases has increased in the past decade. The aim of this study was to estimate the density of *Ixodes ricinus (I. ricinus*) ticks, the prevalence of *Borrelia burgdorferi sensu lato* (*B. burgdorferi*) in them, and entomological risk index (ERI) at 19 Belgrade localities which were grouped into three categories (forests, park-forests, parks). The values of ERI were compared with the number of tick bites in humans. **Methods.** Ticks were collected monthly by using the flag hours method and the infection rate was determined by using dark field microscopy. The ERI value was calculated for each locality where the ticks were collected. The related data about tick bites was obtained from the patient protocol of the Institute of Epidemiology, Military Medical Academy, Belgrade. **Results.** The total number of collected ticks, the number of nymphs and the infection rates of the nymphs were significantly higher in forests ($p < 0.05$) than park-forests and parks. Statistically, the ERI value was significantly higher in forests than parks of Belgrade ($\chi^2 = 7.78$, $p < 0.01$). In March and July, the ERI value was also significantly higher in forests, than park-forests ($p < 0.01$) and parks ($p < 0.01$). May was the month with the highest ERI value in each ecological category (forests $p < 0.05$; park-forests $p < 0.01$; parks $p < 0.001$). However, the number of tick bites in humans did not correlate with ERI values. **Conclusion.** The obtained results indicate that the risk of tick bite and human exposure to *B. burgdorferi sensu lato* is present at all selected localities in Belgrade. For a more comprehensive Lyme disease risk assessment the method of entomological risk index assessment should be combined with other methods, taking into consideration all tick stages and the behaviour and habits of people who may get infected *B. burgdorferi sensu lato*.

Key words:
ticks bites; ixodes; borrelia burgdorferi; lyme disease; prevalence; population density; health status indicators; serbia.

Apstrakt

Uvod/Cilj. Prvi slučaj lajmske borelioze (Lyme borreliosis, LB) u Srbiji zabeležen je 1987. Broj prikazanih bolesnika sa LB porastao je tokom poslednje dekade. Cilj ovog istraživanja bio je da se procene gustina krpelja *Ixodes ricinus (I. ricinus),* prevalencija *Borrelia burgdorferi* (*B. burgdorferi)* u njima i entomološki indeks rizika (ERI) na 19 beogradskih lokaliteta grupisanih u tri ekološke kategorije (šume, park-šume, parkovi). Vrednosti ERI upoređivane su sa brojem uboda krpelja kod ljudi. **Metode**. Krpelji su prikupljani mesečno pomoću metode *flag* časa, a stopa infekcije određivana je u tamnom polju mikroskopa. ERI vrednost je izračunavana za svaki lokalitet na kome su sakupljeni krpelji. Podaci o ubodima krpelja stanovnika dobijeni su iz Protokola ispitanika za ubod krpelja Instituta za epidemiologiju Vojnomedicinske akademije u Beogradu. **Rezultati.** Ukupan broj prikupljenih krpelja, broj nimfi i stopa infekcije nimfi bili su značajno viši u šumama ($p < 0,05$) nego u park-šumama i parkovima. Utvrdili smo statistički značajno višu vrednost ERI u šumama nego u parkovima Beograda ($\chi^2 = 7,78$, $p < 0,01$). U martu i julu, značajno viša vrednost ERI ustanovljena je u šumama nego u park-šumama ($p < 0,01$) i parkovima ($p < 0,01$). Maj je bio mesec sa najvišim vrednostima ERI u svakoj ekološkoj kategoriji (šume $p < 0,05$; park-šume $p < 0,01$; parkovi $p < 0,001$). Broj uboda krpelja kod ljudi nije bio u korelaciji sa vrednostima ERI. **Zaključak.** Dobijeni rezultati pokazuju da na svim odabranim lokalitetima Beograda postoji rizik od uboda krpelja i ekspozicije ljudi *B. burgdorferi*. Za sveobuhvatniju procenu rizika od lajmske bolesti, metodu procene ERI trebalo bi kombinovati sa drugim metodama, uzimajući u obzir sve stadijume krpelja, kao i ponašanje i navike ljudi, koji se mogu inficirati *B. burgdorferi sensu lato*.

Ključne reči:
krpelj, ubodi; ixodes; borrelia burgdorferi; lajmska bolest; prevalenca; populacija, gustina; zdravstveno stanje, indikatori; srbija.

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Introduction

The first case of human Lyme borreliosis (LB) in Serbia was recorded in 1987 [1]. The number of reported LB cases has increased in the past decade. According to the reports from the Institute for Public Health of Serbia, a total of 3,860 patients were registered in the period 2002–2007, with the average annual incidence of 10.7/100 000. Between 2006 and 2008 more than 200 cases of LB were reported in Serbia. The majority of LB cases were found in Belgrade. In the period from 2000 to 2007, a total of 3,126 persons with tick bites were referred to the Institute of Epidemiology, Military Medical Academy in Belgrade [2].

Due to the high number of LB cases in Belgrade, the Program of Prevention and Chemical Fighting of Ticks was implemented in 1994. The application of preventive measures (personal protection and landscape management) has priority in the Program, but according to some ecological and epidemiological criteria (an increasing number of tick bitten humans, an increasing incidence of LB, an increasing number of ticks and the infection rate of *B. burgdorferi sensu lato*), it is necessary to perform spraying of chemical insecticides for reduction of tick population in green surfaces such as forests, park-forests and parks. The chances of being bitten by a tick can be decreased by taking a number of precautions: avoid tick-infected areas, walk on paths away from vegetation, wear light-coloured clothing so that ticks can be spotted more easily, conduct careful examination of your body and arrange for prompt removal of any ticks and use tick repellents for skin or clothing. Moreover, to reduce the number of ticks in the surrounding nature it is recommended to remove leaves, litter, woodpiles, cut grass and brush from the area [3, 4].

Investigations of ecology of *B. burgdorferi sensu lato*, vectors and reservoirs in our environment have been conducted for more than 20 years. *Ixodes ricinus (I. ricinus)* was confirmed as a vector of LB in 1990 in former Yugoslavia [5]. The first isolation of *B. burgdorferi sensu lato* from *Apodemus flavicollis* was performed [6]. All the three patogens of the complex *B. burgdorferi sensu lato* were isolated in Serbia: *Borrelia sensu stricto, Borrelia afzelii* and *Borrelia garinii.* The prevalence of *B. burgdorferi sensu lato* in *I. ricinus* ticks collected in different regions in Serbia between 1990–2005 ranged as follows: Zaječar 26.0 %, Pančevo 19.5%, Zrenjanin 19.8%, Kraljevo 16.1%, Knjaževac 15.4% and Despotovac 33.3% [7].

Previous studies done in Belgrade estimate that the average infection of ticks with *B. burgdorferi sensu lato* was 21.9% [8]. In the period from 2002 to 2007, the infection rate of *I. ricinus* varied from 17.5 to 21.3% depending on the month and locality [9]. The territory of Belgrade, with numerous green surfaces in various ecological categories (forest, park-forests, parks) and the presence of many host reservoirs (dogs-rambling, game, birds) create an ecological environment fruitful for the appearance of *I. ricinus*, as well as maintaining its population, which thus causes a high occurrence of LB.

In this paper the density of *I. ricinus* ticks and their infection rates with *B. burgdorferi sensu lato* were estimated. We estimated ERI value and how it correlated with tick bites in people who were present at Belgrade's 19 localities included in the study.

Methods

The study was carried out in March-October 2009 in Belgrade (Serbia). The research covered two stages of ticks, but only nymphs were used for calculating the entomological risk index (ERI).

Site selection

The study was carried out at 19 localities in Belgrade classified in three ecological categories: forests (Lipovica, Bojčinska, Avala, Miljakovačka, Makiš), park-forests (Ada Ciganlija, Zvezdara, Banjica, Košutnjak, Jajinci) and parks (Hajd park, Bele vode, Usće, Šumice, Kalemegdan, Topčider, Tašmajdan, Banovo brdo, Pionirski park). All three ecological categories have conditions for maintaining *I. ricinus* tick population.

The parks predominately consisted of annual vegetation and brushes, although there was perennial vegetation, as well. The basic characteristics of the areas were their connection with the surrounding roads and the routine maintenance of the areas throughout the year (pruning trees, mowing lawns, removing leaves, litter accumulations, cut grass, weeds and brush). These areas are also regularly visited by pets and stray dogs. Finally, certain areas in parks are characterized by favorable conditions for the appearance of rodents, squirrels, hedgehogs and birds, too. There are paths, benches and gazebos for persons participating in recreational activities in parks too.

Park-forests are slowly but surely, from year to year changing in favor of parks. A park area is an ideal habitat for ticks, since rodents, lizards and birds live there, where forest areas are characterized by a big number of birds, small and large rodents, reptiles and deer which also host *B. burgdorferi sensu lato*. Park-forests are characterized by the abundance of annual and perennial vegetation.

Forests are covered by perennial deciduous forest vegetation (oak, bitter oak, beech, dogwood, and timber), as well as evergreen vegetation (pine juniper-tree), ivy, mistletoe and annual vegetation. Forests are interspersed with small clearings and roads leading to restaurants. Bojčinska and Makiš forests are located near the Sava and Danube. Throughout the woods there are paths for hikers and vehicles. In the areas of Avala, Bojčinska, and Lipovička forests, there are parts arranged to serve as resting and recreational points (benches, tables, canopies, paths for walking and running).

Ticks sampling

Ticks were collected monthly in forests (5 localities), park-forests (5 localities) and parks (9 localities), using a flannel cloth of a 1 m^2 surface area (flag hours method) in the duration of 1h. The cloth was checked every 20 min when the attached ticks were removed, counted and placed into humidifi-

ed vials and transported to the laboratory for further investigation. Tick density was expressed by flag/hour (f/h) value – number of ticks collected *per* 1 hour [10, 11].

Detection of *B. burgdorferi sensu lato*

Each tick was identified by taxonomic keys and the descriptions of species [12, 13]. The method used to identify the tick infection rate was dark field microscopy in tick midgut tissues with the 400-fold magnification [14].

Entomological risk index (ERI)

ERI was calculated for each locality where the ticks were collected. The ERI value represents the number of nymphs of *I. ricinus* infected with *B. burgdorferi sensu lato* collected *per* minute of flag sampling [15].

Tick bites in humans

Tick bites of nymphs in humans were registered from March to October at each of the 19 localities in Belgrade. The people bitten sought help with the removal of ticks and further prophylactic recommendations from doctors-epidemiologists at the Institute of Epidemiology, Military Medical Academy in Belgrade.

Statistical analysis

Analysis of variance (ANOVA) was conducted to compare average tick densities, average tick infection rates and average ERI values between ticks from various ecological categories (forests, park-forests and parks). Secondary analysis was performed by using Tukey test. In cases of considerable variability of investigated values, Kruskal-Walis and Mann-Whitney tests were used. The correlations of each locality's ERI value with the number of tick bites in humans was assessed using Pearson′s correlation coefficient. Three rates of statistical relevance were considered: $p < 0.05$; $p < 0.01$; $p < 0.001$.

Results

A total of 3,199 ticks *I. ricinus*, adults and nymphs, were collected from the selected 19 localities in Belgrade. The total infection rate of ticks *I. ricinus* with *B. burgdorferi sensu lato* was 22.0%. Out of all the ticks sampled, 989 (30.9%) were nymphs. The total number of 302 (30.5%) out of all nymphs examined were established infected with *B. burgdorferi sensu lato*. The highest number of nymphs were collected in forests (10.65 ± 4.52), and nymphs in park-forests belonged to the most infected group (34.14 ± 4.82) with *B. burgdorferi sensu lato* (Table 1).

The total number of collected ticks was significantly higher in forests ($p < 0.05$) than parks. The density of nymphs was significantly higher in forests ($p < 0.05$), than park-forests and parks. For ticks originating from various ecological categories no significant difference in infection rates of nymphs was established (Table 2).

ERI value at 19 selected localities was on average 0.49 and varied depending on the ecological category of the locality. The highest average annual ERI value of 1.00 was established for forests, and the lowest for parks 0.19 (Table 3).

The highest ERI values were obtained for Lipovica forest (2.04), park-forest Ada Ciganlija (0.44) and Hajd park (0.38),

Table 1

The total number of collected ticks, only nymphs and percent of nymphs infected at selected localities of Belgrade (f/h)

Ecological category	The total number of collected ticks $\bar{x} \pm SD$	Number of collected nymphs $\bar{x} \pm SD$	Percent of infected nymphs $\bar{x} \pm SD$
Forests	31.8 ± 9.58	10.65 ± 4.52	32.12 ± 6.02
Park-forests	21.4 ± 4.82	5.67 ± 1.24	34.14 ± 4.82
Parks	14.9 ± 9.15	4.67 ± 1.83	26.79 ± 4.92

Table 2

Comparison of avarage ticks yearly densities and tick infection rates values among various ecological category (forests, park-forests and parks)

Parameters	ANOVA			Tukey-test
	F	df	*p*	
Number of collected ticks	6.52	16	0.008	
Forests : park-forests				ns
Porests : parks*				$p < 0.05$
Park-forests : parks				ns
Number of collected nymphs	8.36	16	0.003	
Forests : park-forests*				$p < 0.05$
Forests : parks*				$p < 0.05$
Park-woods : parks				ns
Percent of infected nymphs	3.72	16	0.05	
Forests : park-forests				ns
Forests : parks				ns
Park-forests : parks				ns

***result statistically significant; ns – non-statistically significant.**

Table 3
Avarage values of entomological risk index (ERI) at selected localities of Belgrade

Ecological category	ERI ($\bar{x} \pm SD$)
Forests	1.00 ± 0.69
Park-forests	0.29 ± 0.11
Parks	0.19 ± 0.11

and the lowest ERI values were established in Makis forest (0.35), SP Jajinci park-forest (0.20) and in Pionirski park (0.02) (Table 4). A significantly higher ERI value ($\chi^2 = 7.78$, $p < 0.01$) was found in forests than the parks of Belgrade (Table 5).

In this study, we analyzed ERI values monthly and compared the values established in forests, park-forest sand parks. In March and July, we encountered a significantly higher ERI value in forests, than park-forests ($p < 0.01$) and parks ($p < 0.01$). In the other six months, that is April, May, June, August, September and October, we did not find statistically significant differences in ERI values for all investigated categories (Table 6). May was the month with a statistically significantly higher ERI value for each ecological category, for all the investigated localities (Table 7).

Table 4
Entomological risk index (ERI) values and frequency of tick bites in humans on selected localities of Belgrade

Ecological category	ERI	Frequency of tick bites (n)
Forests	1.02	70
Lipovica	2.04	21
Bojcinska	1.03	2
Avala	1.17	26
Miljakovačka	0.53	20
Makiš	0.35	1
Park-forests	0.29	76
Ada Ciganlija	0.44	5
Zvezdara	0.22	16
Banjica	0.22	24
Košutnjak	0.39	21
SP Jajinci	0.20	10
Parks	0.19	83
Hajd park	0.38	27
Bele Vode	0.36	7
Ušće	0.21	15
Šumice	0.20	2
Kalemegdan	0.14	4
Topčider	0.14	21
Tašmajdan	0.15	2
Banovo brdo	0.11	4
Pionirski park	0.02	1

Table 5
Comparison of entomological risk index (ERI) values among ecological categories of Belgrade

Comparison of ecological category	Kruskal-Walis test		
	χ^2	df	p
General analysis	7.94	2	0.02
Forests : Park-forests	3.60	1	0.05 (ns)
Forests : Parks*	7.78	1	0.005 ($p < 0.01$)
Park-forests : Parks	2.80	1	0.09 (ns)

***result statistically significant; ns – non-statistically significant.**

Table 6
Entomological risk index (ERI) values analyzed monthly, March and July

Comparison of ecological category	Kruskal-Walis test		
	χ^2	df	p
March (general analysis)	10.3	2	0.006
Forests : park-forests			$p < 0.01$
Forests : parks*			$p < 0.01$
Park-forests : parks			ns
July (general anlysis)	9.34	2	0.009
Forests : park-forests*			$p < 0.01$
Forests : parks*			$p < 0.01$
Park-forests : parks			ns

***result statistically significant; ns – non-statistically significant.**

Table 7
Entomological risk index (ERI) value in May in ecological categories of Belgrade

Ecological category	Mann-Whitney test Z	*p*
Forests*	2.40	< 0.05
Park-forests*	2.61	< 0.01
Parks*	3.57	< 0.01

***result statistically significant.**

Tick bites of nymphs were registered in residents who live or have recreational activities in all 19 localities. All the cases of bites were reported to the Institute of Epidemiology, Military Medical Academy in Belgrade from March to October 2009 (Table 4). In spite of the fact that our results established that the number of tick bites in humans did not correlate with ERI values (r = -0.31; *p* = ns), we observed higher ERI values for some localities where the number of registered tick bites was higher. We found the highest frequency of tick bites of nymphs in Banjica (24), Avala (26), Topčider (21), Košutnjak (21) and Hajd park (27). In the ecological category of forests, the lowest number of tick bites (1) was found in Makis, in a number of selected park-forests at Ada Ciganlija (5) and in Pionirski park (1).

Discussion

In spite of all efforts to establish supervision and control, LB remains the leading arthtopod-related disease in the majority of countries around the world [16]. It is caused by spirochete *B. bugdorferi sensu lato* and is associated with the bite of certain *Ixodes* ticks, particularly the *Ixodes scapularis* in the northeastern and north-central United States, *Ixodes pacificus* on the Pacific Coast, *Ixodes persulcatus* in Asia, Europe, Russia, China, Japan, *Ixodes ricinus* in Europe and Euroasia. The secondary vectors of LB are another ticks species: *Haemaphysalis, Hyalomma, Dermacentor, Amblyomma, I. hexagonus, I. ovatus*, depending on the geographical location [17, 18]. All ticks feed on three different host animals during their lives. *I. ricinus* is known to feed on more than 300 different kinds of mammals, birds and reptiles. The genera of rodents *Peromyscus* and *Apodemus* are important reservoirs of *B. burgdorferi sensu lato* in the North America and Europe [19].

In the USA there are 20,000–24,000 human LB case reports annually [3]. About 60,000 cases are reported each year in Europe [20]. The highest reported frequencies of LB occur in the middle Europe, particularly in Germany 25/100,000, Sweden 69/100,000, Austria 130/100,000 and Slovenia 120/100,000 [18, 21]. In accordance with the current legislation LB reporting is mandatory in Serbia. As the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut" reports, the number of reported LB cases averaged 784 annually with the incidence of 10.63 /100,000 in 2006–2010 [22]. In the period 2011–2012 LB incidence in Serbia averaged 13.49/100,000 *per* year [23]. In Serbia, as well as in the aforementioned European countries and the USA, LB is diagnosed based on the signs and symptoms of LB, a history of possible exposure to infected *I. ricinus* ticks and laboratory blood tests which are helpful if used correctly and performed by using validated methods. The two steps of Lyme disease testing are: using a testing procedure called enzyme immunoassay (EIA) or rarely, an indirect immunofluorescence assay (IFA). The second step uses Western blot test (immunoblot test). Results are considered positive only if EIA/IFA and immunoblot are both positive [24, 25].

The risk of LB infection is determined primarily by the density of vector ticks, the prevalence of *B. burgdorferi sensu lato* infection in ticks, seasonal tick activity and the extent of person-tick contact, which is related to the type, frequency, and duration of a person's activities in a tick-infested habitat [4]. Moreover, some ecological factors, as for instance region, climate and landscape, influence the risk of LB infection [26]. The number of ticks varies with geographical position and depends on humidity, daylight and the presence of hosts of infected ticks (wildlife, rodents, birds, stray dogs) [27]. Apart from the abovementioned ecological factors of habitats of infected ticks, in order to assess the risk of *B. burgdorferi sensu lato* infection, some researchers use the value of ERI [26]. It is possible to calculate the ERI value for each separate habitat of infected ticks as an abundance of nymphs (number of nymphs collected *per* unit of time of sampling) and the local *B. burgdorferi sensu lato* infection rate in nymphs. In the analysis of risk of human LB infection human behaviour and habits formed when on green surfaces should both be taken into consideration [4, 28].

Our results of the density of ticks that ranged from 18.87 to 45.5 f/h in 5 selected forests localities of Belgrade were compared with the results which were obtained by a great number of researchers [11, 29–32]. The comparison shows that the abundance of ticks is the highest in forests, ecotones, flowery vegetation and grassy surfaces. The f/h value at localities depended on the ecological category and varied between 14.9 f/h in parks and 31.8 f/h in the forests. The lowest value 9.75 f/h was found in the park Banovo Brdo and the highest 45.5 in Lipovica forest. The abundance of nymphs was higher in forests, on the average 10.65 f/h, than park-woods 5.67 f/h and parks 4.67 f/h. The density of the total number of ticks and the density of nymphs alone were significantly higher in forests ($p < 0.05$), than park-forests and parks. Our results confirm similar observations in Czech Republic [11] and Belgrade [31] where the f/h values were the lowest (Czech Republic 1986: 2.8–15.1; Belgrade 1993: 4.2–14.2). A smaller number of *I. ricinus* found in parks when compared to other selected localities is due to differences

between ecological categories. Parks have less vegetation, but more concrete paths for recreational activities and walking, regular maintenance, and frequently visiting pets and stray dogs which carry *I. ricinus* on their fur.

During the investigation we found an average tick infection of 22.0% at all selected localities, similarly to our recent results of investigation conducted in Belgrade and the results from Vojvodina and other regions in Serbia [8, 9, 33]. The infection rates obtained by some researchers (Finland 32.0%, Italy 40.0%, Croatia 45.2%) were higher than in our study [30, 34, 35] whereas some were lower, in Poland 14% and Denmark 6% [36, 37]. The findings about *Borrelia* infection of ticks in Germany (21.8%) [38]. Poland's forests from period 1996–1998 (22.9%) [39] and at workplaces of forestry workers in eastern Poland (22.1%) [40], are comparable with our data. Researchers from Estonia have found lower values of *B.burgdorferi sensu lato* prevalence 9.7 % [41].

Nymphs are thought to be responsible for the majority of tick bites since they are more numerous than adult ticks and are also more likely to avoid detection when attached [4, 18]. Due to that we specially investigated nymph stage and the infection rate of nymphs. The infection rate of *I. ricinus* nymphs may vary from 0% to 66% [42] but mostly varies from 10% to 30%. In our study the infection rate was the highest in park-forests, about 34.1% and the lowest in parks 26.8%, on the average 30.5% in all observed ecological categories, but it did not vary significantly ($F = 3.72$; $df = 16$; $p = 0.05$). Similarly to our results, some authors observed an infection rate nymphs from 13% to 46% and more than 20% [43, 44] while others found a lower value of 21.0 %, and 4.9–23.1% [45]. In the forests of Germany, researchers observed about five times lower infection rate, 6.9% [46].

Just like in previous investigations on Belgrade's green surfaces, the ERI value varied at different localities and was 0.02–2.04, but the values in this study were 2–5 times higher [9]. We found a significantly higher ($p < 0.01$) ERI value (1.00) in the selected forests than in the selected parks (0.19) of Belgrade. The values were greater than ERI values obtained by American researchers [15]. Researchers from Vojvodina calculated the highest ERI in the town of Bačka Palanka, 0.158, slightly lower than that obtained from parks in our study [33]. In March and July, we encountered a significantly higher ERI value in the forests than park-forests ($p < 0.01$) and parks ($p < 0.01$). Vegetation in forest is richer than in two others ecological categories and various species of *I. ricinus* hosts live there as well. The ERI value in May was statistically significantly higher for each ecological category, for all investigated localities. That occurred as a result of a greater activity of nymph stage ticks in this period [37, 47].

Similarly to the other observations, which proved a correlation between the ERI value and LB incidence, and a correlation between the ERI value and seropositivity of outdoor workers [9], we analyzed the correlation between ERI value and the number of tick bites [15, 28, 48, 49]. In spite of a great numbers of registered tick bites, somewhere the highest (in category of parks: Hajd park), the number of tick bites in humans did not correlate with ERI values. In order to explain our results, it is important to take into consideration the other factors that depend on the residents' activity in the selected places (behaviour in the nature and the use of preventive measures for avoiding tick bites or fast detection of tick bites). Also, it is presupposed that not all people report to a doctor after being bitten by a tick. In rare cases, it is possible for the person not to notice a tick bite, and the tick gets torn off by accident after scratching or releases itself after getting enough blood. Removal of ticks can be carried out by a doctor in any ambulance (which are available at all locations), and again in rare cases, people remove it by themselves and bring it for examination. Still most of the bitten people, report themselves to an epidemiologist in our institution, having in mind that tick testing to *Borrelia* existence is done only in the Military Medical Academy in Belgrade. If *Borrelia* is present in the tested tick, the analysis is positive and it is suggested that the patient see an infectologist who will prescribe antibiotics for LB prevention (therapy lasts 2 weeks). If the person does not bring the tick which bit him or her to get tested and the early signs of infection have already appeared, he or she is immediately sent to an infectologist for further testing, diagnosis and treatment. Also, it should be noted that there are other methods of risk assessment involving tick adults and other environmental habitat parameters, which are applied by some researchers [33, 50, 51].

Among the selected five park-forests Košutnjak was the most frequently visited place. A great number of residents take recreational activities there, or go for daily walks because they live near to this park-forest. The ERI value in Košutnjak (0.39) was higher than in Banjica (0.22), but the frequency of tick bites was higher in Banjica. A great number of persons with tick bites who live near Banjica, visit doctors in the Institute of Epidemiology, because the Military Medical Academy is situated in Banjica. On the other hand, a certain number of tick bites from Košutnjak may have remained unregistered, because the persons bitten did not visit a doctor or did not detect ticks on their body. The ERI value at the park-forest Ada Ciganlija was paradoxically high (0.44) compared to just one tick bite, which is explained by the influence of other ecological factors in the environment and factors relating to the activities and behaviour of people [28]. Among the five selected forests the highest ERI (2.04) was calculated for the Lipovica forest and then for Avala (1.17). However, the number of tick bites at Avala (26) was the highest, because that place, as it is arranged and adapted for human leisure activity in a more appropriate manner, is visited by more people than Lipovica. Among the parks, the highest ERI value (0.37) and the number of nymphs (27) were encountered in the Hajd park.

Conclusion

The study indicates the risk of tick bites, the risk of human *B. burgdorferi sensu lato* exposure and getting infected by LB at all the selected localities in Belgrade. For a more comprehensive Lyme disease risk assessment it is necessary to incorporate other stages of ticks (apart from the nymph stage) into the assessment using appropriate evaluation methods. Also, human behaviour as well as habits of people who visit parks, park-forests and forests of Belgrade should be taken into consideration. With a view to conducting a thorough LB risk assessment, the method of entomological risk index assessment should be combined with other methods taking into consideration all the previously mentioned.

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Upper extremity function and quality of life in patients with breast cancer related lymphedema

Funkcija ruke i kvalitet života kod bolesnica sa limfedemom nakon lečenja karcinoma dojke

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Abstract

Background/Aim. Upper limb lymphedema is one of the most frequent chronic complications after breast cancer treatment with a significant impact on the upper extremity function and quality of life (QoL). The aim of this study was to estimate health-related quality of life (HRQoL) in patients with breast-cancer-related lymphedema and its correlation with upper limb function and the size of edema. **Methods.** The cross-sectional study included 54 breast-cancer-related lymphedema patients. The quality of life was evaluated by the Short Form 36-Item Health Survey (SF-36). Upper limb function was assessed by the Quick Disability of the Arm, Shoulder and Hand questionnaire (Quick DASH). The size of lymphedema was determined by the arm circumference. **Results.** The higher HRQoL score was assessed for mental health (47.0 ± 12.2) than for physical one (42.2 ± 7.5). The highest values of SF-36 were found in the domains of Mental Health (67.7 ± 22.9) and Social Function (70.1 ± 23.1). The lowest scores were registered in the domains of Role Physical (46.9 ± 39.1) and General Health (49.3 ± 20.1). Upper extremity function statistically significantly correlated with the domains Role Physical, Bodily Pain and Physical Composite Summary and also, with the domain Role Emotional ($p < 0.01$). There was no statistically significant correlation between size of lymphedema and tested domains of quality of life ($p > 0.05$). **Conclusion.** Physical disability in patients with breast-cancer-related lymphedema influences quality of life more than mental health. Upper limb function has a significant impact on quality of life, not only on the physical, but also on the mental component. The presence of breast-cancer-related lymphedema certainly affects upper limb function and quality of life, but in this study no significant correlation between the size of edema and quality of life was found.

Key words:
breast neoplasms; carcinoma; upper extremity; lymphedema; quality of life.

Apstrakt

Uvod/Cilj. Limfedem ruke je jedna od najčešćih komplikacija nakon lečenja karcinoma dojke koja može da ima značajan uticaj na funkciju gornjeg ekstremiteta i na kvalitet života. Cilj ove studije bio je da proceni kvalitet života kod bolesnika sa limfedemom nakon lečenja karcinoma dojke i njegovu povezanost sa funkcijom ruke i veličinom edema. **Metode.** Ova studija preseka obuhvatila je 54 bolesnice sa limfedemom nakon lečenja karcinoma dojke. Za merenje kvaliteta života korišten je opšti upitnik *Short Form 36-Item Health Survey* (*SF-36*). Za procenu funkcije ruke korištena je kratka verzija specifičnog upitnika Nesosobnost ruke, ramena i šake (*Quick Disability of the Arm, Shoulder and Hand questionnaire- Quick DASH*). Veličina limfedema je određivana merenjem obima ruke. **Rezlutati.** Veća vrednost kompozitnog skora SF-36 upitnika dobijena je za mentalno (47,0 ± 12,2), nego za fizičko zdravlje (42,2 ± 7,5). Najveće vrednosti pojedinačnih skorova kvaliteta života dobijene su za domene mentalnog zdravlja (67,7 ± 22,9) i socijalnog funkcionisanja (70,1 ± 23,1). Najniže vrednosti su registrovane za domene onesposobljenost zbog fizičkog zdravlja (46,9 ± 39,1) i opšteg zdravlja (49,3 ± 20,1). Funkcija gornjeg ekstremiteta je statististički značajno korelisala sa domenima onesposobljenost zbog fizičkog zdravlja, bolom i fizičkim kompozitnim skorom, kao i sa domenom onesposobljenosti zbog emocionalnog stanja ($p < 0,01$). Nije bilo statistički značajne povezanosti između veličine otoka i testiranih domena kvaliteta života ($p > 0,05$). **Zaključak.** Fizička onesposobljenost kod bolesnica sa limfedemom nakon lečenja karcinoma dojke više utiče na kvalitet života, nego mentalno zdravlje. Funkcija ruke ima značajan uticaj na kvalitet života, ne samo na njegovu fizičku komponentu, već i na mentalnu. Prisustvo limfedema utiče na smanjenje funkcije ruke i kvalitet života, ali u ovoj studiji nismo dobili uzajamnu vezu između kvaliteta života i veličine otoka.

Ključne reči:
dojka, neoplazme; karcinomi; ruka; limfedem; kvalitet života.

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Introduction

Upper limb lymphedema is one of the most frequent chronic complications after the breast cancer treatment. The incidence of breast cancer related lymphedema (BCRL) varies from 0% after sentinel lymph node dissection to 56% after axillary lymph node dissection and radiation therapy to the axilla [1–4]. Its incidence is not precisely established because of unpredictable onset (it can develop immediately after the breast cancer treatment or many years later) and the lack of consensus about clinical criteria for the diagnosis and standard methods of assessment [1, 3–5].

Several symptoms and impairments often occur in these patients: heaviness, tightness, numbness, weakness and pain (due to brachial plexopathy, peripheral neuropathy, rotator cuff disease, adhesive capsulitis, De Quervain tenosynovitis) as well as susceptibility to infection of an edematous limb. All of these impairments can cause functional problems (range of motion reduction, decreased shoulder and arm muscles strenght) and limitations in activities requiring use of the affected extremity [1, 6, 7].

Disfiguring, disabling and chronic nature of BCRL and activity limitations may have significant influence on patient' daily life and, hence, quality of life (QoL) [5, 8]. Reduced QoL is not just a consequence of reduced physical functioning but also derives from adverse effects on the psychosocial and social domains of function [9].

Therefore, the relationship between lymphedema, upper limb function and quality of life has emerged as an important component in caring for breast cancer survivors [4].

The aim of this study was to estimate a health related quality of life (HRQoL) in patients with lymphedema after breast cancer treatment and its correlation with upper limb function and the size of edema.

Methods

This cross-sectional study included 54 BCRL patients. All the patients had unilateral axillary lymph node dissection. Exclusion criteria were: metastatic cancer patients, shoulder and arm impairments due to neurologic, rheumatologic or orthopedic conditions, diagnosed before surgery, persisting infection, psychiatric disorders diagnosed and treated with drugs.

The quality of life was evaluated with the Short Form 36-Item Health Survey (SF-36). The SF-36 is a widely used, generic, self-report measure of health status and it has good internal consistency, convergent and divergent validity and moderately good construct validity within breast cancer survivors [10]. It contains 36 items that are combined to form four physical domain scales: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), summarized as the Physical Component Summary (PCS) measure; and four mental domain scales: Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH) summarized as the Mental Component Summary (MCS) measure. Each scale is standardized on a 0 to 100 score; higher scores indicate better health status. The PCS and MCS were designed to have the mean score of 50 and a standard deviation of 10 in a representative sample [11]. (To calculate PCS and MCS, we used norms for the United States, from 1998.

Upper extremity function was assessed by the Quick Disability of the Arm, Shoulder and Hand questionnaire (Quick DASH), which is valid and reliable instrument for measurement of upper extremity disability in breast cancer survivors [12]. The Quick DASH was developed as a shortened version of the DASH Outcome Measure [13]. Instead of the 30 items of the DASH, the Quick DASH uses 11 items to measure physical function and symptoms related to upper limb musculoskeletal disorders during a 7-day period before adminstration. Each item has 5 response options, with a patient's answering 1 for activities performed with "no difficulty", and 5 for activities unable to perform or performed with "extreme difficulty". The final score is calculated by the first summing total responses and then dividing this figure by the total number of completed items. From this figure 1 is subtracted and then multiplied by 25. A score can only be calculated with a maximum of 1 omitted item [12].

The lymphedema was determined by the arm circumference measured at the 7 points of the affected and contralateral side. The size of lymphedema was expressed as the relation between total circumference of healthy and affected arm, and calculated according to the following formula: [(total circumference of affected arm – total circumference of healthy arm) / total circumference of healthy arm] ×100.

Statistical analysis included descriptive statistics (arithmetic mean, standard deviation, median, range, minimum, maximum) and correlation analysis. Pearson's correlation coefficient was used to examine the relation between variables. Testing was two-sided, with sets at 0.05 for a statistical significance and 0.01 for a high statistical significance. The SPSS 15.0 statistical software package was used for all calculations.

Results

The study included 54 BCRL patients treated at the Institute of Physical Medicine and Rehabilitation "Dr Miroslav Zotović", Banja Luka, Bosnia and Herzegovina. Table 1 shows the clinical characteristics of the patients.

The higher HRQoL score was assessed for mental health (47.0 ± 12.2) than for physical one (42.2 ± 7.5) and it was statistically significant ($p < 0.05$). The highest values of SF-36 were found in the domains of Social Functioning (70.1 ± 23.1) and Mental Health (67.7 ± 22.9). The lowest scores of SF-36 were registered in domains of Role Physical (46.9 ± 39.1) and General Health (49.3 ± 20.1). The results of the domain scales of the SF-36 questionnare are shown in Figure1.

The mean Quick DASH score was 30.04 (SD = ± 10.95; range 14.4–59.0).

Upper extremity function was statistically significantly correlated with the domains Role Physical, Bodily Pain and the Physical Component Summary ($p < 0.01$). There was

Table 1

Clinical characteristics of the patients

Variable	n (%)	Mean (SD)	Median	Range (min–max)
Age (years)		56.04 (± 9.03)	57.00	(38–72)
< 50	14 (25.9)			
50–69	37 (68.5)			
> 70	3 (5.6)			
Time from surgery (months)		46.41 (± 31.96)	38.00	(6–117)
Type of breast surgery				
radical mastectomy	36 (66.7)			
partial mastectomy	3 (5.5)			
segmentectomy	15 (27.8)			
Number of lymph nodes removed		13.78 (± 5.39)	14.00	(6–35)
Therapy				
chemotherapy	44 (81.5)			
radiotherapy	36 (66.7)			
hormonal	37 (68.5)			
Duration of lymphedema (months)		33.37(± 26.04)	23.00	(6–114)
BMI (kg/m^2)		27 (± 4.32)	26.90	(18.36–37.64)
underweight (< 18.50)	1 (1.8)			
normal range (18.50–24.99)	17 (31.5)			
pre-obese (25.00–29.99)	25 (46.3)			
obese (> 30)	11 (20.4)			
Comorbidity (medications for)				
heart disease	14 (25.9)			
thyroid problems	12 (22.2)			
diabetes	3 (5.5)			
circulation problems	6 (11.1)			
osteoporosis	9 (16.7)			

BMI – body mass index; SD – standard deviation.

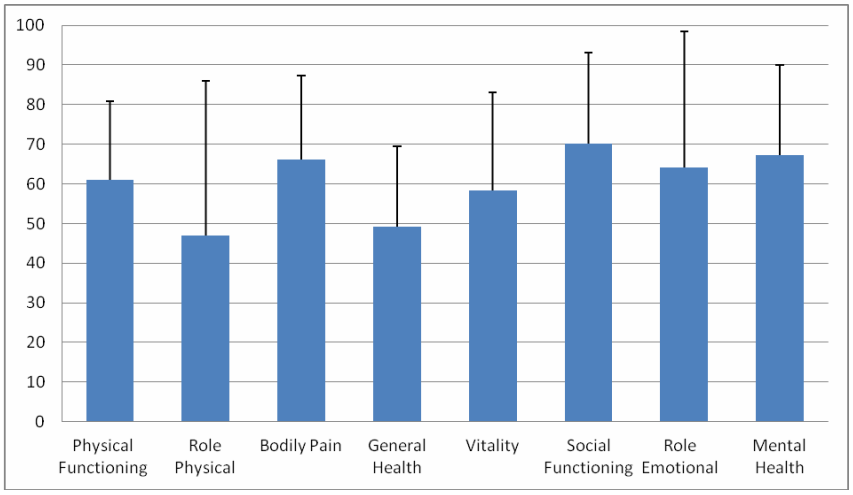

Fig. 1 – Domain scales of Short form 36-item Health Survey (SF-36).

also a negative correlation between Quick DASH and Role Emotional ($p < 0.01$) and between Quick DASH and Vitality, Social Functioning and Mental Component Summary at the level $p < 0.05$ (Table 2).

The mean size of lymphedema was 4.56% (SD = ± 3.52; range 0–14.18%). There were 2 patients without changes in the arm circumference**.** We had not excluded them from the study, because they had edema of breast and axilla. The majority of women (90.74%) had mild or moderate lymphedema (difference between total circumference of healthy and affected arm < 10%). Severe lymphedema (the difference between total upper limb circumferences > 10%) was found in 9.26% women. The dominant arm was involved in 40.62% of cases. There was no statistically significant correlation between the size of lymphedema and tested domains of quality of life questionnaire (Table 3). Also, there was no correlation between the size of edema and the Quick DASH score.

Discussion

Many studies compared the quality of life between breast cancer survivors and general population. Other studies are mostly focused on comparison HRQoL of patients with lympedema and patients without lymphedema. Although there have been some differences between studies in specific domains

Table 2

Correlation between Quick Disability of the Arm, Shoulder and Hand Questionnaire (Qiuck DASH) and quality of life [Short Form 36-Item Health Survery (SF-36) scores]

PCS, MCS and domain scales of SF-36	r*	*p*
Physical QoL		
Physical Functioning	-0.247	0.071
Role Physical	-0.364	0.007
Bodily Pain	-0.577	0.001
General Health	-0.154	0.270
PCS	-0.503	0.001
Mental QoL		
Vitality	-0.283	0.038
Social Functioning	-0.318	0.020
Role Emotional	-0.444	0.001
Mental Health	-0.185	0.186
MCS	-0,322	0.018

***Pearson's correlation coefficient.**

PSC – Physical Component Summary; MCS – Mental Component Summary; Physical QoL – Physical quality of life; Mental QoL – Mental quality of life; SF36 – Short Form 36-Item Health Survery.

Table 3

Correlation between the size of edema and scores of Short Form 36-Item Health Survey (SF -36)

PCS, MCS and domain scales of SF-36	r*	*p*
Physical QoL		
Physical Functioning	-0.075	0.591
Role Physical	-0.080	0.563
Bodily Pain	-0.117	0.401
General Health	-0.030	0.828
PCS	-0.079	0.572
Mental QoL		
Vitality	-0.085	0.542
Social Functioning	-0.095	0.494
Role Emotional	-0.033	0.815
Mental Health	-0.095	0.493
MCS	-0.106	0.445

***Pearson's correlation coefficient.**

For abbreviations see under Table 2.

of HRQoL affected, the general consensus is that HRQoL is lower in breast cancer survivors with lymphedema or related arm symptoms compared with breast cancer survivors without lymphedema or arm symptoms [2, 3, 14–16]. This study did not have a control group. But, the results of this study related to the lower physical component of quality of life of patients with lymphedema are similar to previous studies [3, 17].

The lowest scores of SF-36 were registered in domains of Role Physical and General Health. Lee at al. [4] have obtained the same results. Velanovich and Szymanski [18] reported that patients with lymphedema had significantly lower median scores in the domains of Role Emotional and Bodily Pain.

All patients in our study had chronic lymphedema (mean duration 33.37 months, range 6–114 months). We believe that the mental component of quality of life is less affected, because they accept their condition as chronic and learn to live with it.

Our results show a strong relationship between arm disfunction and BCRL patient's quality of life. These results are complementary to the findings of other researchers [3, 19–22].

Hormes et al. [19] found that arm swelling and lymphedema severity were less correlated with quality of life than total number of arm symptoms and specific individual symptoms. Pain in the affected arm correlated with poor quality of life outcomes, regardless arm swelling [19].

In the Munich Field Study of the quality of life of breast cancer patients it was also reported that arm problems had the strongest influence on quality of life [20].

Neswold et al. [21] found that breast cancer survivors with other self-reported arm symptoms than lymphedema had significantly poorer quality of life and that breast cancer survivors with clinically assessed restricted mobility showed significant associations with all SF-36 domains except Social Functioning, Mental Health and MCS and no significant associations with lymphedema based on clinical examinations [21].

In our study, all the SF-36 domains, except Physical Functioning, Mental Health and General Health, significantly correlate with self-reported upper limb function.

A relationship between upper extremity function and physical quality of life scores in our study was expected. It is interesting to find a significant correlation between upper extremity function and all the mental domains of quality of life, except Mental Helath. A posible explanation can be that pain and related arm symptoms, existing in patients with poorer upper extremity function, might have influence on mental component of quality of life, like vitality, emotional and social functioning.

Our results also demonstrate that the size of lymphedema, defined by interlimb circumference differences, can not properly reflect the negative influence of lymphedema on the functioning and HRQoL. Swelling is a defining characteristic of lymphedema, but it is not the only symptom; the results of earlier studies suggest that other aspect of lymphedema (in addition to swelling), such as pain and altered function may have impact on HRQoL [3, 14, 19, 23, 24].

When evaluating the impact of lymphedema on quality of life, we stress the importance of lymphoedema presence more than size of lymphedema. Secondly, the difference between upper limb circumferences might not be as significant as the total number and specific types of existing arm symptoms. The largest lymhedemas are not the most severe. We suggest the use of both, the subjective and objective parameters, in determining the severity of lymphedema.

Our study supports earlier findings that the severity of lymphedema is not significantly correlated with worse outcomes QoL and that volume reduction treatments, although useful, may not be sufficient to provide better functioning and quality of life of these patients [14, 16]. Rehabilitation assessment should include quantification of pain, limb size, range of motion and strength in all segments of the upper extremity and identification of potential causes of arm symptoms and disfunction. Early rehabilitation programs should be implemented to minimize risk of BCRL and upper body morbidity development and optimize function and quality of life [25].

The most important message of this paper is that disfunction of the upper limb has stronger influence on quality of life than the size of edema. It can be recommended that assessment of the quality of life of breast cancer patients should include different aspects of lymphedema and upper extremity function.

There are some limitations of this study: small sample size – future studies should include a larger number of patients to reduce statistical limitations; the study was not a longitudinal but cross-sectional one – further studies on longitudinal change of the quality of life in patients are needed; the study did not have a control group; the SF-36 does not capture specific symptoms in patients suffering from BCRL such as heavy and swollen arms or difficulty in holding or carrying objects. For this reason, the use of a lymphedema-specific instrument, with breast cancer and arm function subscales, along with a generic instrument for HRQoL is recommended [13, 26]; Quick DASH is a self-report measure of upper limb function. For optimal assessment of upper limb disfunction we need to use both, self-report and objective measures of upper limb function such as shoulder range of motion, strength and fine motor coordination.

Conclusion

Physical disability in patients with breast-cancer-related lymphedema influences quality of life more than mental health. Upper limb function has a significant impact on quality of life, not only on the physical, but also on the mental component. The presence of breast-cancer-related lymphedema certainly affects upper limb function and quality of life, but, in this study, no significant correlation between the size of edema and the quality of life was found. Having in mind that lymphedema can cause functional problems and activity limitations, we must emphasize the importance of the early diagnosis and rehabilitation treatment.

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The impact of motivation, personal traits of managers and management education on the performances of public healthcare facilities

Uticaj motivacije, ličnih osobina rukovodilaca i obrazovanja u oblasti upravljanja na rezultate zdravstvenih ustanova u javnom sektoru

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Abstract

Background/Aim. Exposed to increasing needs of users for better and faster services, more medications and innovative health technologies, managers of healthcare services in the public sector need motivation, permanent updating of information and constant personal development. The aim of this paper was to evaluate, on the basis of experienced healthcare managers, the impact of their motivation, selected character traits, managerial skills and formal education in management on healthcare facilities performances in the public sector. **Methods.** For the purposes of this study, 97 experienced managers from public hospitals and primary health centers in Serbia answered to 30 questions on the motivation of managers, essential skills for successful management and formal education in management in health facilities. The obtained data about their motivation, governing experience, personal skills and formal education in management were systematized and processed by the Statistical Package for Social Sciences (SPSS). Healthcare facilities performances were expressed by the healthcare facilities ranks in the official annual rankings according to the quality improvement, conducted by the Institute of Public Health of Serbia. Pearson's or Spearman's correlation coefficients were used for proving the potential impact of selected factors on performances of healthcare facilities. **Results.** This study confirmed the association between the healthcare facilities ranks and managers' abilities to organize the working process (t = -2.453; p = 0.018); expressed high managers' motivation (ρS = 0.206; p = 0.048) and the length of governing experience (r = -0.198; p = 0.043). Within a 3-year follow-up, this study also confirmed a positive correlation between annual ranks of healthcare facilities and managers quality management courses (ρS = -0.238; p = 0.017) and managers education in human resources management (ρS = -0.234; p = 0.027). **Conclusion.** In addition to management education, permanent personal development and higher motivation of managers have positive influence on healthcare performances.

Key words:
hospitals, public; organization and administration; motivation; questionnaires; quality control; quality assurance, health care.

Apstrakt

Uvod/Cilj. Zbog sve veće potrebe korisnika za kvalitetnijim zdravstvenim uslugama, savremenim lekovima i novim zdravstvenim tehnologijama, neophodno je da rukovodioci u zdravstvenim ustanovama budu motivisani, dobro informisani i da stalno rade na svom ličnom razvoju. Cilj ovog rada bio je da se na osnovu iskustava rukovodilaca procene uticaji faktora motivacije, nekih ličnih osobina, veština upravljanja i formalnog obrazovanja u oblasti upravljanja na rezultate zdravstvenih ustanova u javnom sektoru. **Metode.** U svrhu ovog istraživanja, 97 iskusnih rukovodilaca državnih bolnica i domova zdravlja u Srbiji odgovaralo je na 30 pitanja o motivaciji rukovodilaca, bitnim veštinama za uspešno rukovođenje i formalno obrazovanju u oblasti upravljanja zdravstvenim ustanovama. Dobijeni podaci sistematizovani su i obrađeni u programu Statistički paket za društvene nauke (SPSS). Postignuti rezultati zdravstvenih ustanova izraženi su u osvojenim mestima (redosleda) koja su zdravstvene ustanove zauzele u godišnjim rangiranjima prema unapređenju kvaliteta koje je sproveo Institut za javno zdravlje Srbije. Za utvrđivanje mogućih uticaja odabranih prediktora na rezultate zdravstvenih ustanova korišćeni su linearna regresiona analiza, Pirsonov ili Spirmanov test korelacije. **Rezultati.** Ovaj rad potvrdio je povezanost osvojenih mesta u rangiranju zdravstvenih ustanova sa stavovima rukovodilaca o značaju njihovih sposobnosti da organizuju posao (t = -2,453; p = 0,018), izraženom visokom motivacijom (ρS = 0,206; p = 0,048) i vremenom provedenim na rukovodećoj funkciji (r = -0,198; p = 0,043). Tokom trogodišnjeg praćenja rezultata rangiranja, takođe je potvrđena pozitivna uzajamna veza između rezultata rangiranja zdravstvenih ustanova i obrazovanja iz upravljanja kvalitetom (ρS = -0,238; p = 0,017) i upravljanja ljudskim resursima (ρS = -0,234; p = 0,027). **Zaključak.** Pored obrazovanja iz oblasti upravljanja u zdravstvu, stalni rad na ličnom razvoju i jaka motivisanost doprinose unapređenju rezultata zdravstvenih ustanova.

Ključne reči:
zdravstvene ustanove; organizacija i upravljanje; motivacija; upitnici; kvalitet, kontrola; zdravstvena zaštita, obezbeđenje kvaliteta.

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Introduction

Healthcare has significantly changed for the last 50 years. It is still based on human potential and knowledge in medicine, but it greatly depends on new technologies and knowledge in the fields of economics and management. At the population level, the improvement of healthcare services in Serbia is significant in relation to the total transition environment, but still below the expected and satisfactory value [1]. Though insufficient, budgetary allocations for health care are decreasing, and the technological development does not meet the needs of the population. Citizens of Serbia slowly adopt healthy lifestyles, and have difficulties in accepting the inevitable narrowing of health insurance rights. In addition to financial capabilities, the effectiveness of healthcare facilities in such an intricate environment is increasingly determined by the abilities of managers to support and adapt to changes in the health care system and the society [2]. Competencies of successful managers include conceptual, technical and interpersonal skills [3]. Conceptual skills involve manager's ability to solve complex problems. Technical skills reflect the ability of a manager to achieve specific work tasks. Interpersonal skills allow a manager to communicate and cooperate well with other employees, regardless of whether it comes to colleagues, supervisors or subordinates. These are the reasons why managers of healthcare services need permanent updating of information, upgrading of skills and knowledge in different fields, as well as permanent personal development and motivation for these complex tasks.

The most of healthcare managers in the public sector of Serbia are clinicians ("hybrid managers") with little adequate professional management education and preparation for all the managerial duties. Despite these facts in the previous years some healthcare institutions showed good results in the annual rankings according to the quality improvement, conducted by the Institute of Public Health of Serbia. We assumed that except for the training in the field of management of health care institutions, a significant impact on better performances of those healthcare facilities could be the result of personal qualities and high motivation of their managers.

The aim of this paper was to analyze the opinions of experienced managers of primary healthcare centers (PHC) and general hospitals (GH) in Serbia, and to assess whether their opinions are confirmed by the success of institutions they govern. Particular attention is given to managers' motivation and their opinions on relevant personal traits, skills, and formal management education that have the potential to improve the performances of public healthcare facilities.

Methods

For the purposes of this paper, which was a part of the wider explorative study, we analyzed the statements of 97 top managers of 79 public health facilities (24 GHs and 55 PHCs) that were ranked in the annual rankings during a 3-year period, from 2008 to 2010. The data were collected in March and April 2013, by the questionnaire containing 30 questions. The questions were divided into 5 categories, formulated to provide the data about: healthcare facilities (kind, level, founder, size, and rank); manager's education, gender, position in the healthcare organization and the length of governing; personal views of managers on motivation for governance (we offered 5 potential motivating factors: striving to confirm their own organizational skills, the desire to improve functioning of the health institution, personal dissatisfaction with the way in which their predecessors performed the work, self-affirmation, and "some other personal reasons"); opinions of managers related to personality traits, skills, and formal education that are useful for good leadership in this field (What are the most valuable managers' personal traits? What profession can successfully manage a healthcare facility? How much they are willing to educate themselves formally in the field of management? Who should be teachers in healthcare management courses? Which form of knowledge transfer suits the managers in healthcare best? What training programs would be most appropriate?); opinions of managers on similarities and differences in managing healthcare and business organization; opinions about the differences between the functions of healthcare and business organization managers; opinions about major limiting factors for better management in healthcare services; opinions about differences between managers of successful and non-successful health care organizations.

In some questions, respondents were asked to rank the offered evidence by the degree of relevance, from 1 (highly significant) to 5 (not important), according the own knowledge and experience.

The attitudes respondents expressed through the questionnaire pointed to the managers' personal traits, skills and formal education in management that potentially affect health facilities management are considered as potential predictive factors for success. These factors were correlated with the official results of annual rankings, conducted by the Institute of Public Health of Serbia. Annual rankings use four groups of indicators – the quality of healthcare facilities, satisfaction with services provided, a professional satisfaction of employees in healthcare services and indicators relating to the education and training of employees. Annual ranking is the original methodology based on the estimation of the quality of work, stemmed from the initiative of the Commission for Improving the Quality of Work (the regulatory body of the Ministry of Health of the Republic of Serbia) [4]. In particular, as a measure of achieved performances of health facilities, we used the winning seats ("ranks") of healthcare institutions in the rankings conducted in 2008 [5], 2009 [6] and 2010 [7]. During this period, all of the respondents were in governing positions in healthcare organizations. For determining a possible relationship between the ranks and potential predictive factors for success, we used Pearson's or Spearman's rank correlation coefficient. Health institutions ranked in the upper third of the ranking tables were considered as "successful". The health institutions ranked in the middle third, and the last third of the tables were considered as "less successful" and "unsuccessful", respectively. The obtained data were systematized and analyzed by the Statistical Package for Social Sciences (SPSS).

Results

The general data about managers involved in this study (age, length of governing, gender, managers' positions in the healthcare institutions, number of PHCs' and GHs' managers and type of education in the field of management) are shown in Table 1. Among surveyed managers, 84.55% were executives of medical profession – physicians, dentists or pharmacists. The majority were medical doctors (78.35%). Managers with non-medical qualifications – economists and lawyers, were presented in a smaller percentage (9.27% and 6.18%, respectively).

The percentages of individual answers to motivation for governing are presented in Figure 1. The study confirmed the association between expressed leader's high motivation to improve the functioning of healthcare facility and institution's rank. The strongest correlations (Spearman's rank correlation coefficient – r_S) with respect to this item were found in the rankings after the first years of managers' mandates (r_S = 0.206; p = 0.048). Pearson's correlation has showed that the length of managers governing experience positively correlated with the institutions ranks in this research (r = -0.198; p = 0.043).

Assessment of opinions about competencies required for governing revealed that more than one-third (37.97%) of the respondents considered that for the successful leadership managers of healthcare facilities in the public sector need the same skills as business leaders. On the other hand, almost half (49.37%) of them do not agree with this statement. The managers also judged and evaluated the impacts of certain managerial skills that they considered as necessary for the successful management of healthcare facilities. According to the responds, the most essential skills for good managing results in health services are: the ability of managers to make decisions based on evidence, ability of prediction, and of good communication. In comparison with the mentioned skills, managers' capacities for adaptation and ability to work under pressure were valued as "less important skills" (Figure 2).

Table 1

Some of the characteristics of the surveyed group of healthcare managers

Parameters	n	%
Gender		
female	37	38.14
male	60	61.86
Position in the health care institution		
general manager	61	62.89
deputy manager	11	11.34
assistant manager	25	25.77
Mangers according the size of PHC centers		
small PHC (≤ 25,000 inhabitants)	17	17.54
medium PHC (25,000–50,000 inhabitants)	19	19.58
large PHC (≥ 50,000 inhabitants)	19	19.58
Total	55	56.70
Managers according the hospital size		
small (≤ 100,000 inhabitants)	18	18.54
large (≥ 100,000 inhabitants)	24	24.76
Total	42	43.30

PHC – primary healthcare centers.

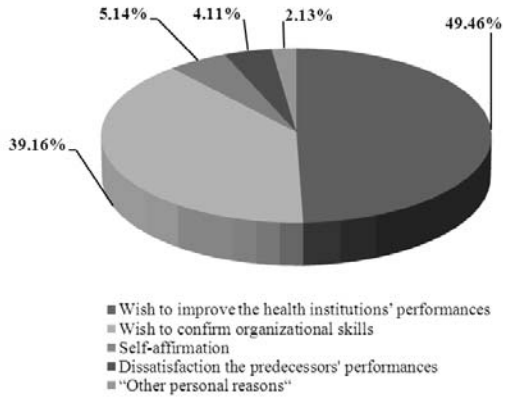

Fig. 1 – Individual answers about the motivation for governing.

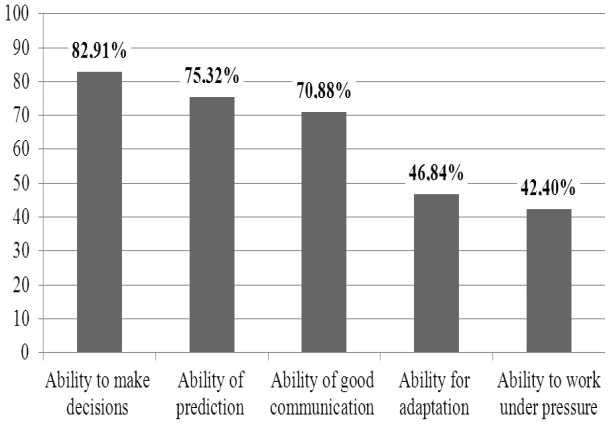

Fig. 2 – Managerial abilities considered necessary for successful management in healthcare facilities.

The dominant opinion among surveyed is that only a medically qualified person can successfully manage healthcare service (Figure 3).

The respondents estimated that responsibility (94.31%), consistency (84.83%) and ability to communicate well (74.68%) were the most important personal characteristics of successful managers in healthcare services. About two-thirds (65.83%) of the respondents believe that flexibility is not necessarily a characteristic of a successful director. Also, even 65.45% of the surveyed do not think that tolerance is an important characteristic of a successful healthcare service manager.

According to the attitudes of managers stated in the questionnaire, some factors (Figure 4) are essential for the success in managing healthcare institutions. These factors are tested by linear regression analysis, as a group of "selected predictors of success". Regression analysis confirmed that this group of selected predictors explains 36.72% of the variance in this sample of managers, and that the obtained model is statistically significant ($R2 = 0.367$; $p = 0.046$). In individual testing of performances of each of the factors of the "selected predictors of success", only the managers' abilities to organize the working process showed a statistically significant connection ($t = -2.453$; $p = 0.018$). Zero correlations of potential positive influence on health facilities performances were found for other enumerated factors (available human resources in the organization, teamwork, financial discipline and a political support for the manager).

The cumulative number of surveyed managers that attended courses dealing with management in healthcare facilities was 65 (67.01%) (Table 2).

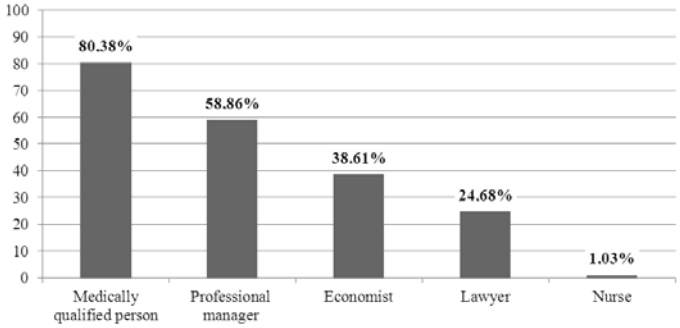

Fig. 3 – Managers' opinions on who is capable to manage the healthcare services.

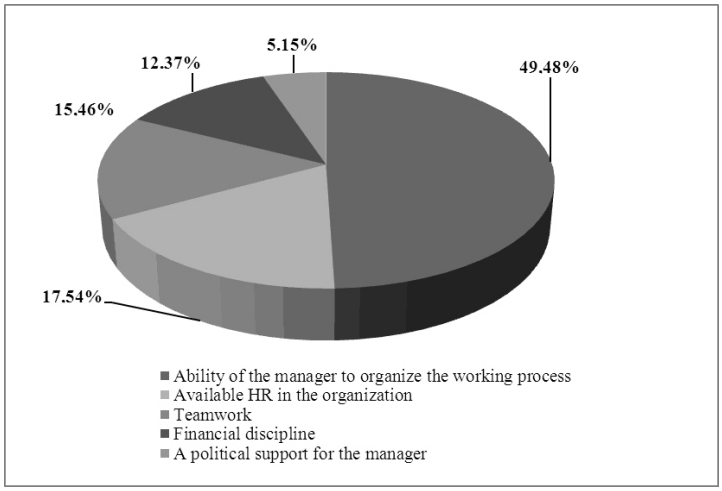

Fig. 4 – Managers' opinions on essential factors for successful governing. HR – human resources.

Table 2

Number of surveyed managers who attended management courses and their opinions about the applicability of some programs

Program	n (%)	HRM	QM	SP	FM
MH	31 (32.96)	31	5	31	31
FOS	5 (5.15)	–	5	5	5
SM	20 (20.62)	20	–	20	20
FBS	9 (9.28)	9	9	–	9
Score	65 (67.01)	59	19	56	65
Applicable for, n (%)		53 (89.83)	17 (89.47)	50 (89.28)	53 (72.31)

MH – specialized courses for hospital managers, Ministry of Health of Serbia; FOS – Faculty of Organizational Sciences, postgraduate course; SM – School of Medicine, Belgrade University, accredited postgraduate course; FBS – Faculty of Business Studies, Megatrend University, accredited postgraduate course; HRM – Human resource management program; QM – Quality management program; SP – Strategic planning program; FM – Financial management program.

According to the personal experience of educated managers, they gained the most applicable knowledge from the programs of human resources management (HRM) – 89.83%, quality management (QM) – 89.47%, strategic planning (SP) – 89.28%, and financial management (FM) – 72.31 (Table 2). A statistically significant positive correlation was found between managers' education in the field of HRM and institutions rank in all three rankings. It means that those facilities whose managers stated that the courses of HRM were very applicable had better rankings than the institutions whose managers did not. The facilities whose managers found the QM program most useful in practice also had better rankings than those institutions whose managers had no such experience (Table 3).

Discussion

Due to the significant influence of healthcare managers on functioning of public healthcare facilities, most of the researchers take into account their experience and opinions. On the other hand, some authors suggest that the observation in this field should be more objective [8]. They point out that observation can generate a partially independent researcher's view, based on the experiences that the respondents drew on to construct their realities [9]. The combination of mentioned approaches would certainly be the most useful one for objective consideration and improvement of management in the field of healthcare in the public sector.

The professional background determines the influence strategies that managers use in healthcare. It may be both a resource and a constraint [10]. According to this survey, the most managers of GHs and PHCs in Serbia are not professional managers, but medical doctors. Initially, they had little knowledge about management in healthcare services. They acquire the managerial knowledge and skills mainly through work in the governing positions. The vast majority of the respondents in this survey believed that clinicians can be the best top managers in healthcare services. This statement is not surprising because most of the responders were medical doctors. However, some of them accepted the fact that a health institution can be successfully run by a non-medical professional manager, lawyer, economist, and even – a nurse.

In Europe, the proportion of top hospital managers with clinical expertise varies from country to country. Managers with clinical degrees run approximately 93% of hospitals in Sweden, 71% in Germany, 64% in France, and 58% in the United Kingdom [11]. According to this survey, there was a strong relationship between an increase in the number of managers with a clinical degree and an improvement in organization's management score. The authors indicate that managers with clinical expertise may have a deeper insight into clinical challenges, better communication with clinical staff in a language they understand and enjoy credibility that non-clinicians rarely achieve. However, these facts do not mean that doctors are fully competent to manage medical facilities.

In a qualitative study made in Australian public hospitals in 2003, the interactive interviews of healthcare managers showed that they supported the hybridized configurations of leadership in public hospitals [12]. The terms "hybrid leadership" and "hybrid management" have been used to describe managers who combine a professional medical background with managerial skills and responsibilities [13]. Some other studies suggest that it is not possible to predict what the impact of leadership concept is likely to be on health services in the future or on those who provide the services [14]. Professional roles and influence strategies should be a significant theme in leadership development programs for health care professionals [15].

There are not enough accurate data about the motivation of managers for taking the responsibility for health institutions' governance in the public sector. The term "motivation" in the available literature usually relates to the managers' impacts on staff and offenders to work better. It deals with

Table 3

Correlation between managers' education in human resource management program (HRM) and quality management program (QM) with the institutions' ranks in the period 2008-2010

Year	HRM education v.s. rank	QM education v.s.rank
2008		
correlation coefficient (Spearman's rho)	-0.275	-0.208
sig. (2-tailed)	0.046	0.046
number of healthcare facilities ranked in the Annual ranking 2008	49	49
2009		
correlation coefficient (Spearman's rho)	-0.292	-0.279
sig. (2-tailed)	0.005	0.007
number of healthcare facilities ranked in the Annual ranking 2009	49	49
2010		
correlation coefficient (Spearman's rho)	-0.234	-0.238
sig. (2-tailed)	0.027	0.017
number of healthcare facilities ranked in the Annual ranking 2010*	47*	47*

***Due to the consequences of earthquakes in Kraljevo (2010) the General Hospital and primary healthcare centers (PHC) in Kraljevo did not participate in the an-**

the ways in which managers encourage assistants and other employees to contribute to organization to achieve its goals. Motivation is also connected with the ways in which managers at various levels of organization motivate their associates and other employees to work to achieve their personal goals [16]. Managerial positions in the public health services in Serbia are relatively poorly financially evaluated in comparison to the wages of doctors. This study proceeded from the assumption that the non-pecuniary compensations are of a particular influence on why physicians replace their profession usually with a dual position of "hybrid manager". It confirmed an assumption that managers of healthcare facilities were mostly driven by a desire to affirm their organizational potentials and to improve the functioning of health institutions.

As with business leaders and other organizations, there are some features of individuals that can help defining who the good managers of healthcare facilities are. These qualities can be character traits (commitment, personal beliefs, analytical thinking, and self-awareness), but they can also be developed like motivation and education [17]. In this study, we proved that public health institutions managed by directors whose primary motivation was the improvement of health facility functioning showed better results in rankings than healthcare services run by leaders whose main motivation was dissatisfaction with results of their predecessors. The results in annual rankings were also good for those managers who were led by self-assertion or the other personal reasons.

The correlations between a manager's motivation and institution's rank were mainly registered in the first year of directors' mandates. In the latter rankings, the direction of the association was positive, but the correlation was not proven. These findings can be explained by assuming that the managers are more motivated in the first years of their mandates. Motivation increases their activities, and they find ways to solve problems. Practice experience has shown that over the time and by facing many problems in the public healthcare sector, the managers' motivation is getting weaker. A higher impact on management outputs in the following years of governing have other factors, such as working experience, practical knowledge, skills, and talents.

Of all the tested predictors of health services' progress in this study (manager's ability to organize the working process; available human resources in the health care institution; importance of financial discipline; teamwork and political support for management), only the "managers' abilities for organizing the working process" had statistical significance. This result means that GHs and PHCs whose managers recognized that the success of health institution depends on managers' abilities to organize the working process had better ranks than those managers who did not recognize it as the most important. The other tested factors mentioned above were not proved to influence the health facilities' performances. These results point to the weakness of the health care system, poor organization and lack of regulation of the system. In the well-organized healthcare systems, personal qualities and attitudes of managers should not predominantly affect the quality of health care facilities, but formal education, continuous training and development of skills that are necessary to perform management functions.

A positive correlation between the length of time that a manager has spent in a managerial position and better institution ranking may derive a logical conclusion that the accumulation of manager's experience reflects the success of the healthcare institution. A statistically significant positive correlation can be interpreted in the opposite direction, that is, the performance of the manager of the health institution "extends the time" of its mandate. In any case, there is a positive and significant correlation of greater experience in management positions with better healthcare facility ranking.

Practice has shown that there are no reliable ways to train the proper healthcare managers. Modern management courses usually suggest to leaders in healthcare to achieve their maximal potentials and to direct resources towards everything that will make their facilities achieve better results. Development of adequate postgraduate management programs for managers of public healthcare services started in Serbia in 2006, through the "Serbia Health Project" of the Ministry of Health. The World Bank financially and technically supported it [18]. In cooperation with the Chamber of HealthCare Institutions of Serbia, within the "Serbia Health Project – Additional Financing", planned activities were also directed towards supporting the improvement of healthcare management. The project also intended to promote the improvement of the legal framework in all the areas where project activities were taking place, as a necessary precondition for the reform of management [19]. Both courses had different curricula, but they mainly focused on the development of management skills that are necessary for training healthcare managers for complex tasks imposed by the health system reform – strategic planning, human resource management, quality management, financial management.

Accredited one-year postgraduate programs started later, in 2009, at the School of Medicine (SM) of the University of Belgrade, as master studies "Management in the healthcare system", through the "Serbia Health Project – Additional Financing" [18] and "The Training in Health Service Management in Serbia" [19] of the Ministry of Health. The specialized academic studies "Management of the healthcare facilities" started the same year at the Faculty of Business Studies of the Megatrend University (FBS). The curricula of both postgraduate programs cover all the areas of management, from health economics, management of finances, through strategic planning and development in the health care system, to HRM, organizational behavior, and QM in healthcare.

Better healthcare services performances in this study were associated with managers' education in the field of HRM and QM, no matter what educational program they attended. This fact suggests that in these areas the educational programs were well programmed and adapted to the needs of the healthcare system in transition. On the other hand, although a great percent of surveys stated that the strategic planning and financial management programs were very applicable, we did not find a significant association with the management success in respect of these items.

Conclusion

Healthcare facilities of the public sector in Serbia became complex organizational and technical systems in the healthcare system with many weaknesses. In that intricate surrounding, their managers have to develop skills in the planned and systematic way – through the formal education and regular training for the responsible tasks they perform. Though the current management programs are still under development in Serbia, this study shows that they have positive influences on better performances in health care, together with the permanent personal development and higher motivations of managers. However, there is the need for evaluation and development of curricula of existing management courses and postgraduate programs. Their quality and applicability could be of particular importance for maintaining and improving the healthcare system. Introducing continuing education in this area and the appropriate licensing of managers for healthcare should also become a real challenge to health authorities in the future.

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Markers of inflammation as risk predictors of lethal outcome in patients diagnosed with delirium

Markeri zapaljenja kao prediktori smrtnog ishoda kod bolesnika sa dijagnozom delirijuma

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Abstract

Background/Aim. Delirium is an acute or subacute, and most frequently reversible syndrome of higher cortical functions disturbances that is manifested as generalized disorder. If not prevented, it is associated with various adverse outcomes. The aim of this study was to determine the connection between the markers of inflammation and lethal outcome in patients diagnosed with delirium, hospitalized in the psychiatric intensive care unit. **Methods.** This retrospective study included 120 patients hospitalized in the psychiatric intensive care unit in whom examination of differences in inflammation markers was done. The examinees have been divided into two groups: the case group of 40 patients who died during the hospitalization, and the control group of 80 examinees who were discharged with the diagnosis *Post delirium status*. The following variables were taken into account: age, gender, clinical diagnosis of infection (pneumonia and urinary tract infection), laboratory parameters (total of white blood cells, granulocytes, monocytes, C-reactive protein − CRP) and type of delirium (withdrawal or organic). **Results.** The average age of the patients was 50.3 ± 13.1 years. The patients who survived delirium, were on the average 10.5 years younger than the deceased ($p < 0.001$). More than half (57.5%) of the deceased had pneumonia. There was a statistically significant correlation between pneumonia and lethal outcome in the patients with delirium ($p < 0.001$). The examinees with lethal outcome had significantly higher median CRP levels than the group of examinees who survived (75.6% ± 54.0 *vs* 30.3 ± 42.5 ng/L, $p < 0.001$). **Conclusion.** Aiming to better and more precise diagnostics of this complicated and still unclear neuropsychiatric syndrome it would be useful to consider introduction of more precise diagnostic algorithms in every unit of intensive care. That would significantly reduce the number of delirium diagnosis overlook, decrease complication of clinical features and would also reduce the unfavorable outcome rate, therefore the total cost of treatment.

Key words:
delirium; intensive care units; inflammation; biological markers; c-reactive protein; prognosis.

Apstrakt

Uvod/Cilj. Delirijum je akutni ili subakutni, najčešće reverzibilni sindrom oštećenja viših kortikalnih funkcija, koji se ispoljava kao generalizovani poremećaj. Ako se ne spreči, povezan je sa mnogostrukim i brzim lošim ishodima. Cilj ovog istraživanja bio je da se ispita povezanost markera zapaljenja i smrtnog ishoda kod bolesnika sa dijagnozom delirijuma, hospitalizovanih u jedinici intenzivne psihijatrijske nege. **Metode.** Retrospektivnom studijom obuhvaćeno je 120 bolesnika lečenih u jedinici intenzivne psihijatrijske nege pod dijagnozom delirijuma kod kojih je sprovedeno istraživanje razlika markera inflamacije. Ispitanici su bili podeljeni u dve grupe: grupu koju je činilo 40 bolesnika umrlih za vreme bolničkog lečenja, i kontrolnu grupu od 80 preživelih ispitanika koji su otpušteni pod dijagnozom „stanje posle delirijuma". Praćene su sledeće varijable: starost, pol, klinička dijagnoza infekcije (pneumonija i urinarna infekcija), laboratorijski parametri (ukupni leukociti, granulociti, monociti, C-reaktivni protein − CRP) i tip delirijuma (apstinencijalni ili organski). **Rezultati.** Prosečna starost ispitanika iznosila je 50,3 ± 13,1 godina. Bolesnici koji su preživeli delirijum bili su prosečno 10,5 godina mlađi od umrlih ($p < 0,001$). Više od polovine umrlih bolesnika (57,5%) imalo je pneumoniju. Utvrđena je statistički značajna povezanost pneumonije i smrtnog ishoda kod bolesnika sa deliri-

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jumom ($p < 0,001$). U grupi umrlih bolesnika, srednja vrednosti CRP-a bila je statistički značajno veća od vrednosti CRP u grupi preživelih (75,6 ± 54,0 *vs* 30,3 ± 42,5 ng/L, $p < 0,001$). **Zaključak.** U cilju bolje i preciznije dijagnostike ovog komplikovanog i još uvek nejasnog neuropsihijatrijskog sindroma, bilo bi korisno razmotriti uvođenje jasnog dijagnostičkog algoritma u svim jedinicama intenzivne nege. To bi moglo znatno smanjiti broj previda delirijuma, odnosno komplikovanje kliničke slike, stopu loših ishoda, a samim tim i ukupne troškove lečenja.

Ključne reči:
delirijum; intenzivna nega, odeljenja; zapaljenje; biološki pokazatelji; c-reaktivni protein; prognoza.

Introduction

Delirium is an acute or subacute, and usually reversible syndrome of higher cortical functions disturbances, manifested as generalized disorder [1]. Its cardinal symptom is attention disorder (includes distractibility, reduced vigilance and tenacity) as well as disturbances of consciousness, predominantly of space orientation. Additional symptoms – disorders of thought, sleep-wake cycle, perception, affect and motor behavior, amend this complex neuropsychiatric syndrome of acute onset and fluctuating course. If not prevented, delirium is associated with multiple and rapid unfavorable outcomes, including the higher risk of institutionalization, as well as of functional deterioration, dementia and death [2]. Contemporary scientific knowledge explains the pathogenesis of delirium by the neurotransmitter imbalance (dopamine, norepinephrine, acetylcholine, serotonin) at the central level, as well as by amino acids level changes, oxidative stress and inflammation [3].

Current studies show a connection between the increase of C-reactive protein (CRP) and interleukin 6 (IL-6) levels on the one hand, and the delirium incidence in postoperative course of surgical patients, on the other hand. These biomarkers could be general indicators of the complex inflammation process that causes delirium. CRP could stimulate series of reactions that lead to the increase of permeability of blood-brain barrier which results in neuronal dysfunction that can be manifested with delirium [3].

A number of meta-analysis find that the prolonged increase of CRP is associated with the increase of mortality rate. Patients in intensive care with high CRP levels have more serious organic dysfunction, longer hospitalization in intensive care unit, and higher mortality rate than patients in intensive care unit with normal CRP blood levels [4, 5]. However, association between CRP and delirium was not yet been proven. Only a few pilot studies have addressed this relation, so far [6]. The first study published in 2007, investigating the relation of CRP level and delirium, found high levels of CRP as a predictor of delirium [7]. Similar results were published in the following years, concluding that control of the blood CRP level can be very effective in prevention and reduction of cost of delirium in the intensive care unit [6, 8].

Considering the exceptional expansion of studies with delirium as a topic in the last ten years, it is expected that soon very complex and heterogeneous pathogenesis of this syndrome will be additionally clarified. The answer to intriguing question on relationship between infection and inflammation syndrome in a seriously ill patient with rapid onset of delirium, its complicated course and general neuronal dysfunction (which today is still described as delirium), could contribute a lot in the field of unfavorable outcome prevention.

The aim of this study was to examine the relation between the markers of inflammation and lethal outcome in patients diagnosed with delirium and hospitalized in the intensive psychiatric care unit.

Methods

In this clinical observational case-control study, the examined group comprised of all inpatients diagnosed with delirium in the period from January 1st 2010 to June 30th 2013 at the Clinic for Psychiatric Disorders "Dr Laza Lazarević", Belgrade, treated in the psychiatric intensive care unit of the Department for Urgent Psychiatry. The examinees were recruited by the consecutive sampling method. The sample was divided into two groups: the case group of the deceased, and the control group of examinees, discharged with the diagnosis "post delirium status".

Delirium was diagnosed according to the criteria of the currently valid International Classification of Diseases (ICD10) and included diagnostic categories F05, F10.4 and F19.4. The sample included adult patients previously examined or treated in other institutions, or previously treated in other departments, as well as the patients first examined in the Clinic for Psychiatric Disorders "Dr Laza Lazarević". The day of admission in the intensive care unit was considered as the first hospital day, disregarding if the patient was previously hospitalized in another institution and diagnosed with other psychiatric disorder.

Patients diagnosed with cancer or other forms of malignity, and those in a postoperative course during the observed period, were excluded from the study.

The group of the deceased was compared with the group of the survived. The following variables were compared: age, gender, clinical diagnosis of infection (pneumonia and urinary tract infection), laboratory parameters (total of white blood cells, granulocytes, monocytes, CRP, erythrocyte sedimentation rate) and the type of delirium (withdrawal or organic delirium). Laboratory parameters taken into consideration were the result of laboratory analysis taken at time when the diagnosis of delirium was suspected.

The data were obtained from the electronic medical records (patients' history, mental status, course of the disease, laboratory analyses). For statistical analysis of the data SPSS (Statistical package for the social sciences) version 22 was used. The data were presented by classical methods of descriptive statistics (arithmetic mean and standard deviation, median and interquartile range, absolute and relative frequencies), and were analyzed using parametric (Student *t*-

test), or nonparametric methods of inferential statistics (Mann-Whitney U-test, Pearson χ^2-test), depending on the nature and distribution of observed characteristics. The normality of distribution of continuous numerical characteristics was examined by inspection of histograms, quintile diagrams and was formally tested by Kolmogorov – Smirnov test. The logistic regression method was used for analysis of relation of binary outcomes and potential predictors.

Results

The study included 120 patients, the average age of 50.3 ± 13.1 years. Men were predominant (80.8%). Those who survived delirium were 10.5 years younger on the average (confidence interval − CI 95% 5.8 to 15.2) than patients with lethal outcome. This difference was statistically significant ($t = 4.462$, df = 118, $p < 0.001$). Frequency of lethal outcomes did not differ significantly between the genders ($\chi^2 = 2.689$, df = 1, $p = 0.101$) (Table 1).

In the group of the survived 16.3% developed pneumonia, in comparison to 57.5% in the group of patients with lethal outcome. There was a statistically significant relation between pneumonia and lethal outcome in the patients diagnosed with delirium ($\chi^2 = 21.607$, df = 1, $p < 0.001$). The patients with urinary tract infection had similar mortality rate (35% patients who survived and 37.5% who died had urinary infection, $\chi^2 = 0.072$, df = 1, $p = 0.788$).

In the group of patients with delirium as part of the withdrawal syndrome 20.2% died, whereas in the group with delirium caused by other reasons 63.9% of the examinees died. In the group of the survived 83.75% had withdrawal syndrome, in comparison to 42.5% in the group of those with lethal outcome. There was a statistically significant correlation between etiology of delirium and lethal outcome ($\chi^2 = 21.607$, df = 1, $p < 0.001$).

The mean of total leukocyte count in the group of the survived was 9.7×10^9/L ± 4.3×10^9/L, while the leukocyte mean level in the group who did not survive was 11.9×10^9/L ± 5.6×10^9/L. The examinees with lethal outcome had a significantly higher number of white blood cells ($Z_U = -2.45$, $p = 0.014$) and granulocytes ($t = 4.976$; $p < 0.001$), but significantly lower values of monocytes ($t = 4.038$; $p < 0.001$) and lymphocytes ($t = 4.903$; $p < 0.001$).

The mean CRP levels in those who survived were 30.3 ± 42.5 ng/L, whereas in the diseased they were 75.6 ± 54.0 ng/L. There was a statistically significant difference in the median CRP levels ($Z_U = 5.328$; $p < 0.001$). Those with lethal outcome had significantly higher median CRP levels.

Table 2 shows regression coefficient of bivariate logistic regression analysis. Statistically significant predictors of lethal outcome in bivariate logistic regression models were age, pneumonia, number of white blood cells, portion of granulocytes in leukocyte formula, as well as CRP concentration. A portion of lymphocytes and a portion of monocytes were protective factors.

Table 3 presents regression coefficient of the final logistic multivariate regression model including predictors: age, pneumonia and CRP. Counts of white blood cells, granulocyte, lymphocyte and monocyte portions were not included in the final model, since after the introduction of CRP as predictor these variables did not contribute significantly to the predictive power of the model. From statistical point of view, this model had significantly higher predictive power comparing to the null model ($\chi^2 = 28.298$, df = 3, $p < 0.001$, pseudo-R2Cox-Snell = 0.331) and could accurately classify 80% of cases (comparing to 66.7 in null model).

Table 1

Characteristics and treatment outcomes of patients with delirium

Variables	Patients (n = 120)		Statistics			
	survived (n = 80)	deceased (n = 40)	T	χ^2	Z_U	p
Age (years), x̄ ± SD	46.8 ± 11.6	57.3 ± 13.2	4.462			< 0.001
Gender, n (%)						
female	12 (15)	11 (27.5)		2.689		0.101
male	68 (85)	29 (72.5)				
Pneumonia, n (%)	13 (16.3)	23 (57.5)		21.607		< 0.001
Urinary infection, n (%)	28 (35)	15 (37.5)		0.072		0.788
Total leukocytes, x̄ ± SD *3.5−10 $\times 10^9$/L	9.7 ± 4.3	11.9 ± 5.6			-2.45	0.014
CRP, x̄ ± SD, *0−5 ng/L	30.3 ± 42.5	75.6 ± 54.0			5.328	< 0.001
Granulocytes, x̄ ± SD *43.0−76.0%	75.7 ± 8.9	84.3 ± 8.9	4.976			< 0.001
Monocytes, x̄ ± SD *4.3−10.0%	5.7 ± 2.1	4.0 ± 2.1	4.038			< 0.001
Limphocytes, x̄ ± SD *17.0−48.0%	18.7 ± 7.5	11.7 ± 7.0	4.903			< 0.001
Type of delirium, n (%)						
withdrawal	67 (83.7)	17 (42.5)		21.607		< 0.001
organic	13 (16.3)	23 (57.5)				

***Interval of reference values of laboratory parameters; CRP – C-reactive protein; x̄ – arithmetic mean; SD – standard deviation.**

Table 2

Bivariate logistic regression model of significant predictors of lethal outcome

Predictors	B	SE(B)	*p*	OR	CI 95% (OR)	
Age	0.074	0.019	< 0.001	1.077	1.037	1.119
Pneumonia	1.942	0.441	< 0.001	6.973	2.940	16.538
Leukocytes	0.093	0.042	0.026	1.098	1.011	1.192
Granulocytes	0.113	0.027	< 0.001	1.119	1.062	1.180
Lymphocytes	-0.139	0.034	< 0.001	0.871	0.815	0.930
Monocytes	-0.380	0.105	< 0.001	0.684	0.556	0.841
CRP	0.018	0.004	< 0.001	1.019	1.010	1.028

CRP – C-reactive protein; B – coefficient for usefulness of predictors; SE – standard error; OR – the ratio-change in the odds of the event of interest for a one-unit change in the predictor; CI 95% – confidence interval for 95%.

Table 3

Regression coefficient of final logistic multivariate regression model of predictors of lethal outcome

Predictors	B	SE(B)	*p*	OR	CI 95% (OR)	
Age	0.080	0.022	< 0.001	1.083	1.037	1.131
Pneumonia	1.916	0.552	0.001	6.793	2.304	20.028
CRP	0.013	0.005	0.012	1.013	1.003	1.023

For abbreviations see under Table 2.

It is evident, in the patients diagnosed with delirium that every year of age increases lethal outcome rate for 8.3% when it is controlled for other factors in the model. Pneumonia increases the risk for lethal outcome 6.8 times when controlled for other factors. For any increase in CRP by 1 mg/L the risk for lethal outcome in delirium diagnosed patients increases for 1.3% when controlled for other factors.

Discussion

In the currently available literature, so far there has not been studies especially examining leading risk factors for mortality of patients with delirium. Previous studies mostly investigated mortality of patients with delirium within certain diagnostic categories.

This study took into consideration age, gender, the type of delirium and markers of inflammation as risk factors for mortality of patients diagnosed with delirium in an intensive psychiatric care unit.

In the year 2013 Zhang et al. [9] published results of meta-analysis of delirium treatment outcomes in inpatients treated in the intensive care unit. Meta-analysis included 14 studies in which the data on mortality were found. Nine studies [10–18] showed the significant relation between delirium and mortality. The increase of mortality in these studies was controlled by the increase of age and seriousness of illness, including infections. The first European report [19] on mortality risk factors in the intensive care units was also published in the year 2013. This study confirmed the significant relation between delirium and mortality rate defining delirium as an independent risk factor for unfavorable outcome (institutionalization and death) during one month period of follow up.

Our study also showed that older and more seriously ill patients diagnosed with delirium die more frequently, but having in mind that patients in this study were, on the average, significantly younger than the patients in studies whose results we compared with ours. The reason is probably that studied patients were hospitalized in the psychiatric institution or already previously treated for some psychiatric disorder. Namely, the previous psychiatric disorder created base for development of delirium in the context of reduced cerebral reserve. Delirium itself is the result of interaction between precipitating factors and acute illnesses added to vulnerability. Higher age directly determines the degree of vulnerability of an individual. That is to say that the level of dependence and comorbidity increases with age [20]. Patients with worse premorbid functional status who develop delirium die significantly more frequently, *ie* delirium directly or indirectly converts vulnerability to unfavorable outcome [2]. The seriousness of illness makes a significant influence on mortality rate in patients with delirium [18, 21, 22]. In contrast to most of authors who tried to measure the seriousness of illness with indexes, this was not possible in our study due to the study design (the data were obtained retrospectively).

In our study, the inflammation syndrome is considered as a potential risk factor for death. Clinical and laboratory markers of inflammation are individually analyzed.

Pneumonia is a frequent disease being a cause of more than one million hospitalizations *per* year in the USA. In this country it is the ninth leading cause of death [23]. It is clinically characterized by a group of signs and symptoms that can vary intensively. Having this in mind, the diagnosis of pneumonia itself can be doubtful and difficult. Although it has very clear respiratory symptoms and marks, pneumonia may have totally atypical clinical course as well, without elevated body temperature, typical respiratory sounds or typical radiologic findings. This occurs most frequently in older people who also have high mortality rates of pneumonia, precisely

for lacking of accurate diagnosis [24]. For this group of patients it is very characteristic that pneumonia is manifested with clinical features of delirium only [25].

In our study, when the presence of pneumonia is taken in consideration, every year of age increases the risk of lethal outcome in patients with delirium for 8.3%. The presence of pneumonia in patients with delirium increases the risk for lethal outcome almost seven times after controlling for age and CRP blood level.

The results of the study by Calle et al. [24] carried out in geriatric intensive care unit, published in 2014, show that the mortality of people with pneumonia is significantly higher if they develop delirium. This rate increases significantly when the variable of consciences disorders is included in the model, and this is explained by the presence of hypoactive form of delirium that often remains unrecognized, and therefore consequently inadequately treated [26–28].

CRP levels as well as total of white blood cells and granulocytes were significantly higher in deceased patients compared to those who survived delirium. This confirms results of previous studies [4, 29, 30]. In other words, elevated level of CRP and granulocytes are significantly correlated to infection, inflammation response and mortality rate in patients with delirium in the intensive care. However, in the logistic multivariate model of prediction the CRP level and granulocytes have no value as lethal outcome predictors. In this model they are overridden by pneumonia. After being controlled for age and other factors in the model, the elements of leukocyte formula do not significantly contribute to prediction in the multivariate regression model. When controlled for age, CRP is a statistically significant predictor of lethal outcome, but only in patients without pneumonia. Every increase in CRP level by 1 mg/L increases the risk for lethal outcome for 1.3%. In patients with pneumonia, after controlling for age, the CRP does not contribute significantly to predictive power of multivariate regression model. CRP is a significant predictor of lethal outcome only in patients with no pneumonia, and this points to possible role of CRP as a predictor of lethal outcome in other diseases. CRP is significantly correlated with elevated risk for myocardial infarction and sudden cardiac death in seriously ill patients [31] as well as with acute renal failure in patients before dialysis [32], and as such could be valid early marker of morbidity and mortality in patients having multiple organ damages. Some future studies should yet clarify the role of CRP in prediction of lethal outcome in infective syndromes, but with look upon other markers as well, such are procalcitonin and Il-6 (3.29 pg/mL).

Delirium is a syndrome that can be prevented in 30–40% of cases [33]. High mortality rates are consequences of frequent overlooking of this diagnosis, especially in hypoactive form. In any case, the British guidance which states that every sudden change of behavior and mental status in both psychiatric patients and those who are not is considered delirium, until proven otherwise, seems useful [1]. According to that concept, in patients with such changes, as well as in patients clearly diagnosed with delirium, it would be useful to conduct comprehensive diagnostic procedures in order to exclude pneumonia or some other infective syndrome, renal and cardiac failure. Etiologic treatment would help to avoid complications of delirium and would also help to prevent bad outcomes such as institutionalization, cognitive deterioration and high mortality of patients with delirium. In this way, the number of days spent in a hospital, patients' personal characteristics, as well as overall costs of treatment that are in charge of health insurance would be significantly reduced. In our country these costs have never been estimated; The data from the USA could serve as an illustration, where costs go from 164 billion dollars *per* year [34], or over 182 billion dollars in eighteen European countries together [35, 36].

The limitation of our study is its retrospective design, which excluded the possibility to consider some significant variables (procalcitonin, Il–6…).

Another limitation could be heterogeneity of the sample (withdrawal deliriums were also included in the study).

Conclusion

Aiming to better and more precise diagnostics of this complicated and still unclear neuropsychiatric syndrome it would be useful to consider introduction of more precise diagnostics in every unit of intensive care. That would significantly reduce the number of delirium diagnosis overlook, especially of hypoactive forms, decrease complication of clinical features and would also reduce the unfavorable outcome rate, therefore consequently the total cost of treatment.

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Gender-related differences in clinical presentation, electrocardiography signs, laboratory markers and outcome in patients with acute pulmonary embolism

Polne razlike u kliničkoj prezentaciji, elektrokardiografskim znacima, laboratorijskim markerima i ishodu kod bolesnika sa akutnom embolijom pluća

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Abstract

Background/Aim. Acute pulmonary embolism (PE) is a potentially life threating event, but there are scarce data about gender-related differences in this condition. The aim of this study was to identify gender-specific differences in clinical presentation, the diagnosis and outcome between male and female patients with PE. **Methods.** We analysed the data of 144 consecutive patients with PE (50% women) and compared female and male patients regarding clinical presentation, electrocardiography (ECG) signs, basic laboratory markers and six-month outcome. All the patients confirmed PE by visualized thrombus on the multidetector computed tomography with pulmonary angiography (MDCT-PA), ECG and echocardiographic examination at admission. **Results.** Compared to the men, the women were older and a larger proportion of them was in the third tertile of age (66.0% *vs* 34.0%, $p = 0.008$). In univariate analysis the men more often had hemoptysis [OR (95% CI) 3.75 (1.16–12.11)], chest pain [OR (95% CI) 3.31 (1.57–7.00)] febrile state [OR (95% CI) 2.41 (1.12–5.22)] and pneumonia at PE presentation [OR (95% CI) 3.40 (1.25–9.22)] and less likely had heart decompensation early in the course of the disease [OR (95%CI) 0.48 (0.24–0.97)]. In the multivariate analysis a significant difference in the rate of pneumonia and acute heart failure between genders disappeared due to strong influence of age. There was no significant difference in the occurrence of typical ECG signs for PE between the genders. Women had higher level of admission glycaemia [7.7 mmol/L (5.5–8.2 mmol/L) *vs* 6.9 mmol/L (6.3–9.6 mmol/L), $p = 0.006$] and total number of leukocytes [10.5×10^9/L (8.8—12.7 $\times 10^9$/L *vs* 8.7 × 109/L (7.0–11.6 $\times 10^9$/L)), $p = 0.007$]. There was a trend toward higher plasma level of brain natriuretic peptide in women compared to men 127.1 pg/mL (55.0–484.0 pg/mL), $p = 0.092$] *vs* [90.3 pg/mL (39.2–308.5 pg/mL). The main 6-month outcomes, death and major bleeding, had similar frequencies in both sexes. **Conclusion.** There are several important differences between men and women in the clinical presentation of PE and basic laboratory findings which can influence the diagnosis and treatment of PE.

Key words:
pulmonary embolism; sex factors; risk factors; signs and symptoms; diagnostic techniques and procedures; electrocardiography; treatment outcome.

Apstrakt

Uvod/Cilj. Akutna plućna embolija (PE) potencijalno je životnougrožavajuće stanje. Podaci u razlikama među polovima u tom stanju oskudni su. Cilj rada bio je da se identifikuju razlike između polova u pogledu kliničke prezentacije, dijagnostičke specifičnosti i ishoda PE. **Metode.** Analizirali smo podatke o 144 uzastopna bolesnika sa PE (50% žene) i uporedili muškarce i žene s obzirom na kliničke prezentacije, elektrokardiografske (EKG) znakove, osnovne laboratorijske markere i šestomesečni ishod. Svi bolesnici su imali potvrđen PE na multislajsnoj kompjuterizovanoj tomografiji sa plućnom angiografijom (MSCT-PA), EKG-u i ehokardiografskoj dijagnostici na prijemu. **Rezultati.** U poređenju sa muškarcima, žene su bile starije i većinom u trećem tercilu životnog doba (66,0% *vs* 34,0%; $p = 0,008$). Univarijantna analiza pokazala je da su kod muškaraca na prijemu hemoptizije bile učestalije nego kod žena [OR (95% CI) 3,75 (1,16–12,11)], kao i bol u grudima [OR (95% CI) 3,31 (1,57–7,00)], febrilno stanje [OR (95% CI) 2,41 (1,12–5,22)] i pneumonija [OR (95% CI) 3,40 (1,25–9,22)], a manje verovatna bila je srčana dekompenzacija u ranoj fazi bolesti [OR (95% CI) 0.48 (0.24–0.97)]. Nije bilo značajnih razlika između polova u pojavi tipičnih EKG znakova za PE. Žene su imale viši nivo glikemije na prijemu [7.7 mmol/L (5.5–8.2 mmol/L) *vs* 6.9 mmol/L (6.3–9.6 mmol/L), $p =$

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0.006] i veći ukupni broj leukocita [10.5 × 10^9/L (8.8–12.7 × 10^9/L) *vs* 8.7 × 10^9/L (7.0–11.6 × 10^9/L), p = 0.0 07] kao i trend ka višem nivou B-tip natriuretskog peptida u plazmi 127.1 pg/mL (55.0–484.0 pg/mL) *vs* [90.3 pg/mL (39.2–308.5 pg/ml), p = 0.092]. Krvarenje i smrt, najvažniji šestomesečni ishodi, bili su ravnopravno zastupljeni među polovima. **Zaključak.** Postoji nekoliko važnih razlika između muškaraca i žena u pogledu kliničke prezentacije i laboratorijskih nalaza karakterističnih za PE, koji mogu uticati na njenu dijagnostiku i lečenje PE.

Ključne reči:
pluća, embolija; pol, faktor; faktori rizika; znaci i simptomi; dijagnostičke tehnike i procedure; elektrokardiografija, lečenje, ishod.

Introduction

A lot of investigation was conducted to study difference in the distribution of risk factors, clinical presentation, recurrence risk and outcome for coronary artery disease among men and women [1]. However, there are only few such investigations of venous thromboembolism VTE [2–4]. The pathophysiology nature of acute myocardial infarction is arterial thrombosis on the ground of atherosclerosis and in the acute pulmonary embolism (PE) the underlying process is venous thrombosis which is quite different in relation to risk factors and the role of coagulation pathways involved. The annual incidence of VTE is 1–2 *per* 1,000, but it is probably underestimated because of a lot of undiagnosed patients [5]. Contrary to myocardial infarction, the incidence rate of PE is similar in men and women. However, the risk factors for VTE are quite different during lifetime between men and women [5]. In the younger age predominant risk factors in men are trauma and immobilization while in women oral contraceptive use, pregnancy and postpartum period [5]. In the older age various comorbidities and especially malignancy, are associated to VTE [6]. Are the efficacy of thrombolysis and bleeding risk similar in relation to gender is the matter of controversy [7, 8]. However, bleeding risk and the efficacy of oral anticoagulants are very similar in both sexes [9]. The recurrence rate of VTE is higher in men [10]. So, there are several important differences in the epidemiology and outcome of VTE associated to gender.

The aim of this study was to compare important clinical manifestations of PE and some biomarkers in relation to those manifestations between men and women.

Methods

The study included patients with PE treated in the Clinic of Emergency Medicine of the Military Medical Academy in Belgrade in the period from January, 2010 till July, 2015. Their data were collected from the database PE created in 2012 year. Due to this, some data were collected retrospectively and some of them prospectively. A total of 144 patients with visualized thrombus in multidetector computed tomography with pulmonary angiography (MDCT-PA) at admission were enrolled in this study. Anamnestic data about symptoms of PE were carefully registered from various doctors who were not involved in the preparing this paper. Pneumonia was defined as the febrile state with clear condensation of pulmonary tissue on MDCT-PA with necessity of parenteral antibiotics treatment for at least 7 days. Patients were considered to have acute heart failure if they had symptoms and signs of congestive heart failure after normalization of arterial blood pressure.

For the purpose of risk stratification all the patients were classified according to the simplified Pulmonary Embolic Severity Score (sPESI) [11] and hemodynamic status and right ventricle dysfunction in low, intermediate and high risk patients [12].

Electrocardiography (ECG) analysis was performed with admission ECG record. Typical ECG signs for pulmonary thromboembolism were registered (S1Q3T3 sign, right bundle branch block, negative T-waves in precordial leads, S-waves in aVL and paroxysmal atrial fibrillation).

Transthoracic echocardiography examination (VIVID 7 Pro, General Electric Medical Systems) was performed at admission in all patients and systolic pressure in the right ventricle was recorded using tricuspid regurgitation method [13].

Embolic burden score [14] was calculated at admission MDCT-PA (Aquilion 64-sliced multidetector computed tomography Toshiba) by the experienced radiologist.

The concentration of venous glycaemia (hexokinase assay, ADVIA 1200, Siemens) and leukocyte count (Advia 120, Siemens) at admission was available in all the patients. Brain natriuretic peptide (BNP) plasma concentration (immunoassay, ADVIA Centaur XP, Siemens) and C-reactive protein (CRP) serum concentrations (immunoturbidimetric assay, ADVIA 1200, Siemens) were measured 24 hours after admission and the results were available in 114 (57 women and 57 men) and 115 (59 women and 56 men) patients, respectively.

The patients had 1 month and 6 months follow-up visits and if they did not appear we contacted them by phone.

Statistics

The main characteristics of patients according to gender were presented as frequencies, mean values ± standard deviation (SD) or as median with interquartile. The percentages of women and men across the age tertiles were presented in stacked bars graph. The significance of differences particular characteristics between genders was calculated with χ2-test or Student's t-test or with Mann-Whitney test according to nature of data and their distribution. Odds ratios (OR) (with 95% confidence intervals (CI) for symptoms according to gender were calculated with binary regression analysis and in multivariate analysis results were adjusted to three confounding characteristics which were differently distributed in men and women (age, smoking status and body mass index). The difference between two main outcomes, death and major bleeding events, was calculated with Kaplan Meier method using log rank test. The significant differences of data according to gender were considered if p was less than 0.05.

Results

The main characteristics of patients are presented in Table 1. The women were significantly older, they had higher body mass index (BMI) and fewer smokers were among them. There was a significant difference between men and women in the distribution of patients according to tertiles of age (Figure 1). According to the clinical presentation, men had more frequently pleural or substernal chest pain (44.4% *vs* 19.4%, $p = 0.002$), hemopyisis (18.1% *vs* 5.6%, $p = 0.036$), fever (34.7% *vs* 18.1%, $p = 0.037$) and severe pneumonia (23.6% *vs* 8.3%, $p = 0.021$) with pulmonary condensation and need for the parenteral antibiotics (Table 2). There was the trend that symptoms of acute heart failure were presented more often in women than in men (27.1% *vs* 47.3%, $p = 0.053$). In multivariate binary regression, adjusted factors

Table 1

Characteristics of the pulmonary embolism (PE) patients at admission and the frequency of thrombolytic therapy according to gender

Characteristics	Men n = 72	Women n = 72	*p*
Age (years), $\bar{x} \pm SD$	56 ± 17	64 ± 15	0.005
Age older than 65 years, n (%)	25 (32.9)	39 (54.2)	0.013
Active smoking, n (%)	20 (29.0)	6 (8.5)	0.002
Obesity, n (%)	10 (13.9)	23 (31.9)	0.017
Positive familial history of venous thrombosis, n (%)	9 (12.5)	6 (8.8)	0.589
Previous DVT/PE, n (%)	14 (19.4)	10 (13.9)	0.503
Diabetes mellitus, n (%)	6 (8.3)	8 (11.1)	0.780
Spontaneous PE, n (%)	39 (54.2)	33 (45.8)	0.405
Surgery inside 6 months, n (%)	17 (23.6)	20 (27.8)	0.703
Surgery inside 3 weeks, n (%)	6 (8,3)	11 (15,3)	0.302
Active malignant disease, n (%)	5 (6.9)	11 (15.3)	0.184
Coronary disease, n (%)	10 (13.9)	3 (4.2)	0.078
Simplified PESI, n (%)			
0	29 (40.3)	19 (26.4)	0.109
1–2	33 (45.8)	35 (48.6)	
≥ 3	10 (13.9)	18 (25.0)	
Risk according to hypotension and righ ventricular (RV) dysfunction, n (%)			
high	10 (13.9)	14 (19.4)	0.647
intermediate	37 (51.4)	36 (50.0)	
low	22 (34.7)	22 (30.6)	
Systolic pressure in RV at admission (mmHg), $\bar{x} \pm SD$	49.3 ± 19.8	49.8 ± 18.6	0.865
Embolic burden score, median (IQR)	12.0 (7.0–18.0)	12.0 (6.0–18.0)	0.817
Thrombolysis, n (%)	42 (58.3)	44 (61.1)	0.865

DVT – deep vein thrombosis; PESI – Pulmonary Embolic Severity Score; IQR – interquartile range.

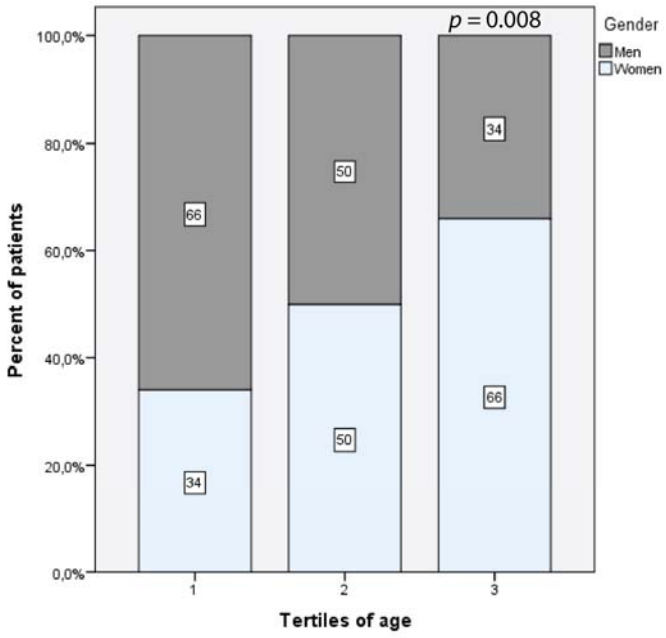

Fig. 1 – Gender distribution according to tertiles of age in the patients with pulmonary embolism.

for which we had found a significant difference in the distribution between the men and the women were included in analysis (Table 2). In such analysis, the difference between genders in the presence of severe pneumonia was lost due to the strong influence of age on the occurrence of pneumonia [non-adjusted HR and 95% CI were 3.40 (1.25–9.22) and was 2.27 (0.78–f6.64)]. There was a much higher number of male younger patients in our cohort and the presence of severe pneumonia was associated very significantly with younger age in PE patients.

There was no significant difference between the men and the women in the frequencies of typical ECG signs of PE at admission (Table 2).

Systolic blood pressure in right ventricle and embolic burden score were very similar in men and women (Table 1).

Admission glycaemia and total leukocyte count (Figures 2 and 3) were significantly higher in the women than in the men [7.7 mmol/L (5.5–8.2 mmol/L) *vs* 6.9 mmol/L (6.3–9.6 mmol/L), $p = 0.006$, and 10.5×10^9/L ($8.8–12.7 \times 10^9$/L) *vs* 8.7×10^9/L ($7.0–11.6 \times 10^9$/L), $p = 0.007$, respectively]. Maximum values of CRP (Figure 4) and BNP (Figure 5) during the first 2 days were not significantly different between the men and the women [52.0 mg/L (17.6–105.5 mg/L) *vs* 44.6 mg/L (26.2–84.9 ml/L), $p = 0.617$ and 90.3 pg/ml (39.2–308.5 pg/ml) *vs* 127.1 pg/ml (55.0-484.0 pg/ml), $p = 0.092$, respectively].

The in-hospital mortality was 12.5% for the women and 5.6% in the men. During the 6-months follow-up 7 (9.7%) men and 10 (13.9%) women died ($p = 0.607$). In the same period, 10 (13.9%) men and 8 (11.1%) women had at least one episode of major bleeding ($p = 0.802$).

Table 2

Frequencies of the most important clinical symptoms and signs of pulmonary embolism (PE) at presentation according to gender. Unadjusted and adjusted odds ratios for symptoms occurrence in the men compared to the women

Symptoms or signs of PE	Men n = 72	Women n = 72	*p*	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[1] (95% CI)
Dyspnea, n (%)	62 (86.1)	65 (90.3)	0.607	0.67 (0.24–1.84)	0.59 (0.20–1.74)
Pleural or chest pain, n (%)	32 (44.4)	14 (19.4)	0.002	3.31 (1.57–7.00)	2.88 (1.31–6.33)
Hemoptysis, n (%)	13 (18.1)	4 (5.6)	0.036	3.75 (1.16–12.11)	2.72 (0.79–9.32)
Fever, n (%)	25 (34.7)	13 (18.1)	0.037	2.41 (1.12–5.22)	2.72 (1.16–6.36)
Syncope, n (%)	11 (15.3)	13 (18.1)	0.823	0.67 (0.27–1.62)	0.80 (0.30–2.09)
Hypotension, n (%)	10 (13.9)	13 (18.3)	0.503	0.76 (0.36–1.61)	0.67 (0.25–1.82)
Tachycardia, n (%)	25 (34.7)	34 (47.2)	0.175	0.59 (0.30–1.16)	0.59 (0.28–1.23)
Severe, n (%)	17 (23.6)	6 (8.3)	0.021	3.40 (1.25–9.22)	2.27 (0.78–6.64)
Signs of DVT, n (%)	39 (54.2)	42 (58.3)	0.737	0.84 (0.44–1.63)	0.80 (0.38–1.66)
Acute heart failure, n (%)	19 (27.1)	31 (43.7)	0.053	0.48 (0.24–0.97)	0.47 (0.21–1.05)
ECG signs at admission, n (%)					
S1Q3T3	17 (23.6)	20 (27.8)	0.703	0.80 (0.38–1.70)	0.72 (0.31–1.66)
RBBB	15 (20.8)	20 (27.8)	0.437	0.68 (0.32–1.47)	0.62 (0.27–1.44)
negative T waves in precordial leads	30 (41.8)	35 (48.5)	0.503	0.75 (0.39–1.46)	1.03 (0.50–2.14)
significant S wave in aVL	35 (48.6)	32 (44.4)	0.738	1.18 (0.61–2.28)	1.24 (0.61–2.53)
paroxysmal AF	3 (4,5)	3 (4.4)	1.000	1.03 (0.20–5.30)	2.14 (0.32–14.54)

In the multivariate model confounding factors such as age, smoking status and body mass index were included.
DVT – deep vein thrombosis; RBBB – right bundle branch block; AF – atrial fibrillation; aVL – lead augmented vector left.

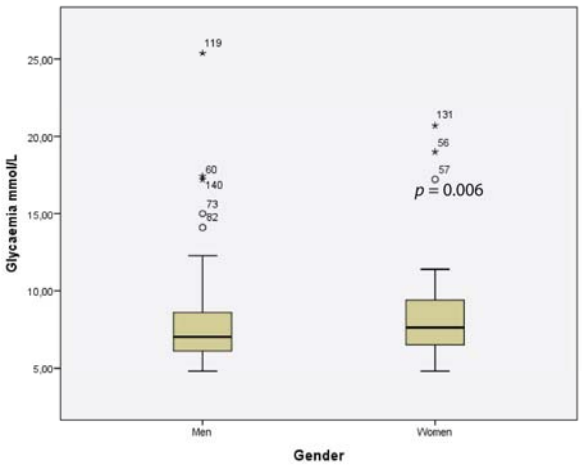

Fig. 2 – Glycaemia at admission in the men and the women with pulmonary embolism.

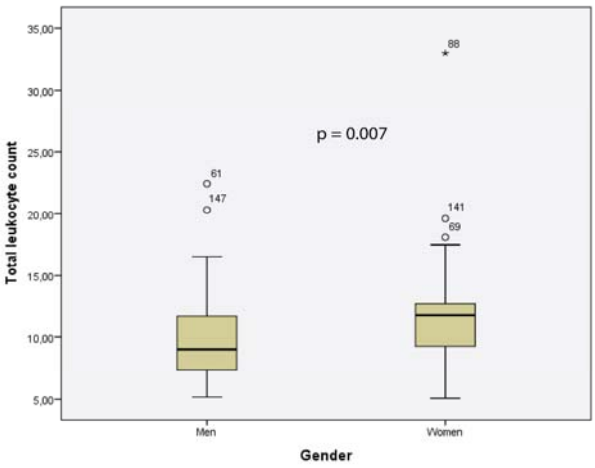

Fig. 3 – Total blood leukocyte count at admission in the men and the women with pulmonary embolism.

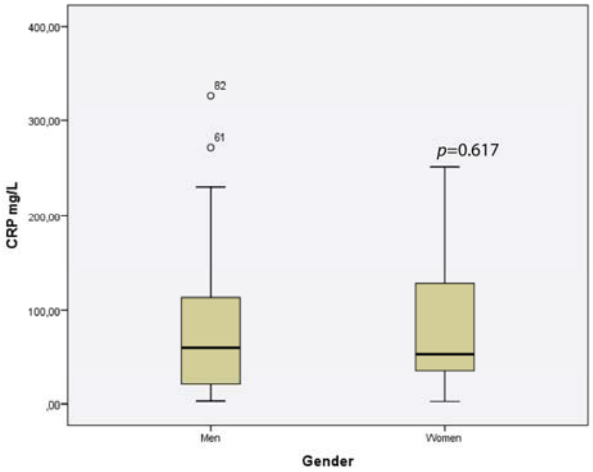

Fig. 4 – C-reactive protein (CRP) serum concentration 24–48 hours after admission in the men and the women with pulmonary embolism.

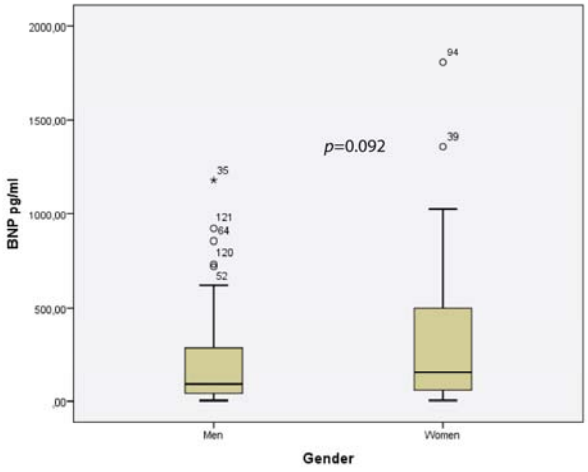

Fig. 5 – Plasma concentration of brain natriuretic peptide (BNP) 24–48 hours after admission in the men and the women with pulmonary embolism.

Discussion

Several interesting findings were obtained in this study. The clinical presentation of PE was quite different between the men and the women despite of similar characteristics of the patients. There was a different distribution of gender across the tertiles of age, with the predominance of the men in the first tertile and the predominance of the women in the third tertile. In the the International Cooperative Pulmonary Embolism Registry (ICOPER) including 2,454 patients with PE from 52 hospitals similar distribution of gender across the age was noticed with significantly higher number of women at the age more than 70 years [2]. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study [15] the proportion of men was much higher under 50 years. The higher percentige of patients with PE in elderly women is probably related to higher proportion of obesity and hypomobility in women and higher proportion of men among younger patients due to higher rate of traumatic immobilization. Symptoms at presentation were significantly different between genders. In our study the men more often had hemoptysis, chest pain, febrile state and pneumonia, and the women were more often decompensated in the early course of PE. Chest pain and hemoptysis were also more frequently presented in the men in ICOPER study [2] and also in the large study of Robert-Ebadi et al. [4] with 1,205 patients with PE [4]. Chest pain and hemoptysis are the consequence of pleural inflammation, pulmonary infarction and myocardial ischemia. Concomitant coronary disease was more often presented in men and it might be the reason for chest pain in some patients [16]. But the majority of patients with chest pain have actually pleural affection and pulmonary infarction and is not clear why it is more often existing in men. In our study men developed more often pneumonia with pulmonary parenchyma condensation and febrile state than women. In the ICOPER study men had more often atelectasis than women on the chest radiography; however febrile state was equally presented in both genders [2]. MDCT-PA was used for the diagnosis of PE in our study and we always carefully examined other structures of chest to diagnosed concomitant pathologies like pneumonias and malignancies. However, in the ICOPER study [2] MDCT of chest it was not available. Congestive heart failure was presented more often in the women in our cohort of PE patients and the same result was recorded in the ICOPER study. The level of BNP was higher in our female patients which supported the clinical diagnosis.

The appearance of ECG typical signs of PE was not different between men and women. The main parameters of PE severity on echocardiography – systolic pressure in right ventricle and on MDCT-PA – embolic burden score, were almost the same in men and women. It is interesting that women had higher level of admission glycaemia and total leukocyte count at presentation which is probably related to older age and higher stress influence in women than in men. Both parameters are prognostically useful in PE patients [17, 18]. CRP levels were almost the same in both genders.

For the outcome of patients according to gender we compared 6-month mortality and major bleeding events. The number of patients precluded analysis of recurrence of disease because of small number of such events. There was no significant difference in the mortality and major bleeding complications in our cohort of patients. In the recently published Italian registry of 1,716 PE patients, female sex was important risk factor for in-hospital death and hemodynamic instability [19]. However, in the recently published study of 815 PE patients followed-up 5 years, male gender was associated with increased risk of post-discharge mortality probably due to increased contribution of other cardiovascular morbidities which were more often presented in men [16]. In our study, the intrahospital mortality was non-significantly higher in women but the small number of patients was very probably the reason for such result. We

also did not find a difference in major bleeding events between the men and the women, although almost 60% of both sexes were treated with thrombolysis. The efficacy of thrombolysis and the risk of bleeding in relation to gender are the matter of controversy [7, 8]. In the summary of 5 prospective multicenter studies of thrombolytic therapy in PE, thrombolysis had equal benefit and safety for both genders [7]. However, in the large Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) women had significantly less benefit with thrombolysis with higher bleeding risk [8]. We developed a strategy of estimation of bleeding risk before introducing the thrombolytic therapy and it may reduce bleeding in both sexes.

Conclusion

To the best of our knowledge this is the first comparison of pulmonary embolism presentation with analysis of symptoms, ECG signs, echocardiography and MDCT-PA parameters between men and women in the era of MDCT with pulmonary angiography. Our results show a significant difference in the presentation of pulmonary embolism between genders across the age. Clinical symptoms and signs were strongly influenced by gender. ECG signs typical for pulmonary embolism were equally presented in both genders. Some biomarkers had significantly diverse blood concentrations. Finally, there was no difference in the mortality and bleeding rate between men and women.

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Stenting *versus* non-stenting following uncomplicated ureteroscopic lithotripsy: comparsion and evaluation of symptoms

Poređenje i vrednovanje simptoma nakon nekomplikovane ureteroskopske litotripsije kod bolesnika sa i bez ugrađenog stenta

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Abstract

Background/Aim. Currently, ureterorenoscopic (URS) stone fragmentation and removal is the treatment of choice for managing ureteral stones, especially mid and distal ones and is advocated as initial management of ureteric stones. The aim of this work was to evaluate the symptoms, necessity, potential benefits and adverse effects of ureteral stent placement after uncomplicated ureteroscopic lithotripsy. **Methods**. This retrospective-prospective study evaluated a total of 125 patients who had underwent ureteroscopic lithotripsy (URSL). The patients were divided into two groups: stented (59 patients) and unstented (controls, 66 patients). The outcomes measured and compared between the two groups included: stone free rate, postoperative patient pain validated by scale, lower urinary tract symptoms (LUTS), the need for unplanned hospital care, stent related complications, and functional recovery in the form return to normal physical activities. **Results.** A successful outcome, defined as being stone-free after 12 weeks, was achieved in all 125 (100%) patients. The stone-free rate showed no significant differences between the two groups. LUTS was a frequent complaint in the stented group, with statistically significant difference in the domain of frequency/urgency (p = 0.0314). There was a statistically significant difference between the groups in the mean operative time and mean hospitalization time, mean pain visual analog scale (VAS) score and in the use of non-narcotic analgesic. On the day of the surgery and until postoperative day 3 (POD 3) and postoperative day 5 (POD 5), the pain score was much higher among stented patients than among the controls (p = 0.0001) and non-narcotic analgesic use (p = 0.001) was frequently required in the stented group. **Conclusion**. Routine placement of ureteral stent after URSL is not mandatory and may be associated with stent side effects. Uncomplicated URSL is safe without stent placement after the treatment.

Key words:
ureteroscopy; lithotripsy; stents; lower urinary tract symptoms; comparative study.

Apstrakt

Uvod/Cilj. Ureterorenoskopsko sitnjenje i uklanjanje kamena predstavlja lečenje izbora prilikom zbrinjavanja ureteralnog kamena naročito srednjeg i donjeg uretera, i smatra se osnovnim zbrinjavanjem. Cilj rada bio je da se ocene simptomi, neophodnost potencijalne koristi i neželjeni efekti plasiranja ureteralnog stenta nakon nekomplikovane ureteroskopske litotripsije (URSL). **Metode**. U ovoj retrospektivno-prospektivnoj studiji, ispitano je 125 bolesnika koji su bili podvrgnuti URSL. Bolesnici su podeljeni u dve grupe: sa ugrađenim stentom (ispitivani bolesnici, 59) i bez stenta (kontrole, 66 bolesnika). Ishodi koji su mereni i poređeni između dve grupe obuhvatali su: stopu odsustva kalkulusa, postoperativni bol kod bolesnika ocenjen pomoću skale, simptome donjeg urinarnog trakta (SDUT), potrebu za neplaniranim bolničkim lečenjem, komplikacije povezane sa stentom i funkcionalni oporavak u formi povratka na uobičajene fizičke aktivnosti. **Rezultati.** Povoljan ishod, definisan kao odsustvo kalkulusa nakon 12 nedelja, postignut je kod svih 125 (100%) bolesnika. Nije bilo statistički značajne razlike između dve grupe u stopi odsustva kalkulusa. SDUT su bili češći u grupi sa plasiranim stentom, sa statistički značajnom razlikom u domenu učestalosti mokrenja, odnosno urgencije (p = 0,0314). Postojala je statistički značajna razlika između grupa u prosečnom trajanju operacije i prosečnoj hospitalizaciji, srednjoj vrednosti ocene bola na vizualnoj analognoj skali (VAS) i u upotrebi neopijatnih analgetika. Na dan operacije i sve do trećeg postoperativnog dana (POD 3), odnosno petog postoperativnog dana (POD 5), ocena bola (p = 0,0001), kao i potreba za neopijatnim analgeticima (p = 0.001) bila je viša među bolesnicima sa stentom u poređenju sa kontrolama. **Zaključak.** Rutinsko ugrađivanje ureteralnog stenta nakon nekomplikovane URSL nije obavezno i može biti povezano sa neželjenim efektima stenta. URSL je bezbedna procedura i bez ugrađivanja stenta na kraju intervencije.

Ključne reči:
ureteroskopija; litotripsija; stentovi; urinarni trakt, donji, simptomi; komparativna studija.

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Introduction

Currently, ureterorenoscopic (URS) stone fragmentation and removal is the treatment of choice for managing ureteral stones, especially mid and distal ones and is advocated as initial management of ureteric stones [1]. There is a controversy regarding the need for ureteral stent insertion after uncomplicated URS stone surgery due to the possibility of complications. Saltzman [2] recommended stenting in patients following URS stone therapy and Aoyagi et al. [3] continued to advocate routine stenting as a security measure. On the other hand, reports in the literature suggest that the use of stents was associated with complications with the incidence of stent-related symptoms and morbidity of 10–85% [4]. As Richter et al. [5] stated, placement of a ureteral stent is "a friendly procedure with unfriendly morbidity" [5]. The key question is the definition of the word 'uncomplicated', and so is the indication for not placing a stent, as well as the decision on which patients can safely be left unstented. Denstedt et al. [6] defined uncomplicated URS as "no evidence of perforation or lack of clinically important edema".

The aim of this study was to evaluate the diference in the postoperative course between stented and nonstented groups, comparing patient's characteristics, stone features, treatment outcome, and functional recovery.

Methods

Patients and study design

This retrospective-prospective chart analysis was conducted at the Department of Urology of Dr. Dragiša Mišović Hospital in Belgrade, Serbia. Between January 2011 and December 2014, a total of 213 patients underwent ureteroscopic lithotripsy (URSL) for ureteral calculi. The eligible patients for this study were adults who underwent URSL without dilatation for ureteral stones, and who had no history of previous ureteroscopy or failed treatment for the same stone. The results thus included 125 patients.

The patients were categorized into two groups depending on whether they received a stent at the end of a procedure or not. When used, stent was placed routinely, without strict indications.

Clinical procedure

All interventions were carried out under general (n = 15) or spinal (n = 110) anesthesia, using semi-rigid single channel OLYMPUS 9.8 Chureteroscope with a 5.5 Fr working channel width, 7° lens, and length of 430 mm. A ballistic (pneumatic) generator, LithotronWalz EL-27 Compact was used. In the cases (stented) group, a double pigtail ureteral 6 Fr polyurethane stent was placed following URSL and removed after 2 weeks. The patients assigned to one day surgery were admitted to the day case ward on the morning of surgery, or one day before surgery. The patients were fully evaluated using routine lab tests, accompanied with ultrasonography (US) and plain abdominal X-ray. Intravenous urography (IVU) and retrograde ureteropyelography were performed in patients optionally.

All the patients were discharged after overnight hospitalization. The discharge criteria included stable vitalparameters, ability to void spontaneously, and satisfactory pain control using oral non-narcotic analgesics. URSL was performed in hemodynamically stable patients.

Follow-up procedure

The patients were initially evaluated in a recovery room and then followed up on postoperative days (POD) 1, 3, 5, and 7, four weeks and three months postoperatively. All events were measured and evaluated using plain abdominal X-ray, renal US, urinalysis and urine culture, laboratory analysis and patient questionnaire. All these analyses were performed on days of follow-up visits during the immediate postoperative period and 12 weeks postoperatively.

The evaluated outcomes were stone free rate, patient reported pain using a validated scale, need for analgesia, LUTS (dysuria, frequency/urgency), postoperative complications (hematuria, fever > 37°C, urinary tract infection…), unplanned medical visits or readmission to a hospital due to postoperative complications and patient functional recovery.

Procedures were considered successful if fragmentized calculi were smaller than the probe tip width and in the absence of residual stones on a plain radiographic film or US 2 weeks after initial lithotripsy. Stone diameters ≤ 4 mm as stone-free rate (SFR) were established as success criteria.

Postoperative pain was defined by the need for oral analgesics in the 1st week and the dose of required analgesics, and in this study was evaluated by how much analgesia was required by patients each day, in addition to the number of readmissions to a hospital for pain control. At follow-up visits on days 3, 5 and 7, postoperative pain was measured using a 10 cm visual analog scale (VAS), where 0 represented no pain and 10 extreme pain. The analgesics that were used were diclofenac sodium tablets 50 mg and patients were instructed to take it only for pain episodes. The patients who reported pain were classified into three groups: those who reported pain score within or at three days, those who reported pain at five days, or after day seven following the procedure.

In an analysis of symptoms of LUTS, we used the IPSS questionnaire that patients were asked to complete two weeks after intervention.

The modified Clavien-Dindo Classification of Surgical Complications (CCS) was used for evaluation of intraoperative and postoperative complications within 15 perioperative days.

Functional recovery was evaluated using specifically tailored questionnaire. The questionnaire was filled out by patients themselves at clinical visits or by doctor during telephone interview at the time of ultimate stone-free status 12 weeks after surgery in the non-stented group and 10 weeks after stent removal in the stented group. The questionnaire used to evaluate patient satisfaction with provided treatment modalities included overall satisfaction (5 choices: very sati-

sfied, satisfied, acceptable, dissatisfied, very dissatisfied) and satisfaction or dissatisfaction with return to normal physical activities, as well as patient willingness to undergo a repeated procedure.

This study protocol was approved by the Ethics Committee of the Hospital Dragiša Mišović and the research was carried out in accordance with Helsinki Declaration. Before inclusion and undergoing ureteroscopy, all the patients provided written informed consent.

Statistical analysis

The Statistical Package for the Social Sciences software (SPSS, version 10.0; SPSS Inc. Chicago, IL, USA) was used for statistical analysis. The results are presented as mean ± SD. The groups were compared using parametric 2 tailed *t*-test and nonparametric Mann-Whitney *U*-test for continuous and semi-continuous variables, as appropriate. We used χ2-test and Fisher's exact test to assess differences in categorical variables between cases and the controls. A *p*-value < 0.05 was considered as statistically significant.

Results

This study included 125 patients. Patient demographic data and stone characteristic are shown in Table 1. The two patient groups were comparable regarding the baseline variables. Table 2 summarizes the results of stone removal. There were no differences between the groups in any of technical aspects or stone-free rates.

Among the total of 125 patients, our study showed 113 (90%) stone-free rate (clearance rate) in the ureter at all levels on the first POD. The stone-free rate was 52 (88%) in the cases group, and 61 (92%) in the control group. When the stone free rate was compared between the groups, there was no statistically significant difference. Plain abdominal X-ray on the 12th postoperative week showed the stone-free rate of 100% (n = 59) among cases and 100% (n = 66) among controls – completely stone free with no ultrasound evidence of obstruction.

The mean operative time was longer in cases of stent placement, and the difference was significant ($p < 0.001$, $t = 6.584$). Furthermore, there was a significant difference in the mean hospitalization time between the groups ($p < 0.001$, $Z = -5,66$).

On the first postoperative day, flank pain rate experienced by stented patients was higher [29 (49%)] than that reported by the patients in the unstented group [12 (18%)], ($p = 0.003$). Suprapubic pain and urethral irritation occurred more often in the cases group.

Table 3 shows the mean visual analog pain scores and analgesic use in the two groups at 3, 5 and 7 days. At the day 3 and 5, the mean visual analog pain score in the cases was significantly higher than in the controls. On the 7th day, the

Table 1

Age, sex and ureteral stone characteristics – distribution of patients

Patients	Cases (stented)	Controls (unstented)	Results
Mean age ± SD (years)	51.97 ± 12.77	52.73 ± 12.58	$p = 0,783$ $t = -0.335$
Males/females (n)	26/33	27/39	$p = 721$ $\chi^2 = 0.127$
Mean stone size ± SD (mm)	10.49 ± 1.06	10.20 ± 1.46	$p = 0.070$ $Z = -1.813$
Stone side: left/right (n)	24/35	32/34	$p = 0.381$ $\chi^2 = 0.768$
Stone level (%)			
iliac	24	33	
pelvic	34	27	$p = 0.065$ $\chi^2 = 5.421$
pelvic and iliac (n)	1	6	

SD – standard deviation.

Table 2

Results of stone removal

Variables	Cases (stented)	Controls (unstented)	Results
SFR – POD 1, n (%)	53 (88.1)	92.4 (61)	$p = 0.416$ X = 0.660
SFR –POD 15, n (%)	56 (94.9)	95.5 (63)	$p = 1.000$ X = 0.200
SFR – 12 weeks, n (%)	59 (100)	100 (66)	-
Mean operative time ± SD (min)	41.53 ± 5.10	37.02 ± 1.21	$p = 0.001$ $t = 6.584$
Mean hospitalization time ± SD (hours)	24.88 ± 0.89	26.03 ± 1.20	$p = 0.001$ Z = -5.667

SFR – stone-free rate; POD – postoperative day; SD – standard deviation.

Table 3

Visual analog pain scores – postoperative pain score

Variables	Cases (stented)	Controls (unstented)	Results
Mean pain score on the day 3 (0–10[a]) ± SD	4.78 ± 0.911	2.83 ± 0.376	$p = 0.0001$ Z = -9.439
Mean pain score on the day 5 (0–10[a]) ± SD	3.34 ± 0.576	2.68 ± 0.469	$p = 0.0001$ Z = -6.115
Mean pain score on the day 7 (0–10[a]) ± SD	2.32 ± 0.600	2.53 ± 0.503	$p = 0.038$ Z = -2.080
POD 3 analgetic usage 1/2/3 tbl	2.14 ± 0.495	1.64 ± 0.485	$p = 0.0001$ Z = -6.911
POD 5 analgetic usage 1/2/3 tbl	2.02 ± 0.293	1.30 ± 0.463	$p = 0.0001$ Z = -7.615
POD 7 analgetic usage 0/1/2 tbl	0.98 ± 0.347	0.26 ± 0.441	$p = 0.038$ Z = -7.618

[a] No pain (0) to extreme pain (10); SD – standard deviation, POD – postoperative day.

patients in overall had few symptoms and the mean visual analog pain scores were not statistically different between the two groups. In the stented group, on POD 5 and POD 7, the rates of patients who required two or more analgesic tablets a day for pain control were 57% and 27%, respectively, but none of them required hospitalization for intractable pain. Analyses of International Prostate Symptome Score (IPSS) on postoperative day 14 showed a significant difference between the groups (Table 4). Dysuria was observed in 33 (56%) of the patients in cases group and 30 (45%) of the patients in the control group ($p = 0.2840$), while frequency/urgency was present in 37 (63%) of the patients among the cases and in 28 (41%) of the patients among the controls ($p = 0.0314$).

The modified Clavien system has been proposed to grade perioperative complications (Table 5). Urinary tract infections (UTI) occurred in 16 (13%) of the patients (symptomatic with positive urine culture results; the most common pathogen was *Escherichia coli*, present in 15 culture samples) which were successfully treated with antibiotic. In the first 24 hours, mild macroscopic haematuria was observed in 11 (18.6%) of the patients among the cases and 8 (12%) of the patients among the controls, and it did not require treatment. The rate of fever (37.5–38°C) was higher among the cases, where 8.5% of the patients developed upper UTI related fever and were treated with oral antibiotics accompanied with excellent response.

Return to emergency room during the first week was necessary in 11 (8.8%) of the patients, 6 (10%) from the cases group and 5 (7.5%) from the control group ($p = 0.7547$). Thirty six hours after URS, one patient from the stented group developed fever due to pyelonephritis (urinanalysis, sonography), without signs of septicemia (nausea, vomiting) and was treated with antibiotics (initially with parenteral fluoroquinolon, and after improvement, the patient was switched to oral regimen).

Figure 1 shows the overall subjective patient satisfaction with the procedure that generally reflects treatment success.

Table 4

International Prostate Symptom Score (IPSS)

IPSS	Stent	n	Arithmet. mean	SD	Median	Min	Max	Result
Obstructive	no	66	5.14	1.487	5.00	2	8	$t = 12.311$
	yes	59	9.19	2.161	9.00	4	14	$p < 0.001$
	total	125	7.05	2.732	7.00	2	14	
Irritative	no	66	3.27	0.869	3.00	1	5	$t = 4.937$
	yes	59	4.08	0.970	4.00	2	7	$p < 0.001$
	total	125	3.66	1.001	4.00	1	7	
Total	no	66	8.39	2.089	8.00	3	12	$t = 11.148$
	yes	59	13.27	2.784	13.00	6	20	$p < 0.001$
	total	125	10.70	3.448	11.00	3	20	

SD – standard deviation.

Table 5

Comparsion of complications, classified according to the modified Clavien-Dindo classification system (CCS) between the groups

CCS grade	Total	Cases (stented)	Controls (unstented)	*p*-value
Grade 1, n (%)				
fever	10 (8)	5 (8.5)	5 (7.6)	1.0000
hematuria –mild	19 (15)	11 (18.6)	8 (12)	0.3306
Grade 2, n (%)				
UTI	16 (13)	8 (13.5)	8 (12)	1.0000
pyelonephritis	1 (0.78)	1 (1.7)	-	0.4720

UTI – urinary tract infection.

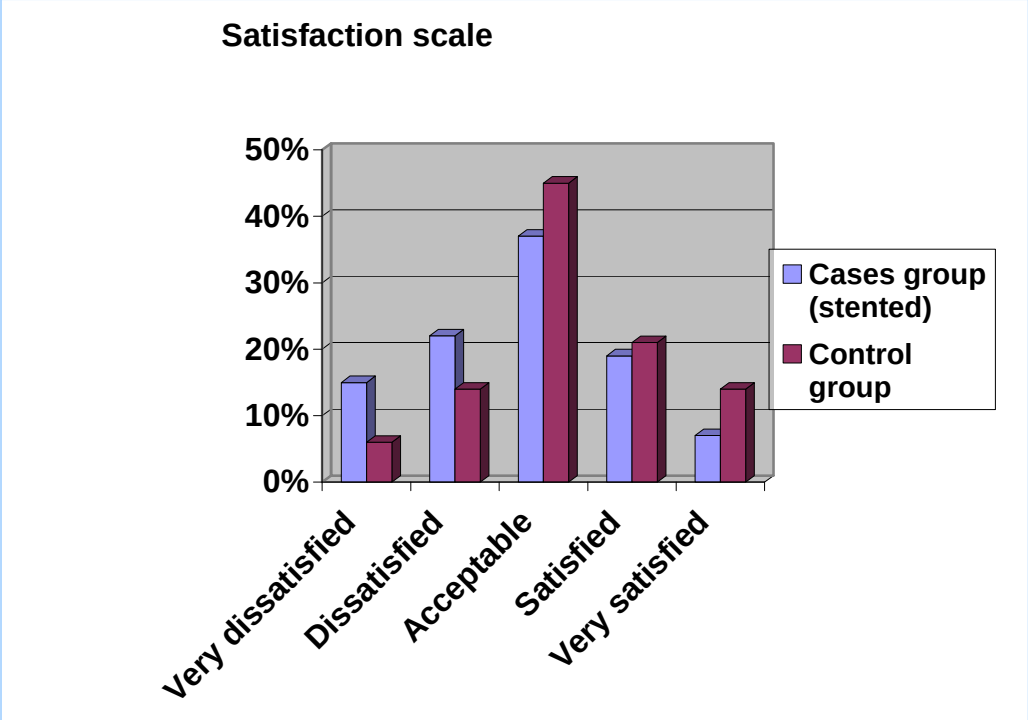

Fig. 1 – Overall subjective satisfaction of patients with treatment outcomes.

According to our results in 90 (72%) of the patents, their expectations were met by the specific treatment, meaning that they were satisfied with chosen therapeutic modality and that they would recommend it to others. There was a significant statistical difference among the patients who were dissatisfied with chosen therapeutic modality (p = 0.0452). Specifically, 22 (37%) of the patients from the stent group were dissatisfied because of discomfort and pain and expressed that they would have not accepted a stent if they had to undergo a repeated procedure. In the group of patients without stent, total dissatisfaction with treatment was lower at 13 (20%) of them. Return to normal physical activities one day after the procedure was reported by 36 (61%) of the stented patients and 52 (79%) of the unstented patients (p = 0.0330).

Discussion

In this study, the overall stone-free rate of URS was comparable to other studies with stone-free rates ranging from 75% to 93% [7]. The stone site has always been noted as an important determinant. In our study, there were 83 (66%) of lower and 39 (31%) of mid ureteric stones. Lower ureteric stones were more easily handled than upper ureteric stones primarily because of accessibility and anatomical reasons.

In this study, there was no statistically significant difference in the success rate between the groups. Similarly, none of the previous trials reported a significant difference in stone-free rates between participants with and without stent [8]. Compared with other published trials, the mean stone size and the number of stones between the two groups in our study are similar. The mean operative time recorded during this study was comparable between the two groups with a significant difference.

Patients with indwelling ureteral stents have a wide range of urinary symptoms that affect their quality of life [9]. Stent discomfort can vary from one patient to another in an idiosyncratic manner, but it is reported to affect over 80% of patients [8]. It has been suggested that irritative symptoms are the result of irritation of neuronal-rich trigone mucosa and flank pain, related with reflux [10]. We noted that patients without stents had fewer postoperative complications in the form of LUTS, which is also consistent with other studies [11]. Pollard at Macfarlane [12] evaluating symptoms associated with ureteral stent, confirmed that the symptoms disappeared after stent removal. Similarly, Bregg and Riehle [13] found that 22 (44%) out of 50 patients experienced moderate to intolerable discomfort that was relieved by removal of the stent [13]. Kuyumcuoglu et al. [14] in their work highlight that the frequency of LUTS increase in patients in whom the double-J stent was applied, with an increase in the International Prostate Symptom Score (IPSS) Quality of life question (IPSS-QOL) and Overactive Bladdetr Questionnaire (OABq) scores. In other words, discomfort continues as long as the stent stays in the body. Stented patients have been documented to have significantly higher pain scores [6, 15]. Our study showed that the presence of stent significantly affected postoperative pain, requiring analgesics.

The ureteroscopic procedure itself often has little impact on patient's quality of life, but the method of ureteral drainage after the procedure may have a significant negative effect on the patient's quality of life. Leibovici et al. [16] suggested that the use of double-J stents can lead to several side effects and cause negative effects on quality of life. Joshi et al. [9, 17] indicate that 76%

of stented patients experienced negative symptoms and 42% had to reduce their activity by half. Stenting adds to the medical expense of the ureteroscopic procedure, and cystoscopy is usually required for stent removal unless a string is attached to the distal end of a stent [18]. By analyzing patient perceptions about the outcome of the treatment, together with the clinical parameters, our results indicate the importance of patient subjective satisfaction. This should be considered as an important parameter when making a decision to place a stent, except in the presence of very strict indications. Although clinical parameters are of major importance, considerations about quality of life and subjective satisfaction assessed by standardized questionnaire are also essential.

Stents can be viewed as kind of insurance policy against postoperative complications, especially those that require intervention. Given the imperative of sending patients home on the day of the procedure, it is not surprising that many urologists choose to stent routinely [19]. Therefore, it may be suggested that stenting should be limited to selective cases, such as patients with a single kidney, urinary tract infection, complications during surgery, and large stones with large residual fragments [20]. Uncomplicated ureteroscopy for removing *calculi* is safe without stenting after treatment, and after considering complications and side effects, routine use of ureteric stents after uncomplicated ureteroscopy for stone extraction may be unnecessary [21]. Patients without stents have significantly fewer lower-urinary symptoms, such as pain, urgency, and dysuria, and are not at risk of increased rate of complications [22].

Some limitations of our study must be highlighted, such as partly retrospective, lack of randomization, decision to put stent intraoperatively. We are well aware that our study does not provide a definitive answer to the actual question, stent or not after URSL. However, we believe that, even the known limitation of our current study, the results can suggest to consider advantages or/and disadvantages of each treatment. Although, further study/investigations, including comparison of long term complications are warranted to clarify, confirm or deny, the need for routine stenting after URSL.

Conclusion

Being stone-free after submitting to the risks and pain of a surgical procedure would be the most important outcome for most, if not all, patients. Most bothersome symptoms and side effects following URS originate from ureteral stent placement. Most untoward effects associated with ureteral stents persist during the entire stenting dwell time and that must be kept in mind when deciding on stent placement.

After analysis of complications and side effects, we consider the routine use of ureteric stents after uncomplicated ureteroscopy for stone extraction to be unnecessary and that it should be used very selectively. In this context, surgeons should be aware of high patient expectations for treatment success and reluctant patient attitudes toward ancillary treatment after surgery.

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Some specificities in the management of hyperglycemia in patients with diabetic kidney disease

Neke specifičnosti glikemijske kontrole kod dijabetičara sa dijabetesnom bolesti bubrega

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Key words:
hypoglycemic agents; renal insufficiency, chronic; diabetic nephropaties; insulin; blood glucose.

Ključne reči:
hipoglikemici; bubreg, hronična insuficijencija; dijabetesne nefropatije; insulin; glikemija.

Introduction

Chronic kidney disease (CKD) is a common condition that is estimated to affect over 50 million people worldwide [1]. Similarly, diabetes takes on epidemic proportions with global prevalence estimates of 382 million people [2]. According to American data, in approximately 45% of incident renal replacement treatment patients, diabetes is the primary cause of their kidney failure. People with CKD due to diabetes have significantly higher incidence of cardiovascular morbidity and mortality compared to diabetics without nephropathy, and it is eighty times higher than in the general population [3].

CKD resulted from diabetes has been termed "diabetic nephropathy" (DN). The Diabetes and Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney disease Outcomes Quality Initiative (NKF KDOQI) in its Clinical Practice Guidelines and Clinical Practice Recommendatione from 2007 has suggested that a diagnosis of CKD as a consequence of diabetes should be reffered to as diabetic kidney disease (DKD). The term diabetic nephropathy should be reserved for kidney disease attributed to diabetes with hystopathological injury demonstrated by renal biopsy [4]. The clinical diagnosis of DKD is primarily based on detection of albuminuria (proteinuria). Microalbuminuria is the term defined as an albumin/creatinine (A/C) ratio of 30–299 mg/g from a spot urine collection, or 30–299 mg/daily in the 24-hour urine collection. Macroalbuminuria is the term, defined as more than 300 mg/g or more than 300 mg/daily in the same tests respectively [5]. The incidence of DN is estimated to be 20–40% in both type 1 and type 2 diabetes. The natural history of DN in type 1 diabetes, typically shows a period of hyperfiltration followed by microalbuminuria (30–299 mg/day) and than by macroalbuminuria (>300 mg/day), accompanied by a decline in glomerular filtration rate (GFR). A similar progression is though to underline the natural course of nephropathy in type 2 diabetes, but other comorbidities, including hypertension or obesity, make a progressive pattern less clear [6].

Microalbuminuria in type 1 diabetes appears to be associated with typical histopathologycal lesions and confers risk for progression of CKD. In contrast to type 1 diabetic patients, the association between DKD and microalbuminuria is not as strong in patients with type 2 diabetes, and only 30% of them demonstrates the typical findings by kidney biopsy. However, if retinopathy is present in patients with type 2 diabetes and microalbuminuria, this is strongly suggestive of DKD, with a sensitivity of 100% and specificity of 46–62% [7]. About 30–40% of these patients remain within microabuminuric interval, and do not progress to higher degree of albumunuria over 5–10 years of follow up. The rest of them will progress to more significant levels of albumunuria, and are likely to progress to the end stage renal disease [8]. For the purpose of emphasizing the continuous nature of albuminuria as a risk factor, according to American Diabetes Association (ADA) recommendations, previous terms microalbuminuria and macroalbuminuria, will be rather reffered to as increased albumin excretion at levels more than 30 mg/daily [9].

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Some studies show that in patients with type 1 diabetes and persistent albuminuria in the range of 30–299 mg/g, screening for albuminuria alone would miss 20% of progressive disease [10]. Serum creatinine with estimated GFR should therefore be assesed at least annually in all adults with diabetes, regardless of the degree of albuminuria. In summary, in patients with diabetes who have persistently high urinary albumin excretion rate (persistent albuminuria) in combination with diabetic retinopathy, kidney disease may be atributed to diabetes and the severity of kidney impairment should be clasiffied depending on the GFR [1].

Intensive blood glycemic control

Glycemic control is fundamental to diabetes management. Chronically uncontrolled hyperglycemia leads to a higher risk of macrovascular and microvascular complications, such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. In large prospective randomized studies, intensive diabetes management with the goal of achieving near-normoglycemia wih HbA1c levels of less than 7%, has been shown to reduce the risk for the appearance of microalbuminuria and delay its progression, in both types of diabetes. The Diabetes Control and Complications Trial (DCCT), a prospective randomised control study of intensive *versus* standard glycemic control, in patients with recently diagnosed type 1 diabetes, showed that intensive therapy significantly reduced the onset of microalbuminuria, after the mean of 6.5 years [11]. Further 16-year follow-up of the DCCT cohort patients demonstrated a long-term persistence of these microvascular benefits in previously intensively treated patients [12]. United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto trial, showed similar benefits of strict glycemic control on the developement of microalbuminuria in type 2 diabetic patients [13, 14].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VAD) studies, have added some new information to the evidence that even more intensive glycemic control reduces the onset and progression of elevated urinary albumun excretion in type 2 diabetic patients with long term diabetes and cardiovascular comorbidites [15–17]. However, comparison of the effects of different levels of the glycemic control in ACCORD trial was stopped early due to an increased all-cause mortality rate in the intensive compared to standard group, without reduction in frequency of major adverse cardiovascular disease (CVD) events, including CVD mortality and non-fatal CVD events. Although the initial analysis of the ACCORD data did not identify a clear explanation for the elevated mortality rate in the intensive treated group, severe hypoglicemia was significantly more frequently observed in patients randomised to the intensive glycemic control arm [15].

Considering all of the above, actual recommendations of the ADA suggest that the HbA1c values below or around 7% are a reasonable goal for most of the diabetic adults. For selected individuals with short diabetes duration, long life expectancy and no cardiovascular comorbidities, more strict HbA1c goal of less than 6.5% are suggested. For patients with long diabetes duration, limited life expectancy, advanced micro- and macrovascular complications and with history of severe hypoglycemia, less strict glycemic control, with the maintenance of HbA1c values below 8% are recommended [9]. Similar recommendations are proposed by the European Association for the Study of Diabetes (EASD) [18]. The American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) Global Guidelines suggest that HbA1c values have to be less than 6.5% for most of the patients, with the exception of the risk population for which HbA1c levels higher than 6.5% could be tolerated [2, 19].

Nevertheless, none of these organisationes has the separate guidelines for patients with diabetes kidney disease; still they all recognise that certain populations may require special considerations and that less intensive glycemic goals must be indicated in patients with severe or frequent hypoglycemia. In 1997, the National Kidney Foundation established the Kidney Disease Outcomes Quality Initiative (KDOQI) to develope clinical practice guidelines for management of all stages of CKD [4]. This guidelines is consistent with that of ADA, and actually recommend a target HbA1c of approximatelly 7% to prevent or delay progression of albuminuria in DKD. This guidelines also suggest that target HbA1c sholud be raised from 7% to 8% in individuals with clinically significant comorbidities, and a risk of hypoglycemia including patients with DKD [9, 18]. Interesting to note, in some [20, 21], but not all observational studies [22], HbA1c values between 7% and 9% were associated with better outcomes for survival, hospitalization and CVD in patients receiving hemodialysis. However, this observation has not been tested and proven in prospective randomised studies, so it cannot be included in the official recommendations yet.

Assessment of long term glycemic control

Glycated hemoglobin (HbA1c) is well-validated test for assessing glycemic control in general diabetic population. It is well-known that neither peritoneal nor hemodialysis acutely change HbA1c levels [23]. However, in patients with decreased kidney function, especially those on hemodialysis, factors such as reduced erytrocyte life span or iron deficiency, recent transfusions, metabolic acidosis and erythropoiesis stimulating agents (ESA) administration, affect the accuracy of this assay. By increasing the proportion of youth erytrocyte forms in blood, anemia can falsely lower HbA1c levels. Namely, the rate of glycation of these young cells is lower than that of old cells, which also contributes to the reduction in measured HbA1c levels. Once treatment with iron supplementation is started, HbA1c levels decreases significantly, as a result of the production of immature cells. Iron supplementation or erythropoietin administration, lead to the modest decrease of HbA1c level of 0.5% to 0.7% along with the rise in total hemoglobin in patients with advanced CKD [24]. On the other hand, iron deficiency increases the level of HbA1c independently on other factors. Each of these parameters increases the

possibility of underestimation of true glycemic control by HbA1c level in the presence of CKD (stages 3–5), making it unreliable for the assessment of glycemic control in the hemodialysis setting [25].

Measurement of glycated albumin (GA) has been shown to provide a more relevant method in assessing glycemic control in diabetic patients with chronic kidney failure. In the study on hemodialysis patients with diabetes, it was observed that the degree with which serum GA correlates with plasma glycemia was identical between diabetics with and without CKD [26]. Similarly to fructosamine, GA provides short term index of glycemic control that is not affected by erythrocyte lifespan or erythropoietine administration. This assay has the strong correlation with glucose and provides a reliable index of glycemic control over the proceeding 2–3 weeks. The evidence from the current literature indicates that in the presence of advanced CKD, glycemic control could be evaluated more trustworthy by measuring GA than HbA1c. Furthermore, it is observed that elevated values of GA are better marker than HbA1c in predicting the developement of vascular complications, cardiovascular death and hospitalization in dialysis diabetic patients [27].

There are also limitations of GA assay. Albumin turnover change in patients receiving peritoneal dialysis and in patients with macroproteinuria, in whom values of this assay, theoretically could be falsely lower as a result of a shorter glycemic exposure of plasma albumin [26]. Consequently, some autors recommend that the use of GA levels might be limited to patients on hemodialysis. Wheather glycated albumin could be a marker of the qualtity of glycemic control in patients with massive proteinuria, and in those undergoing peritoneal dialysis is still unclear. At present, there is still no consensus on discriminative values of this assay, which makes different target values for different stages of CKD highly needed. Until then, according to current recommendations, HbA1c remains the best clinical marker of long-term glycemic control in patients with DKD, particularly if combined with self-monitoring of blood glucose level [1].

Pathogenesis and risk for hypoglycemia in patients with CKD

Patients with decreased kidney function (CKD stages 3–5) have increased risk for hypoglicaemia, due to impaired gluconeogenesis in kidney, and decreased clearance of insulin and some oral hypoglicemic agents. In humans, only the liver and the kidney contain significant amounts of the enzyme glucose-6-phosphatase, and therefore are the only organs that are able to perform gluconeogenesis. As the result of differences in the distribution of various enzymes along the nephron, glucose utilization is occurring predominantly in the renal medulla, while glucose release is limited to the renal cortex. Like the brain, renal medullary cells are obligate users of glucose, but they can phosphorylate and accumulate glycogen. These cells, however lack gluconeogenic enzymes, and hence are not able to release free glucose into circulation. On the other hand, renal cortex cells do possess gluconeogenic enzymes (including glucose-6-phosphatase), and therefore can generate and release glucose into the blood stream [28]. After an overnight fast, 75–80% of glucose released into the circulation derives from the liver, and the remaining 20–25% derives from the kidneys.

In healthy subjects, hypoglycemia promotes three-fold increase of renal glucose release, while hepatic glucose release increased only 1.4-fold above ordinary rates, suggesting the important role of kidneys in human glucose counterregulation. With the reduction of cortical mass in DKD, a reduction in glucose delivery appears, thus contributing to higher hypoglicemic risk. Patients with type 1 diabetes and long term type 2 diabetes, lose their glucagon response to hypoglycemia and become dependent on catecholamine response. Consequently, type 1 diabetic patients with both reduced glucagon and epinephrine responses have decreased both hepatic and renal glucose release during hypoglycemia [29].

The kidney is the main organ responsible for metabolizing exogenous insulin administered to diabetic patients. About 65% of systemic insulin that reaches the kidney is filtered at the level of glomerulus, and is subsequently metabolized in the proximal tubular cells; furthermore it is eliminated via the peritubular endothelium and less than 1% of filtered insulin appears in the urine [16]. As renal failure progresses, peritubular insulin uptake increases. Until GFR decreases to less than 20 mL/min, this compensates for the decline in degradation of filtered insulin and afterwards half-life of insulin increases, due to its reduced clearance [30].

Insulin treatment-dose adjustment

The reduction of insulin clearance and catabolism leads to increased frequency of severe hypoglycemia, especially in patients with insulin dose not adequately modified. The reduction in insulin requirements seem to be similar for both type 1 and type 2 diabetic patients. In patients with type 1 diabetes mellitus and mean GFR of 54 ml/min some authors have observed that clearance of regular human insulin is reduced by 30–40% [31, 32]. Patients with residual diuresis less than 500 mL/day show a reduced demand for insulin by oboout 29%. It has been reported than one year after initiation of hemodialytic procedure, approximately one third of insulin threated type 2 diabetics didn't need insulin therapy at all [33]. A logical consequence of this observation is the reduction in insulin dose requirements. For patients with GFR >50 mL/min/1.73 m^2, no dose adjustment is required. For those with GFR values between 50–10 mL/min/1.73 m^2, it is recommended to decrease daily insulin doses by 25%, and even by 50% when GFR is less than 10 mL/min/1.73 m^2 [2, 4, 34].

Similar modifications applies to administration of insuline analogues. In patients with GFR reduction of less than 60 mL/min, the mean dose of insulin lispro should be reduced for aproximately 30% [33]. In contrast, patients with diabetes treated with insulin aspart do not show any singinificant change in the insulin dosage in relation to the renal filtration rate [35]. Recent studies show that type 1 diabetics with GFR less than 60 mL/min/1.73 m^2 requires daily dose reduction of insulin glargine by 32% and insulin detemir by 26% [33, 36].

Although current guidelines recommend maintaining of normoglycemia by implementing intensive treatment in diabetics with CKD, the potential benefits of this modality must be balanced against risk of hypoglycemia. Some authors recommend avoiding intermediate and long-acting insulin preparations in patients with CKD, while others advocate for their use. Individual approach when using combination of intermediate-acting and regular insulins or similarly acting analogues, seems to be the most acceptable for the achievement of satisfactory assessing glycemic control in this population [4].

Oral antidiabetic agents-dose adjustment

In contrast to scarce information concerning insulin treatment modifications in DKD, phamacological properties of oral antidiabetic agents and non-insulin injectables in chronic kidney failure, are rather well characterised throughout current literature.

Renal clearance of metformin is approximately 3.5-fold greater than creatinine clearance (CrCl), which indicates that tubular secretion is the major way of metformin elimination. After oral administration, approximately 90% of the absorbed medication is eliminated through the kidneys within the first 24 h, with the plasma half-life of approximately 6 h. In patients with decreased renal function based on measured CrCl, the plasma half-life of metformin is extended. Therefore, metformin should be avoided in patients with moderate to severe CKD. This refers to those on dialysis since the risk of metformin accumulation and lactic acidosis increases in line with the degree of reduction in GFR [37, 38].

The evidence suggests that metformin can be safely used in patients with plasma creatinine level less than 132 mmol/L. Since serum creatinine level may overestimate renal function, it is recommended to assess GFR. The clearance of metformin decreases by about 75% when the GFR is less than 60 mL/min/1.73 m^2 without any additional changes until the GFR reduction reaches value of 30 mL/min/1.73 m^2. With this value of the renal impairment, serum levels of metformin is only about two-fold higher than with normal kidney function, and these levels are still only about 3% of those found in patients with true metformin-associated lactic acidosis [39]. According to this, the use of metformin in moderate CKD disease is still controversial. Most of authors agree that the use of metformin should be avoided in patients with CKD stages 3–5 and with other risk factors that increase the possibility for lactic acidosis (congestive heart failure, chronic obstructive lung disease and liver disease) [38]. In patients without these risk factors, they suggest that metformin may be safely used without dose adjustment in CKD stages 3A and with half-dose reduction in stage 3B. For instance, the United States Food and Drug Administration (FDA) indicates that the use of metformin is forbidden for males with serum creatinine level equal or above 132 mmol/L and for female with serum creatinine level equal or higher than 124 mmo/L [18]. Other authors claim that the restriction of metformin use based on creatinine cutoffs provided by FDA, or a GFR cutoff of less than 60 ml/min is questionable, based on its clear clinical benefit [40]. This advice was adopted by current United Kingdom guidelines, as well as the Japanese Society of Nephrology, allowing metformin use until GFR drops below 30 mL/min/1.73 m^2 with the caution and dose reduction recommended at its level of 45 mL/min [18, 41].

First generation sulfonylureas are strictly forbidden in patients with CKD [1]. Glipizide is rapidly absorbed, reaching peak concentrations after 1.5 hours and is eliminated primarily by hepatic biotransformation. Approximately 90% of absorbed glipizide is excreted as biotransformation products in urine and feces, while less than 10% of a dose is excreted without any change [38, 39]. Glipizide is therefore a preffered oral anti-diabetic agent as it does not have active metabolites and does not increase the risk of hypoglycemia in patients with CKD stages 3–5 [1]. Gliclazide is extensively metabolised into various inactive metabolites and mainly excreted by the urine. Chronic kidney failure has little effect on the pharmacokinetic profile of this drug, and does not require dose adjustment for GFR from 30 to 60 mL/min [42]. After oral administration and absorbtion, glimepiride undergoes extensive hepatic metabolism to the inactive M2 metabolite, with the elimination half-life of 5-8 hours. Glimepiride clearance tends to increase in patients with CKD as GFR decreases, the terminal half-life is unaffected. Since the urinary clearance of its metabolites decreases with decreasing creatinine clearance, this drug can be used in patients with chronic kidney failure stages 3 and 4 with dose adjustment to the maximum of 1 mg daily [42, 43].

Glibenclamid should be avoided in patients with moderate to severe CKD (GFR less than 60 mL/min/1.73 m^2 [1].

The two available representative of thiazolidinediones (rosiglitazone and pioglitazone) are extensively metabolized by the liver. Rosiglitazone is mainly metabolized into inactive metabolites and less than 1% of the given drug dose appears in the urine in unchanged form. The half-life of rosiglitazone is similar in patients with end stage renal disease and in healthy individuals [44]. The same applies to pioglitazone. Its pharmacokinetic profile is similar in patients with normal renal function and CKD, as well as in those undergoing dialysis treatment [45]. These two drugs might also improve uremia-associated insulin resistance. So, this class of drugs can be administered without dose adjustment to patients with CKD stages 3 to 5, including those receiving dialysis. Potential side effects of peroxisome-proliferator-activated receptor-gamma (PPAR-gamma) treatment include fluid retention, hemodilution, bone loss and weight gain. Therefore, glitazones must be used with caution as they can increase fluid retention and deteriorate congestive heart fauilure, in the same as they can worsen underlying bone disease (renal osteodystrophy) [1].

Acarbose is the alfa-glucosidase inhibitor. This drug is only minimally absorbed after oral administration, but with the progression of kidney failure, serum level of acarbose and its metabolites increase significantly. In patients with severe renal failure and creatinine clearance less than 25 mL/min, the serum level of this drug become 5-fold higher than in healthy controls [38]. Therefore, American giudelines recommend that alfa-glucosidase inhibitors, including acar-

bose and miglitol, should be avoided in patients with GFR less than 25 mL/min/1.73 m^2 (or serum creatinine levels above 176 mmol/L) [44]. Despite this, Japanese autors recommend administration of acarbose without dose adjustment even in the dialysis population [46].

Exenatide and liraglutide are injectable incretine mimetics. Incretins, such as human glucagone-like peptid-1 (GLP-1), are hormones that are produced by the intestine and secreted into the blood stream, after food ingestion. On the other hand, the dipeptidyl-peptidase (DPP-4) inhibitors, such as sitagliptin, saxagliptin and linagliptin, decrease the degradation of GLP-1 and improve post-prandial glucose level. The kidney provides the main route for elimination and degradation of exenatide. In patients with modetare renal failure and CrCl more than 30 mL/min exenatide exposure was similar to healthy controls [47]. In subjects on dialysis, mean exenatide exposure increases 3.4 fold compared to subjects with normal kidney function. Therefore, according to the US guidelines, exenatide is not recommended for use in patients with a GFR less than 30 mL/min/1,73 m^2 [1].

The metabolism of liraglutide is similar to that of other large peptides, and there is no indications that the kidney is the major organ for its elimination. However, according to KDOQI recommendations, use of liraglutide should be avoided in patients with GFR less than 60 mL/min/1,73 m^2 [1].

Sitagliptin is primarily eliminated by the kidney *via* active secretion and glomerular filtration with approximately 80% of the oral dose excreted unchanged in the urine. As a consequence of this, it is recommended to adjust oral dose of sitagliptin for CKD stage 3 (50 mg daily) and stage 4 and 5 (25 mg daily). In contrast to other DPP-4 inhibitors, the major metabolite of saxtagliptin, is also pharmacologicaly active, but with only half of original potency. This drug is cleared by both hepatic metabolism and renal excretion. Therefore it is recommended to estimate the kidney function before starting saxagliptin therapy [38, 39]. Renal excretion is a minor elimination pathway of linagliptin at therapeutic dose level; therefore, a dose adjustment in subject with CKD is not required for this drug [38].

SGLT2 inhibitors are novel glucose-lowering agents that have been approved for the treatment of adults with type 2 diabetes. These drugs decreases reabsorption of filtered glucose in the renal tubule, and increases urinary glucose excretion with a consequent lowering of its plasma levels. The associated reduction in blood pressure may be related to adverse events of these drugs including urinary tract infections, osmotic diureasis and volume depletion. SGLT2 inhibition has been associated with modest, transient decrease in GFR, ranging from 3% to 10% that attenuated with continued treatment, and are consistent with volume loss associated with the osmotic diuresis [48]. Therefore, with progression of renal failure the treatment with SGLT2 becomes gradually ineffective. Canagliflozin therapy should not be started in patients with end-stage renal disease, on dialysis, or in those patients with GFR less than 60mL/min/1.73m^2. In canagliflozin-treated patients whose GFR falls below 60 ml/min/1.72 m^2 dose should be adjusted to 100 mg once daily [49]. In patients with moderate renal impairment, use of dapagliflozin was associated with increased incidence of renal-related adverse events [50]. Although renal function does not seem to be affected, the use of dapagliflozin in subjects with moderate to severe CKD (CrCl less than 60 mL/min) is not recommended [39].

Conclusion

Measurement of HbA1c remains the best clinical marker of long-term glycemic control in patients with diabetes and CKD. Glycated albumin might be more useful for assesment of glycemic control in patients with advanced stages of DKD. A HbA1c target value associated with the best outcome in predialysis and dialysis diabetics has not been established so far. According to recent longitudinal clinical trials, intensified glycemic control in diabetics with CKD leads to a substantial increase in severe and non-severe hypoglycemia, without reduction in the risk of major adverse cardiovascular disease events. Therefore it is recommended that the target HbA1c values for patients with long-standing diabetes and comorbidities including those with CKD, should be raised from 7% to 8%. Maintaining good glycemic control in the presence of reduced kidney function is complicated by altered glucose and insulin homeostasis. Decreased renal gluconeogenesis accompanied with a reduction in clearance of insulin and certain oral hypoglycemic agents, leads to an increased risk of hypoglicemia. Therefore, kidney function of each patient should be monitored and meticulously assessed. Oral antidiabetic drug selection, insulin dosage or the choice of insulin regimen type, as well as the maintenance of the best possible glycemic control must be individualy modified, taking into account that potential benefits must be balanced against potential risks.

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CASE REPORTS

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Aortoesophageal and aortobronchial fistula caused by *Candida albicans* after thoracic endovascular aortic repair

Aortoezofagusna i aortobronhijalna fistula posle endovaskularnog lečenja torakalne aorte od infekcije koju je izazvala *Candida albicans*

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Abstract

Introduction. Endovascular stent-graft placement has emerged as a minimally invasive alternative to open surgery for the treatment of aortic aneurysms and dissections. There are few reports on stent graft infections and aortoenteric fistula after endovascular thoracic aortic aneurysm repair, and the first multicentric study (Italian survey) showed the incidence of about 2%. **Case report.** We presented a 69-year-old male patient admitted to our hospital 9 months after thoracic endovascular aortic repair, due to severe chest pain in the left hemithorax and arm refractory to analgesic therapy. Multislice computed tomography (MSCT) showed a collection between the stent graft and the esophagus with thin layers of gas while gastroendoscopy showed visible blood jet 28 cm from incisive teeth. Surgical treatment was performed in collaboration of two teams (esophageal and vascular surgical team). After explantation of the stent graft and *in situ* reconstruction by using Dacron graft subsequent esophagectomy and graft omentoplasty were made. After almost four weeks patient developed hemoptisia as a sign of aortobronchial fistula. Treatment with implantation of another aortic cuff of 26 mm was performed. The patient was discharged to the regional center with negative blood culture, normal inflammatory parameters and respiratory function. Three months later the patient suffered deterioration with the severe weight loss and pneumonia caused by *Candida albicans* and unfortunately died. The survival time from the surgical treatment of aortoesophageal fistula was 4 months. **Conclusion.** Even if endovascular repair of thoracic aortic diseases improves early results, risk of infection should not be forgotten. Postoperative respiratory deterioration and finally hemoptisia could be the symptoms of another fistula.

Key words:
aortic aneurysm, thoracic; surgical procedures, minimally invasive; stents; postoperative complications; reoperation; candida albicans.

Apstrakt

Uvod. Endovaskularno lečenje aortnih oboljenja je minimalno invazivna alternativa otvorenim hirurškim procedurama. Infekcije implantiranog stent-grafta do sada su opisane sa incidencijom od 2%, ali nije bilo slučajeva aortoezofagusne i aortobronhijalne fistule kod istog bolesnika. **Prikaz bolesnika.** Bolesnik star 69 godina, primljen je u našu ustanovu devet meseci nakon endovaskularnog lečenja posttraumatske hronične aneurizme torakalne aorte zbog naglo nastalih bolova u grudnom košu i ruci refraktarnih na terapiju. Multislajsna kompjuterska tomografija pokazala je nakupinu između stent-grafta i ezofagusa sa tankim slojem gasa, dok je gastroskopija pokazala krvarenje na 28 cm od sekutića. Hirurško lečenje primenjeno je u saradnji vaskularnog tima i tima za hirurgiju jednjaka. Nakon eksplantacije stent-grafta i *in situ* rekonstrukcije Dakronskim graftom učinjena je ezofagektomija i omentoplastika grafta. Nakon četiri nedelje bolesnik je dobio hemoptizije kao znak aortobronhijalne fistule koja je uspešno lečena implantacijom aortne ekstenzije. Bolesnik je otpušten u regionalnu ustanovu sa negativnom hemokulturom, normalnim inflamatornim parametrima i respiratornom funkcijom. Nakon tri meseca, usled novog respiratornog pogoršanja u vidu pneumonije uzrokovane gljivicom *Candida albicans* bolesnik je preminuo. Vreme preživljavanja od operacije aortoezofagusne fistule iznosilo je četiri meseca. **Zaključak.** Iako je endovaskularno lečenje oboljenja torakalne aorte značajno unapredilo rane rezultate, ne treba zaboraviti na rizik od infekcije stent-grafta. Pogoršanje respiratorne funkcije i hemoptizije nakon operacije mogu biti znak nove fistule kod ovakvih bolesnika.

Ključne reči:
aneurizma, torakalna; hirurgija, minimalno invazivne procedure; stentovi; postoperativne komplikacije; reoperacija; candida albicans.

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Introduction

Endovascular stent graft placement has emerged as a minimally invasive alternative to open surgery for the treatment of aortic aneurysms and dissections [1, 2]. The incidence of early and major complications is low, however long term results are about to come. There are few reports of stent graft infections and aortoenteric fistula (AEF) after endovascular thoracic aortic aneurysm repair; small series have reported rates of up to 5% after stent graft placement, and the first multicentric study (Italian survey) showed the incidence of about 2% [3, 4].

Case report

We presented a 69-year-old male patient admitted to our hospital due to dysphagia, hoarseness and chest discomfort. After examination by means of chest radiography and multislice computed tomography (MSCT), posttraumatic thoracic aneurysm of 65 mm in diameter was revealed, due to frontal chest trauma 30 years ago in a car accident. The patient was successfully treated by endovascular stent graft implantation (Medtronic, Santa Rosa, CA-Valiant) using 12% of oversize. Perioperative antibiotics were used in usual prophylactic dosage (cephazolin 1.5 g i.v. at the beginning of the procedure, and every 8 hours for 72 hours). Postoperative recovery was uneventful and the patient was discharged after control MSCT had shown complete exclusion of aneurysm with the correct position of the stent graft, and preservation of left subclavian artery flow. First month control MSCT was also correct, while 9 months later the patient was admitted to the regional hospital with severe chest pain in the left hemithorax and the left hand refractory to analgesic therapy. The patient was treated with symptomatic therapy and 3 weeks later refered to our hospital with the same symptoms of inflammatory syndrome (leucocytes 18×10^{-9}, sedimentation rate 105 of the first hour, C-reactive protein 150 mg/L, incipient anemia, fever and malaise), and blood culture test positive on *Candida albicans*. MSCT was performed showing the normal stent graft position, no fracture, no endoleak, and a collection between stent graft and the esophagus with thin layers of gas (Figure 1).

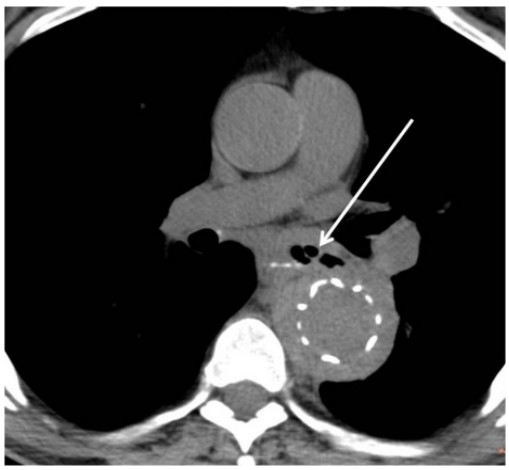

Fig. 1 – Axial image of the stent-graft implanted in the thoracic aorta with a gas collection in the surrounding tissue (arrow).

Gastroendoscopy was performed, and visible blood jet 28 cm from incisive teeth was visualized. Short after this examination the patient had first time hematemesis of 500 mL of fresh blood. Blakemore tube was used to control hemorrhage temporarily. Surgical treatment was performed in collaboration of two teams (esophageal and vascular surgical team). In condition of partial femoro-femoral extracorporal bypass (ECBP), through left thoracotomy in the 4th intercostal space, there was no visible hematoma, and no visible hemorrhage, but diffuse inflammation was noticed, with adhesions between the thoracic aorta, the esophagus and the left lung. Proximal control was gained between the origins of the left common carotid and the left subclavian artery, while distal control was secured in the distal thoracic aorta, 3 or 4 cm distal from the lower margin of the stent graft. After resection of the thoracic aorta and explantation of the stent graft, *in situ* reconstruction by using Dacron graft was made. After that it was much easier to divide esophagus from severely inflammation of periaortic tissue, and to perform esophagectomy. Midline laparotomy, mobilization of peritoneum and its transposition through diaphragm incision, and omentoplasty of Dacron graft were followed by nutritive gastrostoma and cervical jejunostoma (Figures 2a, b and c).

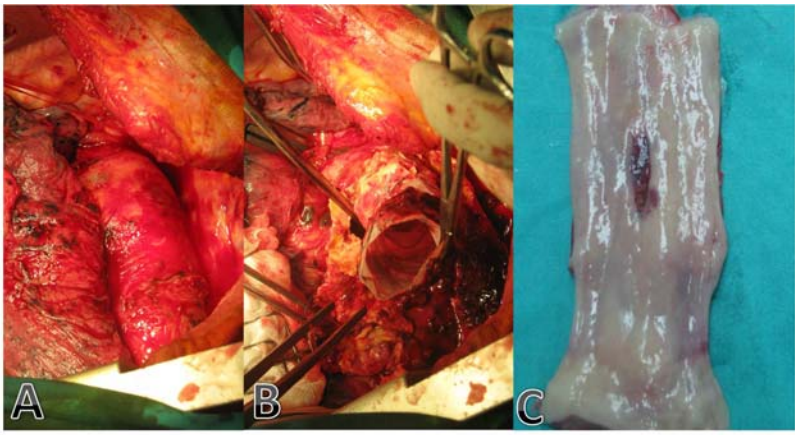

Fig. 2 – A) Inflammation of the thoracic aorta and surrounding tissue without extravasation of blood; B) Explantation of the thoracic stent-graft; C) Short lesion on the inner wall of the explanted esophagus.

Culture of the aneurysmatic sac and explanted stent graft was positive on *Candida albicans*, as well as was sputum culture. In the long lasting postoperative recovery time a lot of problems occurred. During almost four weeks of slow recovery, several evacuations of 500–1000 mL of pleural effusion (positive on *Candida albicans*) were performed. Eventually, the patient developed hemoptisis. Control MSCT revealed a n aortobronchial fistula at the level of proximal anastomosis and the left principal bronchus. According to the patient general condition we decided to perform endovascular treatment with implantation of another stent graft. The only stent graft available on shelf was aortic cuff of 26 mm that was successfully implanted and patient respiratory function recovered slowly, as was further general recovery (Figures 3a and b).

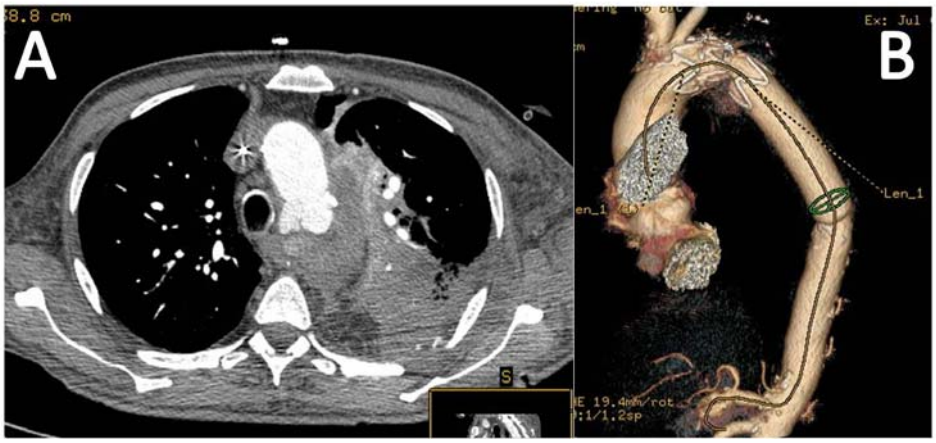

Fig. 3 – A) Periaortic hematoma and extravasation of blood at the level of the proximal anastomosis causing hemoptisia; B) Short aortic cuff implanted in the thoracic aorta due to suspected aortoesophageal fistula.

All these procedures and difficult recovery caused severe muscle atrophy and needed weeks to recover. The patient was discharged and referred to the regional center with negative blood culture, normal inflammatory parameters and respiratory function. Three months later the patient suffered deterioration with a severe weight loss and pneumonia caused by *Candida albicans* and unfortunately died. The survival time from the surgical treatment of aortoesophageal fistula was 4 months.

Discussion

Introduction of new technologies and minimally invasive surgery did not change our relation to one of the biggest challenges in vascular surgery – graft infection: it still happens! Minimally invasive surgery increased the number of treated patients, as well as the total number of patients with this complication. Thoracic endografting not only increased the number of treated patients, and the frequency of comorbid conditions, but it also consequently devastated the immune system making the patient more susceptible to infection. In addition, endovascular stent grafts are more susceptible to infection than grafts for open surgery [5].

Treatment of this severe and devastating condition in the presented patient was even more difficult because of the delayed diagnosis partly because of the fact that clinical presentation was unusual. The patient complained of left arm and hemithoracic chest pain with no inflammatory syndrome. Very thin periaortic inflammation was visible but inexperience made us not be act. Probably it could be much more easier to treat this initial infection – periaortitis. Later on, the patient was admitted with severe infection and active bleeding. Surgical repair of infection in thoracic cavity is much more demanding than the same complication in the abdominal position when extra-anatomic reconstruction (axillobifemoral) is feasible. Extra-anatomic reconstruction due to thoracic graft infection considers a two-stage procedure: bypass from the ascending to distal descending thoracic aorta, or supraceliac aorta, as the first and extirpation of the stent graft and ligature of the thoracic aorta as the second stage [6]. This kind of procedure is possible when the diagnosis is established timely, because the first stage does not resolve bleeding that can be dreadful. Alternative could be another endovascular procedure as a bridge to control bleeding, and then the two stage procedure with removal of the infected graft and adjusted structures in the second stage. However, since we did not have any stent grafts on the shelf, we performed the one-stage procedure due to unstable condition with esophageal bleeding of the patient.

Causes of stent graft infections have several explanations: it could be an already present fistula, or contamination from intraluminal aneurysmatic thrombus, or surgical primary contamination during surgical manipulation (more frequent in radiology suits). There are some other theories like ischemia of esophageal or bronchial wall caused stent implantation, or aggressive oversizing [7, 8]. A lot of possible causes of this complication suggest that the multifactorial pathogenesis is most probable. An isolated infected organism could reveal a possible cause, if skin bacteria are isolated than skin contamination is more probable. In the presented patient *Candida albicans* was isolated from blood, aneurysmatic sac and stent graft specimens. Even more in postoperative recovery *Candida albicans* was isolated from pleural effusions as well as from sputum during pneumonia just before death - it has never been eradicated. Only three cases with *Candida albicans*

contamination were reported and all with lethal outcome. The early diagnosis could give us time for initial antifungal therapy with modern developed drugs, however due to unstable condition in the presented case there was no time for this.

Conclusion

Although endovascular repair of thoracic aortic diseases improves early results, risk of infection should not be forgotten. Close follow-up and the timely diagnosis could give us time for preparing a patient with potential antimicrobial medications, and for extra-anatomic, two-stage reconstruction. Postoperative respiratory deterioration and finally hemoptisia could be the symptoms of another fistula.

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C A S E R E P O R T

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Central retinal vein occlusion – A patient with systemic sclerosis

Okluzija centralne vene retine kod bolesnice sa sistemskom sklerozom

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Abstract

Introduction. Scleroderma (systemic sclerosis) is a severe chronic connective tissue disease, which results in involvement of numerous internal organs. Changes in the eye are the consequences of organ-specific manifestations of scleroderma or adverse effects of immunosuppressive treatment applied. **Case report.** We reported a 42-year-old woman with systemic sclerosis and acute deterioration of vision in the left eye, with visual acuity 0.9. After thorough clinical examination, including fluorescein angiography and optical coherence tomography, the diagnosis of nonischemic central retinal vein occlusion was made. Further biochemical, rheumatological and immunological investigation, apart from inactive systemic sclerosis, showed normal findings. Therefore, the cause of central retinal vein occlusion could only be attributed to the microvascular changes in systemic sclerosis. After three months, visual acuity deteriorated to 0.6 due to the development of cystoid macular edema. The patient received intravitreal injection of bevacizumab and after a single dose visual acuity improved to 0.9. After a 6-month follow-up, macular edema resolved and visual acuity stabilized. **Conclusion.** According to our knowledge and current data from the literature, central retinal vein occlusion is a rare vision threatening manifestation of scleroderma. There are only few published case reports on central vein occlusion in scleroderma patients. Examination of the ocular fundus is recommended for evaluation of vascular disease in patients with systemic sclerosis.

Key words:
scleroderma, systemic; retinal vein occlusion; diagnosis; angiogenesis inhibitors; treatment outcome.

Apstrakt

Uvod. Skleroderma (sistemska skleroza) je ozbiljna hronična bolest vezivnog tkiva, koja zahvata brojne unutrašnje organe. Promene u oku mogu da budu posledica organ-specifičnih manifestacija skleroderme ili se mogu javiti usled neželjenih efekata imunosupresivne terapije koja se koristi u lečenju. **Prikaz bolesnika.** U radu je prikazana 42-godišnja bolesnica sa dijagnozom sistemske skleroze i naglim pogoršanjem vida na levo oku (sa vidnom oštrinom 0,9). Nakon detaljnog kliničkog pregleda, uključujući fluoresceinsku angiografiju i optičku koherentnu tomografiju, postavljena je dijagnoza neishemične forme okluzije centralne vene retine. Dalja biohemijska, reumatološka i imunološka ispitivanja, osim inaktivne sistemske skleroze, pokazala su normalan nalaz. Stoga je utvrđeno da je jedini uzrok venske okluzije predstavljaju mikrovaskularne promene u sklopu sistemske skleroze. Nakon tri meseca, vidna oštrina levog oka se pogoršala na 0,6 usled razvoja cistoidnog makularnog edema. Bolesnica je primila intravitrealnu injekciju bevacizumaba i nakon samo jedne doze vidna oština se popravila na 0,9. Nakon šest meseci praćenja, makularni edem se povukao, a vidna oština je ostala nepromenjena. **Zaključak.** Prema našim saznanjima i uvidom u literaturu, okluzija centralne vene retine je retka manifestacija skleroderme, koja može da ugrozi funkciju vida. Postoji svega nekoliko objavljenih radova u kojima je prikazana centralna venska okluzija kod ovih bolesnika. Kod bolesnika sa sistemskom sklerozom preporučuje se pregled zadnjeg segmenta oka radi procene mogućih vaskularnih promena.

Ključne reči:
sklerodermija, sistemska; okluzija retinalne vene; dijagnoza; angiogeneza, inhibitori; lečenje, ishod.

Introduction

Systemic sclerosis (scleroderma – SSc) is an autoimmune disorder with fibrovascular manifestations that may affect many organ systems [1]. It is an unusual but not rare disease [2], characterized by immune system disorders and altered structure and function of blood vessels [3]. Clinical forms of SSc can range from limited skin involvement (limited cutaneous systemic sclerosis) to forms with diffuse skin sclerosis and severe and often progressive internal organ involvement (diffuse cutaneous systemic sclerosis) [4]. Criteria for the diagnosis of SSc established by the American College of

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Rheumatology include major and minor criteria. Major criteria consist of anterior scleroderma (thickening of the skin) affecting the arms, face, and/ or neck, while minor criteria include digital pitting scars or the loss of the volar pads of the finger tips, pulmonary fibrosis and sclerodactyly (sclerosis affecting the fingers or toes). SSc is diagnosed when a patient has one major or two minor criteria [5].Treatment of SSc comprises the use of drugs that affect collagen formation such as D-penicilamin, colchicine and interferon gamma [6].

Scleroderma patients often report eye problems, although there are few reports available concerning ophthalmological manifestations in systemic sclerosis [7]. Because of the rare nature of the disease, most papers had single case reports or small case series [8]. Ocular symptoms may occur at any stage of the disease. Their course may be clinically latent or very intensive, and they may involvenumerous ocular structures [7]. Although patients with SSc are known to have variety of vascular abnormalities, retinal vascular changes are not well understood. Only a few published case reports have referred to occlusion of retinal arteries or veins in SSc [2, 8–10]. The aim of this paper was to review the variety of ocular manifestations in patients with systemic sclerosis. We also reported a case of central retinal vein occlusion (CRVO) as a rare manifestation of scleroderma.

Case report

A 42-year-old woman presented with acute, painless vision loss in the left eye of 10 days duration. In her medical history was noted systemic sclerosis that was treated for 22 years in the rheumatology and dermatology clinic. The patient underwent complete ophthalmological examination at baseline including medical history; visual acuity assessment (measured by Snellen chart); applanation tonometry; slit lamp examination; indirect ophthalmoscopy with 90D lens; optical coherence tomography (OCT); fundus photography and fluorescein angiography (FA); immunological and biochemical investigation.

General examination revealed terminal ulceration and flexion deformity of the digits (Figure 1). The skin on her face and upper limbs was taut, thickened and hidebound with scattered telangiectatic changes. The nose was pinched and the mouth slightly smaller than normal and puckered. History was negative for any other medical problems such as pulmonary, cardiac or renal diseases. The admission best corrected visual acuity (BCVA) was 1.0 and 0.9 in the right and left eye, respectively; intraocular pressure was within the range. Both pupils were normal with no relative afferent pupillary defect. Slit-lamp examination revealed reduced tear meniscus. Schirmer's test showed diminished tear secretion after 5 minutes, right 5 mm and left 8 mm. Fundus examination of the right eye showed no abnormalities, while in the left eye central retinal vein occlusion (CRVO) was noted (Figure 2). Fluorescein angiography of the right eye had normal findings for her age, while in the left eye delayed filling of choroidal lobules, enhanced perivascular leakage and macular edema were present (Figures 3, 4). Optical coherence tomography of the left eye showed cystoid macular edema with the central macular thickness of 377 μm (Figure 5).

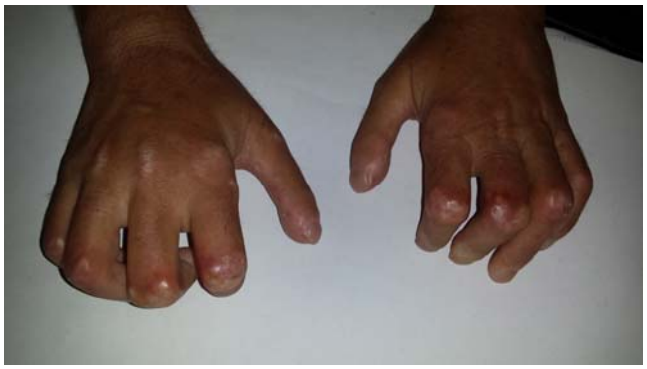

Fig. 1 – The fingers were fixed in a flexion deformity and terminal ulcers were present on both hands.

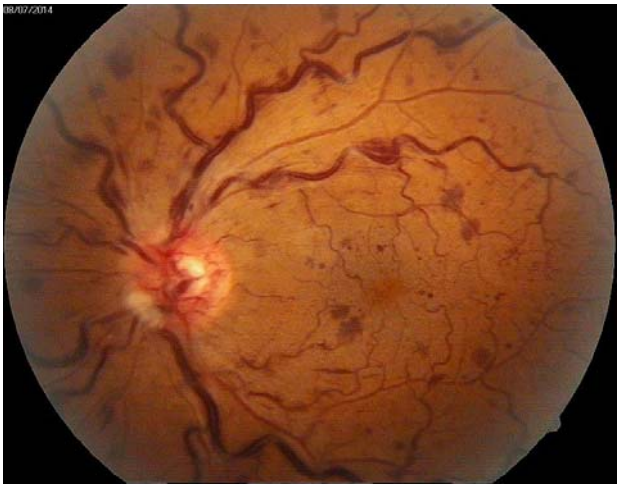

Fig. 2 – Fundus photography of the left eye showed central retinal vein occlusion.

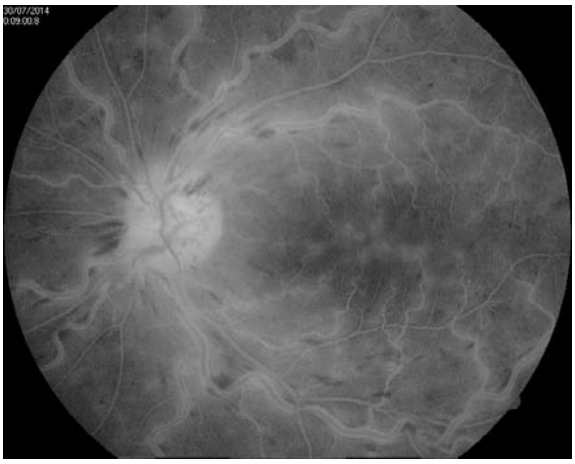

Fig. 3 – Fluorescein angiography of the left eye showing enhanced perivascular leakage, macular edema and capillary closure.

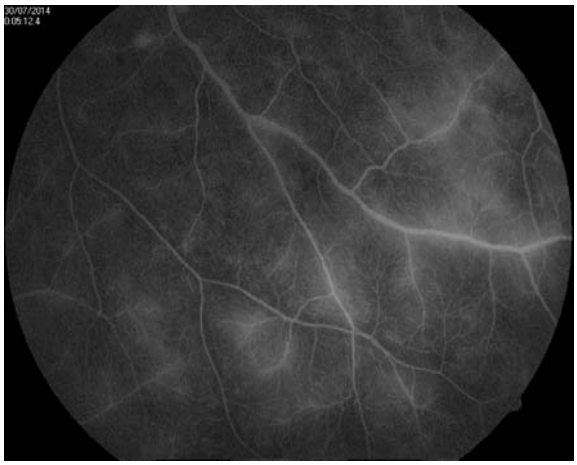

Fig. 4 – Fluorescein angiography of the left eye in the late venous phase shows inflammatory reaction within the peripheral venous vessel with increasing dye leakage.

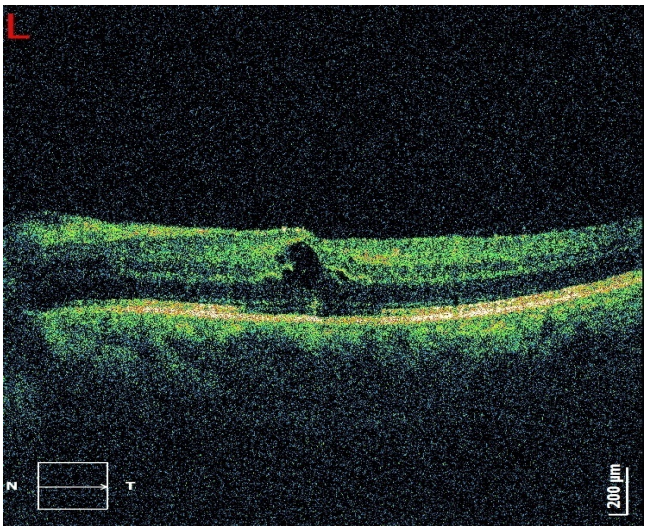

Fig. 5 – Spectral Domain (SD) optical coherence tomography of the left eye showing macular edema.

All investigations at presentation such as complete blood count (white blood cells 7.7 × 10^{-9}/L; neutrophils 64.2%; lymphocytes 25.8%; monocytes 8.4%; eosinophiles 1.5%; basophiles 0.1%; erythrocytes 5.0 × 10^{-12}; platelets 265 × 10^{-9}/L); parameters of inflammation (erythrocyte sedimentation rate 10 mm/h; fibrinogen 3.61 g/L; C-reactive protein 0.2 mg/L); parameters of hemostasis (prothrombin time 12 s; partial thromboplastin time 28 s); blood glucoselevel (5.2 mmol/L); parameters of renal function (urea 4.7 mmol/L; creatinine 62 mmol/L; uric acid 289 mmol/L); parameters of liver function (AST 16 U/L; ALT 12 U/L; total bilirubin 9.5 mmol/L); total serum proteins (70 g/L) and protein fractions (albumin 53.6%, α1 3.4%, α2 13.2%, β1 9.0%, β2 5.9, γ 14.9%); serum lipids (cholesterol 4.8 mmol/L; triglycerides 1.3 mmol/L) and homocistein (14.75 µmol/L) were within normal limits. Immunofixation of serum proteins did not reveal M component. Serum autoantibody profile was obtained and only titer of anti-nuclear antibodies (ANA Hep-2, IIF) were positive (in > 1:640 dilution), while other autoantibodies including anticardiolipin antibodies, anti-β2 glycoprotein antibodies, antineutrophil antibodies (IIF) and ANCA were negative. Lupus anticoagulant was absent (activated partial thromboplastin time –APTT 27.9 s; LA1 40.80 s). Hematologist was consulted and genetic analyses including polymerase chain reaction (PCR) for mutations of clotting factor II (prothrombin G20210A), factor V (Leiden G1691A) and methylene tetrahydrofolate reductase (MTHFR C677T) genes were performed showing no genetic predisposition for hypercoagulability state. Also, other potential causes of CRVO, such as arterial hypertension, diabetes and glaucomawere assessed and excluded. After workup, patient underwent rheumatological treatment that included D-penicillamine (Metalcaptase®), calcium channel blockers (nicardipin 50 mg) and vitamin D drops.

Based on the ophthalmological findings, the diagnosis of nonischemic CRVO in the left eye was established. Three months after the onset of CRVO, best corrected visual acuity of the left eye decreased to 0.6 due to the development of macular edema. The patient received intravitreal injection of bevacizumab and after a single dose, the central retinal thickness (CRT) decreased to 229 µm and BCVA of the left eye improved to 0.9. The patient was followed up for 6 months

and although partial capillary nonperfusion on the periphery of the retina was noted (Figure 6), no other complications including retinal neovascularization, occurred.

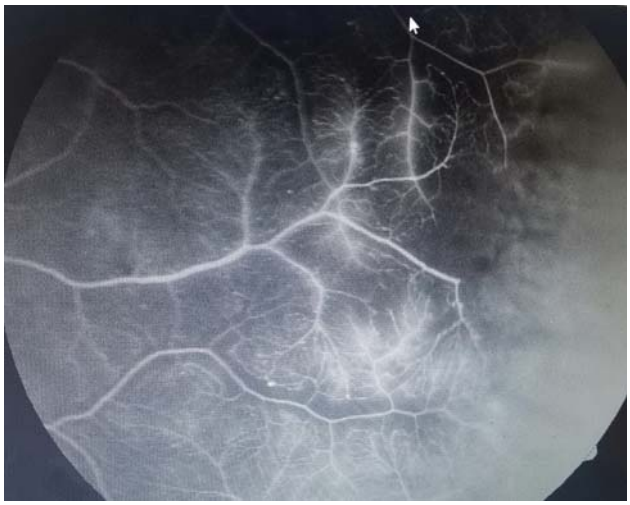

Fig. 6 – After a 3-month follow-up fluorescein angiography of the left eye showed areas of partial capillary nonperfusion on the periphery of the retina, with no neovascularization.

Discussion

Systemic sclerosis is an immunological connective tissue disease, which results in involvement of numerous internal organ systems [7]. The most characteristic feature of scleroderma is the increased collagen content in the skin and visceral organs, while the second feature is vascular disease, including Raynaud's phenomenon and diffuse microvasculopathy [11]. Our patient fulfilled diagnostic criteria for SSc provided by The American College of Rheumatology [5], as she had thickening and tightening of the skin of her face and arms, sclerodactyly, facial telangiectasia and digital pitting scars.

The ocular manifestations of scleroderma have not been sufficiently previously reported in the literature. Ocular changes can be one of the manifestations of scleroderma or adverse effects of immunosuppressive treatment applied [7]. Changes in the eye which are specifically related to scleroderma are: telangiectasia and dermal sclerosis of the eyelids, a tear defect of varying severity, injection and slugging of the blood column in conjunctival vessels and possibly punctate defects of the iris pigment epithelium [8]. Involvement of the posterior segment is frequently subclinical and visual loss as a direct result of the disease is not very often [12]. The retinal and choroidal microvascular changes are important because systemic sclerosis is practically a disease of small arteries [2]. Reported changes seen in the retina in patients with SSc are intraretinal hemorrhages, cotton wool spots and optic disc edema, which are most often related to malignant hypertension [13]. Ushiyama et al. [14] found that the main retinal changes in patients with SSc are hard exudates and tortuous vessels, most of whom were not hypertensive. They also reported that patients with SSc had a higher incidence of retinal changes associated with vascular damage than controls (p = 0.01) [14]. Fluorescein angiography from previous studies demonstrated abnormalitis of perfusion, which affected the chorio capillaris and small choroidal arterioles [15]. In addition, Milenkovic et al. [16] presented a case of localized scleroderma with well demarcated areas of choroidal sclerosis and retinal capillary nonperfusion. These observations suggest that vascular alterations in scleroderma, does occur, although uncommonly [15].

Besides SSc, the presented patient had no related systemic diseases that could cause CRVO and this manifestation of scleroderma was reported only few times in the literature [9, 10, 14, 17]. The cases reported by Saari et al. [9] and Gomes et al. [10] suffered from other systemic diseases such as secondary polycythemia, cardiovascular insufficiency and pulmonary fibrosis which could contribute to the pathogenesis of CRVO and therefore, scleroderma could not be considered as the direct cause of CRVO. On the other hand, Malik and Al Habash [17] excluded diabetes, hypertension, blood dyscrasias, clotting disorders and sickle cell disease as the causes of CRVO.

No signs of retinal neovascularization were noted in the presented case during the follow-up period, although partial capillary nonperfusion on the periphery of the retina was present. Waszczykowska et al. [7] in their study of 27 patients with SSc found no case of retinal neovascularization, even with significantly advanced ischemic retinopathy, which could be contributed to the impairment of angiogenesis that is typical in the course of scleroderma [7]. However, Minasian et al. [12] first reported a case of bilateral ischemic retinopathy with neovascularization of the disc with beneficial response to laser photocoagulation [12]. To date, only two cases of proliferative retinopathy in SSc patients with concomitant autoimmune diseases, including dermatomyositis and polymyositis, have been reported in the literature [18].

Previous reports warrant further investigations to evaluate the involvement of small choroidal and retinal arterial system in systemic sclerosis, since small vessels are involved in other organs [16].

Conclusion

Ocular symptoms are relatively common manifestation of systemic sclerosis. However, they can greatly vary from discomfort due to dry eye symptoms to complete blindness and should be systemically looked for during ophthalmological exam. In the presented case, ocular symptoms were caused by nonischemic central retinal vein occlusion. Thorough work-up and timely treatment was needed in order to prevent more serious irreversible changes in the organ of vision, such as retinal neovascularization and neovascular glaucoma. An ophthalmologist should look for the presence of even subtle retinal vascular abnormalities in patients with systemic sclerosis since the presence of those can aid in proper monitoring of the disease progression and indicate the need for more aggressive systemic treatment.

Declaration if interest

The authors declare no conflict of interest.

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CASE REPORT

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Kartagener's syndrome: A case report

Kartagenerov sindrom

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Abstract

Introduction. Kartagener's syndrome is a recessive autosomal disease which is mainly seen to affect ciliary movement. The symptoms of the syndrome are the consequence of the defective motility of the cilia found in the respiratory tract and that results with recurrent lung infections caused by mucus stasis in the bronchi. **Case report.** A 37-year-old married male, father of one child, presented with the history of productive cough, wheezing, dispnea, headache, temporary fever. In his 9th year of age, in 1986, *situs inversus*, sinusitis and *pectus excavatum* were diagnosed. In 1994 he was operated for correction of *pectus* excavatum. Bronchial asthma was diagnosed in 2008 when he was 31. In the last 2 years he had episodes of breathlessness, wheezing, cough, expectoration, headache, fever and fast declining lung function. The patient was treated with combination of inhaled bronchodilatators (inhaled corticosteroids + long-acting β-2 agonist), and occasional administration of antibiotics, oral prednisolone, mucolytics in episodes of exacerbations of disease over a period of 7−14 days. **Conclusion.** Treatment for patients with this syndrome has not been established yet, but it is important to control chronic lung infections and prevent declining of lung function.

Key words:
kartagener syndrome; respiratory tract infection; bronhiectasis; therapeutics; fertility.

Apstrakt

Uvod. Kartagenerov sindrom je recesivno autozomno oboljenje koje se uglavnom ispoljava kao zahvatanje cilijarnog kompleksa. Simptomi se ispoljavaju kao posledica poremećaja u pokretljivosti cilija u respiratornom traktu, što rezultira ponavljanim infekcijama uzrokovanim zastojem sekreta u bronhijama. **Prikaz bolesnika.** Muškarac, star 37 godina, oženjen, otac jednog deteta, javio se na pregled sa simptomima produktivnog kašlja, zviždanja u grudima, gušenja, glavobolje i povremeno povišene telesne temperature. U devetoj godini života, 1986. godine, dokazan mu je *situs inversum*, sinuzitis i deformitet grudnog koša u vidu kokošijih grudi; 2008 godine dokazana mu je bronhijalna astma. U poslednje dve godine bolesnik je imao epizode otežanog disanja (sa „kratkim dahom"), zviždanjem u grudima, kašljem i iskašljavanjem, glavoboljom, groznicom i brzim pogoršanjem plućne funkcije. Lečen je kombinacijom inhalacionih bronhodilatatora (inhalacioni kortikosteroidi + dugodelujući β-2 agonisti) i povremenom primenom antibiotika, oralno prednizolona i mukolitika, tokom 7–14 dana, u epizodama pogoršanja bolesti. **Zaključak.** Lečenje bolesnika sa Kartagenerovim sindromom još uvek nije usaglašeno, ali treba da bude usmereno na kontrolu hroničnih plućnih infekcija i sprečavanje opadanja plućne funkcije.

Ključne reči:
kartagenerov sindrom; respiratorni trakt, infekcije; bronhiektazije; lečenje; plodnost.

Introduction

Kartagener's syndrome is a recessive autosomal disease which is mainly seen to affect ciliary movement [1]. The incidence of Kartagener's syndrome is 1–2/30,000 births. Siewert first described the combination of *situs inversus*, chronic sinusitis and bronchiectasis in 1904 [2]. Manes Kartagener, a pulmonologist in Zurich, first recognized this clinical triad as a distinct congenital syndrome in 1933. Kartagener described this syndrome in detail, so it bears his name [2]. The symptoms of the syndrome are the consequence of the defective motility of the cilia found in the respiratory tract and that results with recurrent lung infections caused by mucus stasis in the bronchi [1–3]. In older children and adults with primary ciliary dyskinesia, 3 diseases of the lower

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respiratory tract have been described: pneumonia, bronchiectasis and asthma [4]. Patients with Kartagener syndrome may have immotile spermatozona as well [5, 6]. Treatment for patients with this syndrome has not be established, but it is important to control chronic lung infections and prevent declining of lung function [7, 8].

Case report

A 37-year-old male, married, father of one child, presented with the history of productive cough, wheezing, dispnea, headache, occasional fever. In 1986 *situs inversus*, sinusitis and *pectus excavatum* were diagnosed. In 1994 the patient was operated for correction of *pectus excavatum*. In 2008 bronchial asthma was diagnosed. In the last 2 years he had episodes of breathlessness, wheezing, cough, expectoration, headache, fever and fast declining lung function.

At clinical bilateral examination, predominantly on the left side, crepitations and rhonchi were evidenced.

A chest X-ray showed dextrocardia, signs of pneumonia in lower pulmonary field on the left side (Figure 1).

Chest and abdominal CT revealed dextrocardia, bronchiectasis in the lower lobes, dominantly on the left side, left liver, gastric bubble and spleen on the right (Figures 2−5).

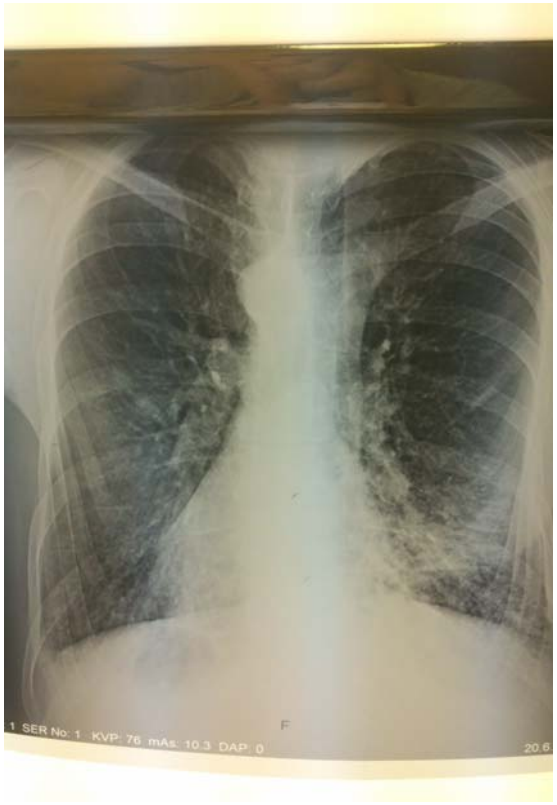

Fig. 1 – Chest radiograph shows dextrocardia and features of pneumonia in the left lower lung field.

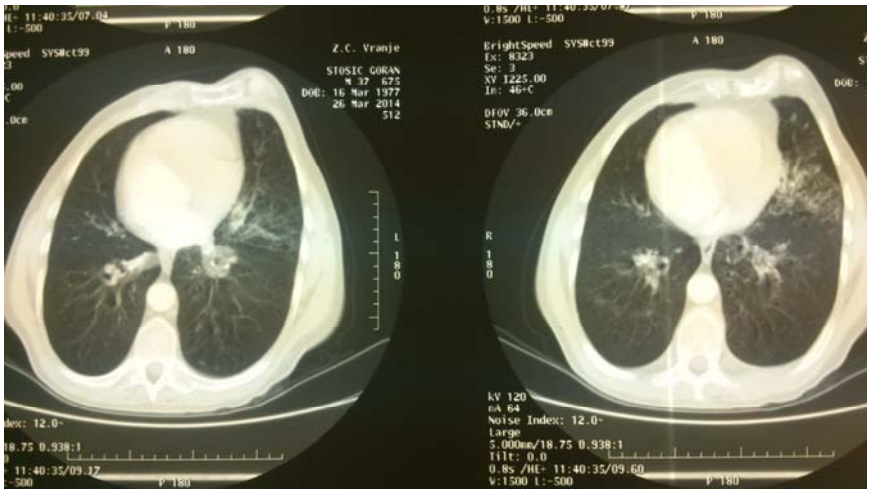

Fig. 2 – Contrast-enhanced computed tomography images show dextrocardia and bronchiestasis in the lower lobes, dominantly on the left side.

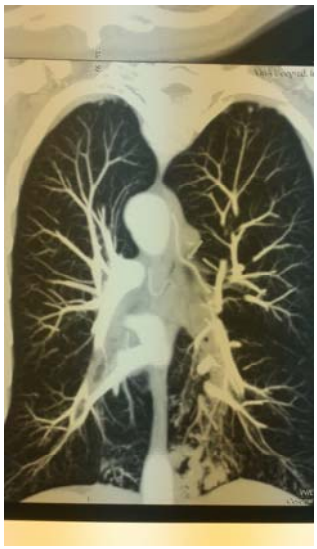

Fig. 3 – Chest contrast-enhanced computed tomography scan showing bronchiestasis in both lower lung lobes, dominantly in the left lower lobe.

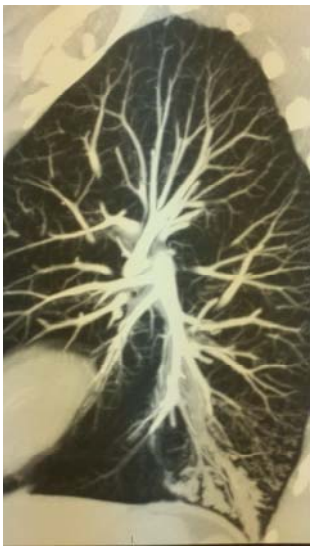

Fig. 4 – Chest contrast-enhanced computed tomography scan showing bronschiectasis, as previously described.

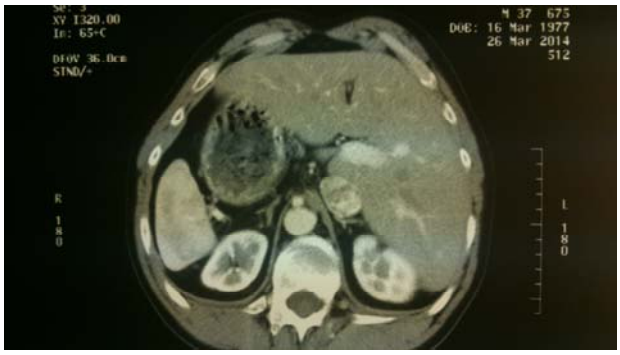

Fig. 5 – Abdominal computed tomography scan shows complete inversion of the internal organs: liver lying on the left side of the abdomen, gastric air bubble and spleen on the right side.

It was difficult to obtain correct images during echocardiography because of the chest abnormality (after the operation of *pectus excavatum*), but transthoracic echocardiogram and transesophageal echocardiography confirmed dextrocardia, too.

Spirometry demonstrated bronchial obstruction forced expiratory volume in 1s (FEV1) 1.6 L, 38% of predicted value (4.26 L), forced vital capacity (FVC) 58% (3.00 L) FEV1/FVC 64%.

As the patient was diagnosed with congenital Kartagener's syndrome 28 years ago, in the last two years he was treated with a combination of inhaled bronchodilatators (inhaled corticosteroids+long-acting beta-2 agonists), and occasional administration of antibiotics, oral prednisolone, mucolytics in episodes of exacerbations of disease over a period of 7–14 days. In the last year the patient was admitted to hospital 4 times because of exacerbations of bronchial asthma and inflmmation bronchiectasis.

Discussion

Kartagener's syndrome is seen in 50% of patients with primary ciliary dyskinesia. Kartagener's syndrome is characterized by *situs inversus*, bronchiectasis, sinusitis and otitis media. In some cases it is inherited with bronchial asthma. Our case is unusual for 2 reasons. Firstly, the presented patient was fertile and had a child. He refused to give a spermogram. Munro et al. [9] their show that 30% of their patients with primary ciliary dyskinesia have normal spermatozoa and that 2 patients are fertile. Secondly, the presented had *pectus excavatum*. In a study by Kennedy et al. [10] it was found that 10% patients with Kartagener's syndrome had *pectus excavatum*.

The presented clinical case demonstrated a progressive course of bronchiectasis, declining lung function, because of recurrent infections which were treated inappropriately in recents period.

Conclusion

We presented this case because the Kartagener's syndrome is a very rare condition.

The prognosis is generally considered favorable, and life expectancy is usually normal. An important part of the clinical visits at regular intervals should be monitoring the progression of the lung disease.

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CASE REPORT

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Primary hyperfibrinolysis as the presenting sign of prostate cancer – A case report

Primarna hiperfibrinoliza kao prezentujući znak karcinoma prostate

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Abstract

Introduction. A bleeding syndrome in the setting of primary hyperfibrinolysis in a prostate cancer patient is only 0.40–1.65% of cases. The laboratory diagnosis of primary hyperfibrinolysis is based on the increase of biomarkers like D-dimer, fibrinogen split products, plasminogen, and euglobulin lysis test. These tests are not specific for primary hyperfibrinolysis. We reported a rare case of hemorrhagic syndrome caused by primary hyperfibrinolysis as the first clinical symptom of metastatic prostate cancer. **Case report.** A 64-year-old male was admitted to our hospital with large hematomas in the right pectoral and axillary areas (20 × 7 cm), right hemiabdomen (30 × 30 cm) and the left lumbal area, (25 × 5 cm). The patient had no subjective symptoms nor used any medication. Initial coagulation testing, prothrombin time (PT), and activated partial thromboplastin time (APTT) were within the normal range, while fibrinogen level was extremely low (1.068 g/L) (normal range 2.0–5.0) and the D-dimer assay result was high 1.122 mg/L (normal range < 0.23). The results obtained by rotation thrombelastometry pointed to primary fibrinolysis. Further clinical and laboratory examination indicated progressive malignant prostate disease. First line treatment for the patient was a combined administration of tranexamic acid (3 × 500 mg *iv*) and transfusion of ten units of cryoprecipitate (400 mL). Next day, fibrinolytic function measurements by rotation thrombelastometry were within the normal ranges. Fibrinogen level was normalized within two days (2.4 g/L). There were no newly developed hematomas. **Conclusion.** This case report shows primary hyperfibrinolysis with bleeding symptoms, which is an uncommon paraneoplastic phenomenon within expanded prostate malignancy. Rotation thrombelastometry in this severe complication helped to achieve the prompt and proper diagnosis and treatment.

Key words:
prostatic neoplasms; blood coagulation disorders; fibrinolysis; hemorrhage; diagnosis; thrombelastography; treatment outcome.

Apstrakt

Uvod. Hemoragijski sindrom uzrokovan primarnom hiperfibrinolizom kod bolesnika sa karcinomom prostate javlja se kod samo 0,40–1,65%. Laboratorijska dijagnoza hiperfibrinolize je bazirana na povećanju biomarkera kao što su: D-dimer, fibrin degradacionih produkata, plazminogena, kao i na testu euglobinske fibrinolize. Prikazali smo bolesnika sa retkom formom hemoragijskog sindroma uzrokovanog primarnom hiperfibrinolizom, koji je bio prva klinička manifestacija metastaskog karcinoma prostate. **Prikaz bolesnika.** Bolesnik, star 64 godine, primljen je u našu ustanovu sa velikim hematomima u desnoj pektoralnoj i aksilarnoj regiji (20 × 7 cm), desnom hemiabdomenu (30 × 30 cm) i levoj lumbalnoj regiji (25 × 5 cm). Bolesnik je negirao subjektivne simptome i uzimanje lekova. Inicijalni skrining testovi koagulacije pokazali su normalne vrednosti protrombinskog vremena (PT) i aktiviranog parcijalnog tromboplastinskog vremena (APTT), dok su vrednosti fibrinogena bile veoma niske (1.068 g/L), a D-dimer visoko pozitivan 1,122 mg/mL. Rezultati dobijeni rotacionom trombelastometrijom ukazali su na postojanje primarne hiperfibrinolize. Dalja klinička i laboratorijska ispitivanja dovela su do saznanja o postojanju progresivne maligne bolesti prostate. Lečenje je započeto kombinovanom primenom traneksamične kiseline (3 × 500 mg *iv*) i transfuzijom 10 jedinica krioprecipitata (400 mL). Sledećeg dana, fibrinolitička funkcija merena rotacionom tromboelastometrijom normalizovala se, dok su se vrednosti fibrinogena regulisale drugog dana (2,4 g/L). Nije došlo do razvoja novih hematoma. **Zaključak.** Ovaj prikaz bolesnika predstavlja primarnu hiperfibrinolizu sa krvarenjem, što je neuobičajeni paraneoplastični fenomen kod progresivne maligne bolesti prostate. Rotaciona tromboelastometrija u ovoj teškoj komplikaciji pomogla je u postizanju pravovremene dijagnostike i primene adekvatne terapije.

Ključne reči:
prostata, neoplazme; krv, poremećaji koagulacije; fibrinoliza; krvarenje; dijagnoza; tromboelastografija; lečenje, ishod.

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Introduction

Hemostatic capacity of a patient depends on the stability in the processes of formation and degradation of a blood clot. Disturbances in the mechanisms of fibrinolysis may lead in some cases to primarily clinical bleeding without the initial thrombotic events that characterize disseminated intravascular coagulation (DIC) syndromes. Malignant disease results in a prothrombotic imbalance of the host hemostatic system. Hematologic disorders are commonly seen in patients with prostate cancer (PCa). The most frequently observed disorder in PCa patients is acute or chronic DIC. The incidence of DIC complication in PCa ranges from 13% to 30%, and can be presented as catastrophic bleeding or various thrombotic events. In contrast, bleeding symptoms in the setting of primary hyperfibrinolysis in this malignancy are seen in only 0.40–1.65% patients, usually provoked by surgical procedures [1]. Laboratory diagnosis of hyperfibrinolysis is based on the increase of biomarkers like D-dimer; fibrin/fibrinogen degradation products (FDP), plasminogen, and euglobulin lysis test (ELT). These tests are not specific for primary hyperfibrinolysis and they are also elevated in other pathological conditions [2]. We presented a rare case of hemorrhagic syndrome caused by primary hyperfibrinolysis, which was the presenting paraneoplastic phenomenon of metastatic PCa.

Case report

A 64-year-old male was admitted to our hospital with a large hematomas in the right pectoral and axillary areas, size 20 × 7 cm, the right hemiabdomen, size 30 × 30 cm and the left lumbal area, size 25 × 5 cm. Hematomas developed two days before hospitalization. The patient denied subjective symptoms and any medication. Performed laboratory analyses showed mild normocytic anemia of chronic disease hemoglobin (Hb) 108 g/L [normal value (NV), 135–175 g/L), mean corpuscular hemoglobin (MCV) 90 fL (NV 80–90 fL), red blood cell (RBC) 3.72 × 10^{12}/L (NV 4.32–5.72 × 10^{12}/L), hematocrit (Hct) 0.331% (NV 38.8–5.0%), platelet (Plt) 419 × 10^{9}/L (NV 150–450 × 10^{9}/L), white blood cell (WBC) 9.5 × 10^{9}/L (NV 3.5–10.5 × 10^{9}/L), neutrophils 60% (NV 50–70%), serum iron 12.9 µmol/L (NV 11–32 µmol/L), ferritin 7,820 µg /L (NV 24–336 µg /L), highly elevated alkaline phosphatase (1,390 U/L, NV 50–130 U/L), lactate dehydrogenase (1,740 U/L, NV 140–280 U/L) and prostate specific antigen (above 150 ng/mL)]. Viral tests were negative (HBs Ag, anti HCV and anti HIV). Initial coagulation testing was performed with: IL ELITE PRO® and ACL 300® analyser. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were within the normal limits (12.4 s and 31.9 s, respectively) as well as anti-thrombin III (86.6%), while fibrinogen level was very low (1.068 g/L, NV 2–5) and the D-dimer assay result was 1.122 mg/L (NV 0.1–0.23) (Table 1).

The thrombin time was prolonged (24.0 s). A reduced level of fibrinogen, and high positive D-dimer with the absence of dramatic disturbances in coagulation screening tests indicated the high level of fibrinolytic activity. The results obtained by rotation thrombelastometry pointed to primary fibrinolysis. The clotting time, clot formation time, maximum clot firmness, alpha angle, and 60-minute lysis index were pathologically changed in INTEM, EXTEM, FIBTEM and APTEM tests (Figure 1).

Table 1

Results of coagulation testing

Coagulation test	Values	Normal ranges
PT (s)	12.4	9.1–12.1
APTT (s)	31.9	24.3–35.0
TT (s)	24.0	11.0–17.8
Fibrinogen (g/L)	1.068	2.0–5.0
D-dimer (mg/L)	1.122	< 0.23

PT – prothrombin time; APTT – activated partial thromboplastin time; TT – thrombin time.

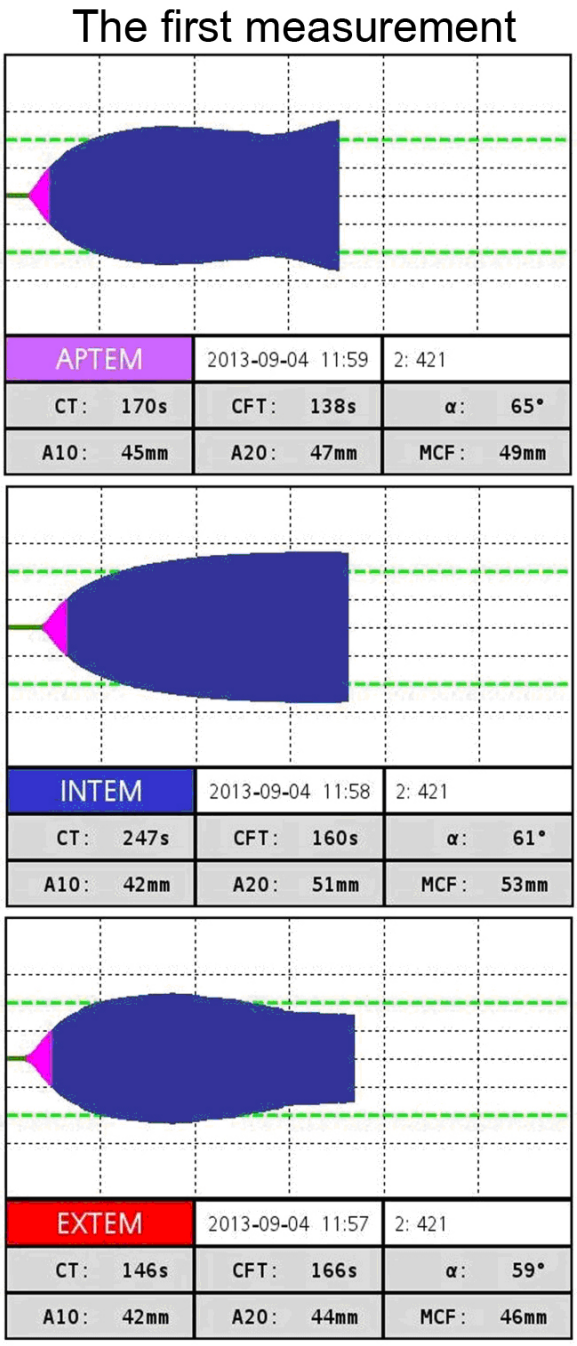

Fig. 1 – Diagnosis of hipefibrinolysis by ROTEM® tests.

First line treatment for the patient was a combined administration of tranexamic acid (3 × 500 mg *iv*) and transfusion of ten units of cryoprecipitate (400 mL). Next day, fibrinolytic function measurements by rotation thrombelastometry were within normal ranges. APTEM test was not registered pathological fibrinolysis (Figure 2).

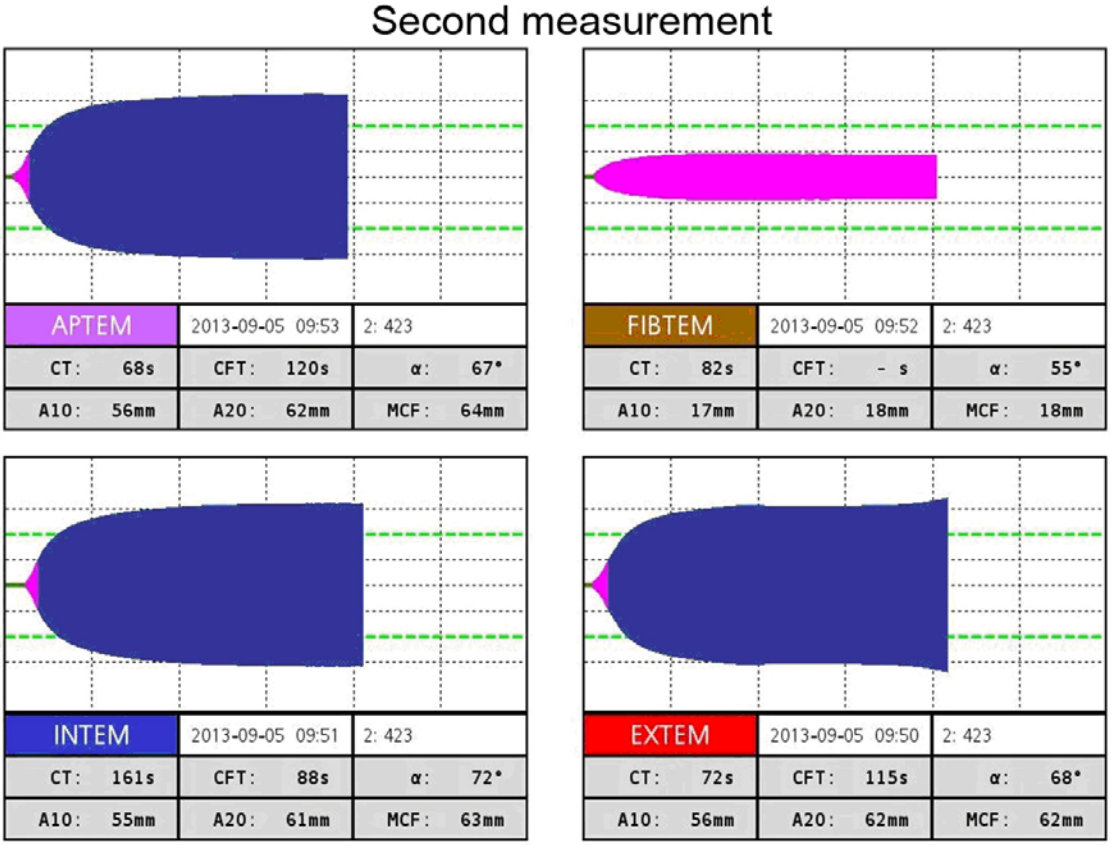

Fig. 2 – ROTEM® test after the treatment.

The fibrinogen level was normalized within two days (2.4 g/L). There were no newly developed hematomas.

The existence of pathological fibrinolysis with a high value of alkaline phosphatase and lactate dehydrogenase directed the diagnostics to detecting malignancy. Laboratory evaluation of patients included determination of prostate specific antigen (PSA), of the values higher than 150 ng/mL (NV 0–4.5 ng/mL). Digital rectal examination established the enlarged prostate with bumps, painless to palpation. The definitive diagnosis of prostate cancer was only possible after the treatment of hyperfibrinolysis which was the cause of hemorrhagic syndrome. Transrectal biopsy of prostate was successfully performed without any hemorrhagic complications, revealing prostate adenocarcinoma G3, Gleason score 9, and bone scans confirmed bone metastases. Afterwards, the patient was referred to the oncologist for further treatment with androgen deprivation therapy and by *per os* administration of tranexamic acid.

Discussion

Paraneoplastic syndromes represent a constellation of conditions that are caused by the presence of malignancy, but not associated with direct tumor invasion or compression. In patients with advanced prostate cancer paraneoplastic syndrome is expressed through a variety of different clinical symptoms [3, 4]. One of them are disorders of hemostasis ranging from bleeding to thrombosis or embolic complications. This case report presented primary hyperfibrinolysis with bleeding symptoms, which is an uncommon paraneoplasic phenomenon within expanded prostate malignancy. The only clinical manifestation of primary hyperfibrinolysis in the presented patient was the presence of large subcutaneous hematoma.

In malignancy hiperfibrinolysis can be activated in two ways. Firstly, tumor cells can produce all the proteins of the fibrinolytic system including the urokinase-type plasminogen activator (uPA) and the tissue-type plasminogen activator (tPA). Secondly, cancer cells also carry on their membranes the specific urokinase plasminogen activator receptor (uPAR), which favors the assembly of all the fibrinolytic components, facilitating the extreme activation of the fibrinolytic cascade [5].

The central event of hyperfibrinolysis is the generation of plasmin within the general circulation [6]. The presence of high activity of the plasmin causes a pathological degradation of fibrin and fibrinogen. It leads to rapid clot breakdown with consequent bleeding. Probably, severe hypofibrinogenemia in the presented patient was caused by fibrinogenolysis due to extreme production of uPA and tPA by prostate cancer cells.

Acquired fibrinolysis occurs as primary process during lung, and gland surgery, in malignant diseases of blood and liver disorders [6]. Other type of acquired hyperfibrinolysis is

DIC. Fibrinolytic process in DIC is always secondary to another underlying pathological state. Clinical presentation of DIC depends on the underlying condition that triggers this medical disorder. In some patients, activation of the fibrinolytic system may dominate over the excessive coagulation, resulting in massive generation of thromboplastic material and consumption of hemostatic elements [7]. In DIC coagulation test the results are obtained with decreasing probability in this order: platelets decreased, FDP increased, PT prolonged, APTT prolonged and fibrinogen decreased. D-dimer test in DIC is highly positive [7, 8]. In patients with prostate cancer DIC is the most frequent coagulation disorder while primary hyperfibrinolysis is unusual. The low fibrinogen with markedly elevated D-dimer and negative test for fibrin soluble monomer complex with no depletion of the coagulation factors can point to primary hyperfibrinolysis. D-dimer is a specific degradation product formed by FXIIa from cross-linked fibrin monomers, followed by plasmin hydrolysis [9], but elevated D-dimer level can be seen in different diseases and it is not specific for primary hyperfibrinolysis. The diagnosis in the presented case was confirmed by rotation thromboelastometry.

Rotation thromboelastometry (ROTEM®) is a viscoelastic point-of-care hemostatic assay designed for full perception of the hemostatic capacity of patients. Also, the method is sensitive for detection and the diagnosis of early fibrinolysis in trauma patients [10]. In contrast to plasmatic coagulation tests, viscoelastic assays like ROTEM® can estimate speed and quality of clot formation, including detection of hyperfibrinolysis, and are performed in whole blood, thus closely reflecting the *in vivo* situation [11]. Comparing the parameters in EXTEM and APTEM test we could detect the moderate form of hiperfibrinolysis.

In the literature we could not find similar examples of hyperfibrinolysis in a prostate cancer patient with the diagnosis made using rotation thrombelastometry. Rotation thrombelastometry is intended for perioperative monitoring of coagulation at active bleeding trauma patients. In cancer patients it was applied in order to detect alterations in the hemostatic capacity, primarily in identification of those patients who are at risk of cancer-induced thromboembolic events [12]. Due to the possibility of rotation thrombelastometry to review all elements of the hemostatic system, particularly the role of platelets and fibrinogen in the formation and stability of a blood clot, its wider application can significantly help in the diagnosis of hemostasis disorders in non-trauma patients.

The diagnosis of primary hyperfibrinolysis is complex and requires the knowledge of the fibrinolytic process nature and clinical circumstances of this pathological condition.

Conclusion

This case report presented primary hiperfibrinolysis with bleeding diathesis as the first clinical sign of previously undiagnosed metastatic PCa. Clinical application of rotation thrombelastometry in a combination with coagulation tests at non-trauma patients, especially oncology patients, can greatly facilitate the diagnosis and therapy of primary hiperfibrinolysis. Rotation thrombelastometry in this severe complication helps to achieve the prompt and proper diagnosis.

The management of hyperfibrinolysis was done within a short period of time thanks to the adequate diagnostic procedure.

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CASE REPORT

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Charles Bonnet syndrome

Šarl Boneov sindrom

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Abstract

Introduction. Charles Bonnet syndrome (CBS) is a condition that causes visual hallucinations in patients without any mental illnesses. CBS is characterized by the presence of vivid, complex and recurrent visual hallucinations, and do not occur in the setting or as part of delirium or other psychological illnesses. The condition is present in patients who have visual loss due to age-related macular degeneration (AMD), cataracts and/or other ocular diseases that influence vision. **Case report.** A 81-year-od woman reported to ophthalmologist complaining of visual hallucinations that consisted of white pigeons. Hallucinations were present for two years and she was well aware that hallucinations were unreal. Mental illnesses were excluded by the psychiatrist. Complete ophthalmologic examination was performed, and finding revealed visual acuity of 0.3 (right eye) and 0.5 (left eye), in both eyes cataracts and AMD (wet form). Optical coherence tomography confirmed the fundoscopic finding of AMD. The patient rejected treatment of cataracts and AMD due to old age, and hallucinations persisted. **Conclusion.** CBS should be considered in patients with visual hallucinations and ocular diseases that influence vision. It is essential to distinguish CBS from mental illnesses, since patients with CBS are fully aware that hallucinations are not real. Awareness of CBS could help physicians upon referring patients to ophthalmologists instead of psychiatrists, and therefore avoid patients being misdiagnosed.

Key words:
hallucinations; vision, ocular; macular degeneration; diagnostic techniques and procedures; diagnosis, differental.

Apstrakt

Uvod. Šarl Bonetov sindrom (CBS) je stanje koje izaziva vizuelne halucinacije kod bolesnika koji nemaju psihička oboljenja. CBS se ogleda u pojavi živopisnih i kompleksnih vizuelnih halucinacija koje se ponavljaju, ali se ne javljaju tokom delirijuma ili drugih psihičkih oboljenja. Stanje se javlja kod bolesnika koji imaju smanjenu vidnu oštrinu zbog senilne degeneracije makule, katarakte i/ili drugih očnih bolesti koje utiču na vid. **Prikaz bolesnika.** Žena, stara 81 godinu, javila se oftalmologu zbog vizuelnih halucinacija koje su činili beli golubovi. Halucinacije su bile prisutne tokom dve godine i bolesnica je bila svesna da one nisu stvarne. Pregledom psihijatra isključena su psihička oboljenja. Urađen je kompletan oftalmološki pregled i nalaz je pokazao vidnu oštrinu 0,3 (desno oko) i 0,5 (levo oko), obostrano kataraktu i senilnu degeneraciju makule (vlažna forma). Optička koherentna tomografija potvrdila je nalaz senilne degeneracije makule. Bolesnica je odbila lečenje katarakte i senilne degeneracije makule zbog starosti, a halucinacije su ostale prisutne. **Zaključak.** Kod bolesnika sa vizuelnim halucinacijama i očnim bolestima koje utiču na vidnu oštrinu, trebalo bi razmotriti postojanje CBS. Od ključne važnosti je razdvojiti CBS od psihičkih oboljenja, jer su bolesnici sa CBS u potpunosti svesni da halucinacije nisu stvarne. Saznanje o postojanju CBS može pomoći lekarima prilikom upućivanja bolesnika oftalmologu, a ne psihijatru, i tako izbeći postavljanje pogrešne dijagnoze.

Ključne reči:
halucinacije; vid; žuta mrlja, degeneracija; dijagnostičke tehnike i procedure; dijagnoza, diferencijalna.

Introduction

Charles Bonnet syndrome (CBS) is an uncommon condition causing visual nontreatening hallucinations in patients without any mental illnesses. It is characterized by the presence of vivid, complex and recurrent visual hallucinations occurring in psychologically normal patients and not in the setting of delirium [1]. Charles Bonnet, a Swiss philosopher, first described the syndrome in 1760 in a publication describing visual hallucinations experienced by his 90-year-old grandfather who was blind secondary to cataracts [2].

Although best described in age-related macular degeneration (AMD), CBS phenomenon may occur in any condition causing vision loss [3]. The symptoms of CBS vary from seeing

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geometric figures to experiences of seeing people or animals [4]. Even though the content of the hallucinations in CBS is generally not distressing to the patient, they may cause fear of impending insanity [5]. The prevalence of CBS has been reported to vary from less than 1% to 40% in different populations, but it is likely that this variation is because of differences in inclusion criteria, inconsistent depth of questioning and reluctance of patients to admit to having hallucinations [1]. Only about 1/5 of the patients admit to have told others about their symptoms [6].

Case report

An 81-year-old woman reported hallucinations during past 2 years. Purely visual hallucinations consisted of white pigeons – walking through the room, sitting on TV set or flying around. At first hallucinations were not upsetting, but later the patient was frightened for her health, since she was aware that the hallucinations were not real. Pigeon hallucinations were mostly appearing in early evening hours and lasted for few minutes. She was not able to specify triggering factors of hallucinations appearance nor their resolution. In the begining, hallucinations were present approximately few times *per* month, but later they occured more often, almost on a daily basis. Hallucinations were visual only, she could not feel or hear the manifestations. The patient denied having any other visual problems. The husband of the patient explained that during these hallucinations no behavioral changes were present, and that she was fully aware of hallucinations and could exactly finger-point where the pigeons were.

The past medical history included arterial hypertension and hip replacement. On physical examination she appeared well, oriented, blood pressure 140/85 mmHg, pulse 84 beats/minute, regular respirations, complete blood count was normal, glucose level of 6.1 mmol/L. The patient was using three antihypertensive drugs and, seldom, painkillers. She was also examined by a psychiatrist, and finding showed no mental pathological changes. Head magnetic resonace imaging (MRI) was done. A finding excluded brain tumor, and only mild cortical atrophy was confirmed.

The ophthalmic medical history showed a preivous eyes examination three years before. The findings were: best corrected visual acuity (BCVA) 0.9 in both eyes, cataracts, intraocular pressure (IOP) of 15 mmHg, AMD (dry form), hypertonic fundus gr. II, cup to disc ratio (CDR) of 0.6, but there was no record of optical coherence tomography (OCT) nor Amsler grid testing. Current ophthalmic exam revealed: BCVA of 0.3 (right eye) and 0.5 (left eye), normal pupillary reaction and eye motility, nucleocortical cataracts, IOP of 16 mmHg; fundoscopic findings included: AMD (wet form), hypertonic fundus gr. II, CDR of 0.6; computed visual field analysis showed no glaucomatous nor vascular defects. OCT was performed, and AMD (wet form) was confirmed in both eyes (Figures 1 and 2). Therefore, Amsler grid testing was also done, and showed defects, more apparent in the right eye.

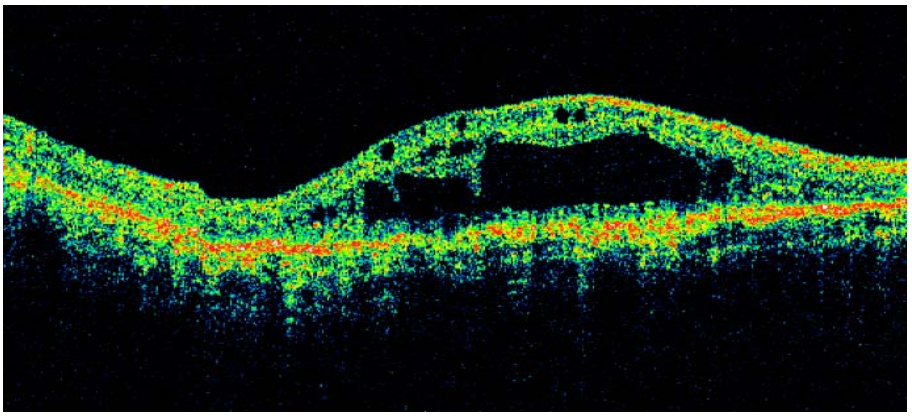

Fig. 1 – Optical coherence tomography finding (right eye): age-related macular degeneration (wet form) – severe pathological changes.

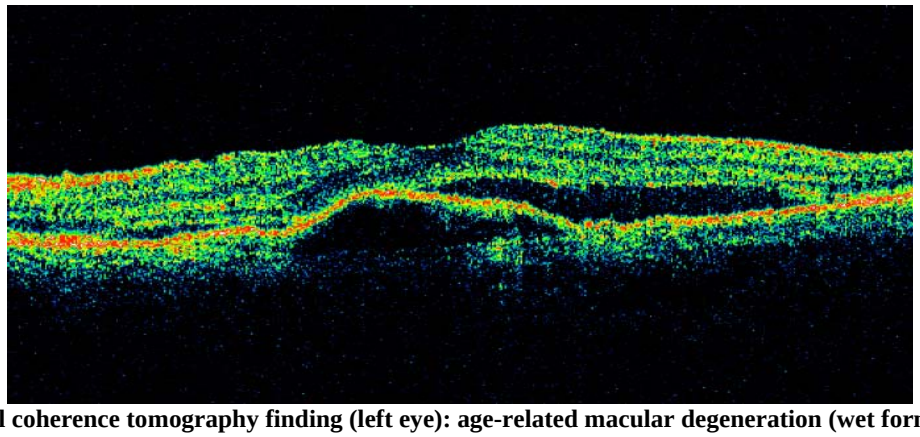

Fig. 2 – Optical coherence tomography finding (left eye): age-related macular degeneration (wet form) pathological changes.

After ophthalmological examination the patient was advised to treat cataracts and AMD, but she rejected to do so due to old age. Follow-up was done in three months. At the follow-up exam ophthalmological status was unchanged, and hallucinations persisted.

Discussion

Increasing life expectancy in population, many of whom show significant visual loss secondary to AMD or glaucoma, is causing an increase in the incidence of CBS [7]. Visual hallucinations in CBS patients are simple or complex in nature, and may be composed of photopsias, simple shapes, grid-like and branching patterns or may be presented by complicated images of people, faces, animals, flowers [8]. The majority of visual hallucinations are strange or bizzare to patients, but are seldom distressing, and do not involve hallucinations in other sensory modalities [2, 9].

The true mechanism in the formation of visual hallucinations in CBS is not exactly known [2, 10]. There are a few theories explaining CBS.

The theory of deafferentation is a hypothesis, accepted most commonly to explain CBS. Deafferentation means the loss of visual input into the brain, which leads to change in the excitability of the visual association cortex [11]. When the sensory visual input into the cortex is removed (with ocular pathology or visual pathway damage) spontaneous neuronal discharge in the visual association cortex occurs, increasing the excitability within the visual association cortex, resulting in visual hallucinations [2, 9].

CBS has been associated with social isolation, cognitive defects, sensory deprivation, as well as low-quality social interaction [5]. Santos-Bueso et al. [7] have concluded that visual loss and advanced age are the two main triggering factors in CBS. Visual deficits are generally the result of macular degeneration, cataracts, glaucoma or diabetic retinopathy. Although macular degeneration is most commonly associated with visual impairment, any condition that diminishes vision can cause CBS, but little or no correlation has been confirmed between the severity of visual impairment and prevalence of CBS [5]. The majority of patients with CBS are elderly (70–85 years), but cases have been reported in all age groups [12]. In our patient, the possible trigger for visual hallucinations, besides age, could be the moment of transition of AMD from dry to wet form, along with progressing cataracts, and together causing vision reduction. Unfortunately, we have no previous OCT recordings to confirm our hypothesis.

It's been well documented that many drugs can be associated with visual hallucinations, such as antibiotics, anticonvulsants, antidepressants, aniparkinsonian drugs, hallucinogenes, stimulants, hormonal and cardiovascular drugs [13]. Of cardiovascular drugs, adverse effects of commonly used angiotensin-converting enzyme (ACE) inhibitors are numeorous. Doane and Stults [14] have reported that in older patients visual hallucinations are very common side effect of ACE inhibitions. The presented patient was also treated for hypertension, but ACE inhibitors were not included in the therapy.

Diagnostic work-up with a patient suspected to have CBS should include a calm, nonjudgmental approach, since clinicians who demonstrate lack of awareness can cause further distress in patient. A full general physical examination should be conducted, with the focus on excluding acute illness as a cause of possible delirium. It is very important to perform ophthalmologic examination [15]. If a patient has an ocular disease that the diminishes vision, and reports visual hallucinations, but is aware that these hallucinations are not real, it is most likely that diagnosis is CBS. In unclear cases it is highly recommended to consult a psychiatrist.

The differential diagnosis that should be considered in patients with visual hallucinations are, among others, Lhermitte's hallucinosis (LH), Parkinson's disease and Lewy body dementia (LBD). In LH visual hallucinations are also vivid, well formed, and recognized as unreal, but in contrast to CBS, LH is associated with dementia, lesions and midbrain infarcts, while in Parkinon's disease and LBD, deficits in higher visual cortex may be present [12, 13].

Currently, there is no universally accepted treatment for CBS. Visual hallucinations often resolve once the underlying cause of vision loss is treated, therefore in CBS confirmed patients with diminished vision, the easiest therapeutic approach is to improve patients' vision. Such measures might include improving lighting at home, to wear glasses or contact lenses, remove cataracts and treat any other eye condition that could improve vision[13]. The hallucinations associated with CBS may diminish and/or resolve as vision worsens or completely fades [5]. Roever et al.[15] recommend increased social contact with patients having visual hallucinations. Pharmacological treatments are largely reserved for patients truly distressed by the hallucinations. Medications are only modestly effective, and they only attenuate the patient's emotional reaction and fail to eliminate the hallucinations [5, 10]. Antipsychotics have shown benefit in individual patients, but there is little evidence to support this therapeutic approach in CBS, since there is a high risk of side effects [16].

Conclusion

Charles Bonnet syndrome should be considered in patients with visual hallucinations and ocular diseases that diminish vision. It is very important to distinguish this syndrome from mental illnesses and delirium, since CBS patients are fully aware that visual hallucinations are not real. Increased awareness of CBS can help physicians in referring the patient to ophthalmologists instead of psychiatrists, and doing so, avoid patients being misdiagnosed.

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LETTER TO THE EDITOR

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Public health risk analysis through evaluation of drinking water safety

Analiza rizika javnog zdravlja kroz procenu bezbednosti vode za piće

To the Editor

Some researches in US and China [1, 2] have revealed a relationship between the increased risk of primary liver cancer (PLC) and the quality of surface water, suggesting that cyanotoxins (CTs) from water reservoirs containing cyanobacteria (CB) can trigger the development of PLC. The data obtained from similar studies in Serbia [3–5] confirm these findings. The highest PLC incidence has been found in Nišavski (31.4/100,000 inhabitants), Toplički (27.3/100,000 inhabitants), and Šumadijski (22.1/100,000 inhabitants) districts where CB blooms occur every year in most reservoirs for water supply *versus* Central Serbia on the average (14/100,000 inhabitants) (Figure 1).

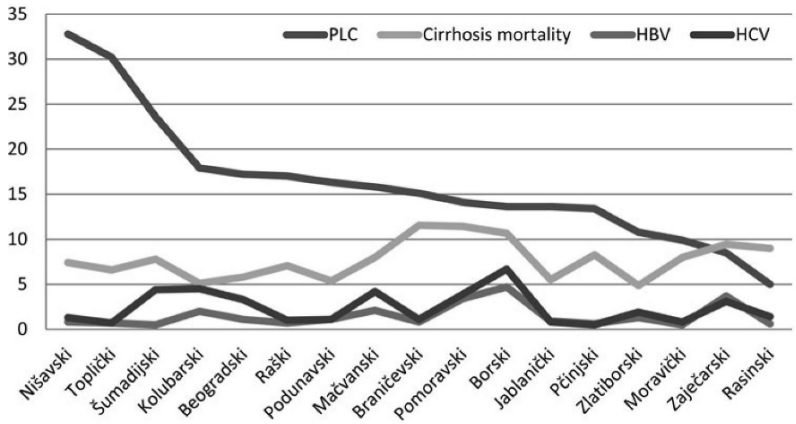

Fig. 1 – Comparison of incidences (*per* 100,000 inhabitants) of primary liver cancer (PLC), cirrhosis, hepatitis B virus (HBV), and hepatitis C virus (HCV) in Central Serbia regions from 2000 to 2006. [5]

The aim of this letter was to point out that the role of drinking water safety in public health (PH) [6], and also to point out the relationship between distal (associated with social, environmental and engineering status) and proximal causalities (associated with microbiological or biological factors) of some water-related diseases.

The current PH risk analysis approach concerning drinking water is based on cause-effect relations and probabilities of unwanted events, i.e. human exposure to CTs. This approach fails to capture all of the risk factors involved, especially distal ones, and has difficulties to cope with unpredictable harmful events.

An indicative example is the Vrutci reservoir case on the river Đetinja (the town of Užice, Serbia), the main source for the Užice Water Supply System (UWSS) which covers more than 60,000 inhabitants, which had experienced a visible bloom of potentially toxic CB at the end of 2013 [7]. The ban on using water from UWSS was in force for one month and a half, which strongly affected PH. In addition to difficulties in determination of probabilities of such an event, it is not possible to determine the incidence and prevalence of diseases dependent on the drinking water hygiene [8].

A research reported by Drobac [9], after Vrutci reservoir CB bloom and water usage ban from UWSS, has provided valuable data on exposure to given hazards. During the water usage ban, the majority of respondents (out of 320 participants in the inquiry) did comply with restrictions, while some of them used water occasionally and daily (Figure 2). These data confirm difficulties in the exposure assessment.

It was evident from Vrutci CB bloom that the whole environmental and engineering sociotechnical structure has contributed to the event which was also extended on sociomedical structure of PH. Partitioned responsibilities in managing different aspects of water among the instituti-

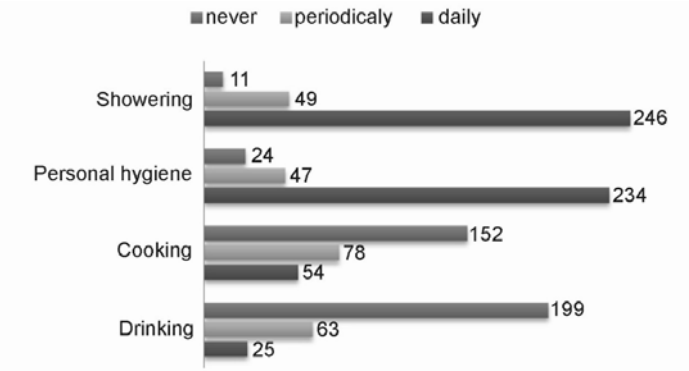

Fig. 2 – Water usage during Užice water ban (number of subjects participated in the inquire, totally 320). [9]

ons/actors at different governance levels (local, national) or at the same level (different departments or Ministries) or different professions (environmentalists, engineers, medical workers) had resulted in the failure of making effective and timely decisions, either to prevent or to mitigate the issue.

After a comprehensive analysis of the event, following aspects related to management, monitoring, reporting and regulation were identified as critical:

Management – the Vrutci reservoir was not protected from untreated waste water from the upstream settlements and rainfall runoff from the nutrient reach agricultural area; sudden (and unnecessary) water level changes did not favor Vrutci water ecosystem, while only CB, as the toughest, prevailed.

Monitoring – In spite of widely accepted recognition of the Vrutci reservoir as the most valuable resource, there was no regular monitoring; UWSS thought were not responsible, Serbian Environmental Protection Agency (SEPA) was short of funding. For example, for the year 2013, monitoring was not scheduled, in spite of the impaired ecological status of the reservoir observed from the monitoring in 2012.

Reporting – None of PH institutions along with SEPA did not report the case in their Annual Public Reports which is an obvious deficiency in communication. In addition, there is no Ministry of Health critical evaluation on the extent of conducted drinking water analyses. One may ask did anything happen?

Regulation – There is no specific regulations of CB monitoring and on the maximum permissible levels of CT concentrations present in waters used for drinking, recreation, aquaculture or irrigation [5].

Experience and good management practice [6] had already shown that medical, environmental and engineering solutions, in isolation, cannot give a long lasting sustainable solution for preservation of human or PH.

The obvious deficiencies presented previously in PH decision making methodology have been augmented and complemented by paradigm shift. Breaking away from risk, which seeks for adverse events, we could look into safety, which seeks for proper way of doing things.

A novel approach, systems-theoretic accident model and processes (STAMP) [10], originated from safety and resilience engineering, is proposed to expand traditional risk analysis which is primarily based on proximal factors to include distal factors originated from environment and engineering. STAMP views accidents (of any kind, like human exposure to CTs in this case) as the result of inadequate control rather than failure events. In that perspective, unacceptable losses can also be the result of interactions between sociotechnical system components, medical, environmental, physical and social, that violate system safety constraints.

Finally, one has to have in mind that since 1980, among the 83 water ecosystems examined in Serbia, 58 were found in algal blooming [5], which is not an immediate PH hazard, but a clear indication that ecosystems are sliding towards unstable/unsafe status, which require stronger attention. Monitoring of health status of the population still remains the main task to determine trends and risk factors involved. However, addressing PLC issue, one should also have in mind that PH risk analysis dealing primarily with medical aspects must not overlook the environmental and engineering aspects, as well. PLC served as the motive of this letter, but also the other waterborne disease outbrakes caused by pathogens or other water-related diseases could be handled as well.

We are aiming at PH professionals, the Ministry of Health and the Ministry responsible for water resources management, to improve monitoring of reservoirs used for water supply, to improve the enforcement of the Water Law and Water Source Protection Zones as well as to support and strengthen both municipal and republic PH institutes.

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Primeri referenci:

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Tabele

Sve tabele pripremaju se sa proredom 1,5 na posebnom listu. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

Ilustracije

Slikama se zovu svi oblici grafičkih priloga i predaju se kao dopunske datoteke u sistemu **aseestant**. Slova, brojevi i simboli treba da su jasni i ujednačeni, a dovoljne veličine da prilikom umanjivanja budu čitljivi. Slike treba da budu jasne i obeležene brojevima, onim redom kojim se navode u tekstu (**Sl. 1; Sl. 2** itd.). Ukoliko je slika već negde objavljena, obavezno citirati izvor.

Legende za ilustracije pisati na posebnom listu, koristeći arapske brojeve. Ukoliko se koriste simboli, strelice, brojevi ili slova za objašnjavanje pojedinog dela ilustracije, svaki pojedinačno treba objasniti u legendi. Za fotomikrografije navesti metod bojenja i podatak o uvećanju.

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