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GYNECOLOGIC ONCOLOGY SURGICAL PROCEDURES IN THE GENERAL HOSPITAL "DR. RADIVOJ SIMONOVIĆ" IN SOMBOR IN THE PERIOD FROM 2011–2021

GINEKOLOŠKO-ONKOLOŠKE OPERACIJE U OPŠTOJ BOLNICI „DR RADIVOJ SIMONOVIĆ" U SOMBORU U PERIODU 2011–2021.

Srđan ĐURĐEVIĆ, Lazar RAČIĆ and Milan ŽAKULA

Summary

Introduction. In the period from 2011 - 2021, 1482 gynecologic surgeries were performed at the Department of Gynecology and Obstetrics of the General Hospital in Sombor, of which 50 (3.4%) were gynecologic oncology surgical procedures. The distribution of the malignant tumor localization was as follows: vulva 4 (8%), cervix 13 (26%), endometrium 24 (48%), and ovary 9 (18%). **Material and Methods.** The preoperative diagnosis of all patients included standard laboratory tests of blood and urine, chest X-ray, internal medicine specialist examination, electrocardiography, and imaging procedures (magnetic resonance imaging or computed tomography) of the small pelvis and abdomen. In all cases, the diagnosis of vulvar, cervical, and endometrial cancer was made preoperatively, based on pathohistological findings of the biopsy samples of tumor tissue or material obtained using exploratory curettage. In ovarian cancer, the diagnosis was made during surgery based on ex tempore pathohistological analysis. **Results.** Most of the operated patients were in the International Federation of Gynecology and Obstetrics stage I - 39 (78%) and the most common pathohistological type of tumor was adenocarcinoma of different localizations - 29 (58%). The number of lymph nodes removed per surgery was 16 - 39 (x: 19) and lymphovascular invasion was present in 31 (62%) operated patients. Intraoperative complications (bleeding, ureteral injury, infection, and wound dehiscence) occurred in 8 (16%) patients, recurrence occurred in 3 (6%), and postoperative lethal outcome occurred in 4 (8%) patients. **Conclusion.** The essential condition for performing gynecologic oncology surgical procedures in a secondary level healthcare facility is a well-trained gynecology surgeon who has received complete training in gynecologic oncology at the tertiary level, as well as the optimal number of gynecologic oncology surgeries in accordance with recommendations of the European Society of Gynecological Oncology.

Key words: Gynecology; Surgical Oncology; Gynecologic Surgical Procedures; Incidence; Neoplasms; Hospitals, General

Sažetak

Uvod. U periodu 2011–2021. godine, na Ginekološko-akušerskom odeljenju Opšte bolnice u Somboru, izvršene su 1.482 različite ginekološke operacije: od toga 50 (3,4%) ginekološko-onkoloških operacija. Distribucija prema lokalizaciji malignih tumora bila je: vulva četiri (8%), grlić materice 13 (26%), endometrijum 24 (48%) i jajnik 9 (18%). **Materijal i metode.** U preoperativnoj dijagnostici kod svih pacijentkinja pored standardnih laboratorijskih analiza iz krvi i mokraće, rendgenskog snimka pluća, internističkog i elektrokardiografskog pregleda, urađena je imidžing dijagnostika (magnetna rezonancija ili kompjuterizovana tomografija) male karlice i abdomena. U svim slučajevima dijagnoza karcinoma vulve, grlića materice i endometrijuma postavljena je preoperativno na osnovu patohistološkog pregleda bioptičkih uzoraka tumorskog tkiva ili materijala dobijenog primenom eksplorativne kiretaže. Kod karcinoma jajnika dijagnoza je postavljena u toku operacije na osnovu *ex tempore* patohistološke dijagnoze. **Rezultati.** Najveći broj operisanih pacijentkinja bio je u I stadijumu bolesti prema Međunarodnoj federaciji za ginekologiju i akušerstvo - 39 (78%) a najčešća patohistološka vrsta tumora bio je adenokarcinom različitih lokalizacija - 29 (58%). Broj uklonjenih limfnih čvorova po operaciji bio je od 16 do 39 (x : 19) a limfovaskularna invazija bila je prisutna kod 31 (62%) operisane pacijentkinje. Različite komplikacije u toku hirurškog lečenja (krvarenje, povreda uretera, infekcija i dehiscencija rane) bile su zastupljene kod osam (16%) pacijentkinja, recidiv se javio kod tri (6%) a letalni ishod posle operacije kod četiri pacijentkinje (8%). **Zaključak.** Osnovni uslov za izvođenje ginekološko-onkoloških operacija na sekundarnom nivou zdravstvene zaštite je postojanje hirurški dobro obučenog ginekologa koji je obuku iz ginekološke onkologije stekao na tercijarnom nivou kao i optimalni broj ginekološko-onkoloških operacija u skladu sa preporukama Evropskog udruženja ginekološke onkologije.

Ključne reči: ginekologija; hirurška onkologija; ginekološke hirurške procedure; incidenca; neoplazme; opšte bolnice

Introduction

Today, it has been established that cancer is a disease of genetic origin caused by mutations in genes that encode molecules responsible for the processes of communication or cooperation between and within cells. Mutations in oncogenes lead to the formation of abnormal proteins that may

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Abbreviations

MRI – magnetic resonance imaging
CT – computed tomography
ECG – electrocardiography
FIGO – International Federation of Gynecology and Obstetrics
ESGO – European Society of Gynecological Oncology
LVI – lymphovascular invasion
UGOS – Association of Gynecologists and Obstetricians of Serbia

transform a normal cell into a malignant. Genetic studies have so far revealed about 600 tumor genes, oncogenes, and tumor suppressor genes, of which about 150 are directly responsible for tumor growth of epithelial origin [1–3]. Malignant tumors of the female genital organs in Serbia account for about 20% of all malignant tumors of the female population. The number of new patients with malignant tumors of the cervix, body of the uterus (endometrium), and ovaries is constantly increasing. In some regions and localizations of malignant tumors, such as cervical cancer, the incidence is the same as in underdeveloped areas that have the highest incidence of this disease in the world. On the other hand, the incidence of endometrial and ovarian cancer is similar to that in developed countries, which is characterized by a high frequency of these tumors [4, 5]. Reliable and accurate reports on the results of treatment of malignant tumors of women's genital organs do not yet exist in Serbia. In the last decades of the 20th century, gynecologic oncology stood out as a separate field in gynecology and oncology and represented a professional orientation of experts in various specialties: gynecologists, radiologists-diagnosticians, radiotherapists, pathologists, medical oncologists, and palliative care specialists [6, 7]. The aim of this paper is to present the results of surgical treatment of various types of malignant tumors of the female genital system at the Department of Obstetrics and Gynecology of the General Hospital "Dr. Radivoj Simonović" in Sombor, in the period from 2011 – 2021.

Material and Methods

Indications for surgical treatment of malignant tumors of the female genital organs included invasive vulvar, cervical, endometrial, and ovarian cancers. The diagnosis of vulvar and cervical cancer was made based on pathohistological examination of tumor tissue samples obtained by biopsy, and in endometrial cancer using diagnostic or exploratory curettage of the uterine cavity. In ovarian cancer, the diagnosis was made during surgery based on ex tempore pathohistological analysis of tumor tissue samples. In all patients, the preoperative diagnostic procedure included blood and urine laboratory tests, computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvic and abdominal organs, a 2 view chest X-ray, electrocardiography (ECG), and general internal examination [8]. In patients with ovarian and endometrial cancer, preoperative detection of the cancer antigen 125 concentration in the peripheral blood was performed, while cancer antigen 19-9 was performed in cases where mucinous ovarian cancer was suspected. The assessment of the extent or stage of the disease was performed based on the current International Federation of Gynecology and Obstetrics (FIGO) classification [9]. Two hours before surgery, all women underwent, bowel preparation, subcutaneous administration of fraxiparin, at a dose of 0.4 - 0.6 IU, and 1 - 2 gr of cephalosporin antibiotics. According to the need for surgery, decanted erythrocytes were reserved, as well as a consultative presence of a general surgeon or urologist. Immediate preoperative preparation was performed in the operating room and it included disinfection of the anterior abdominal wall and vagina using a solution of povidone iodide (povidone, Hemofarm) or octanisept (octenidine, phenoxyethanol, Schülke & Mayr GMBH) as well as placement of a Foley catheter into the urinary bladder [10]. Surgical treatment of vulvar cancer included radical surgical excision with pathohistological confirmation of negative edges around the tumor (at least 10 mm) and covering the defect with local skin flaps in two patients, and in the remaining two patients, classic radical hemivulvectomy was performed on one side [11]. Surgical treatment of cervical cancer was performed using the Wertheim-Meigs surgical technique, which in addition to removing the uterus includes removal of connective tissue or parameters around the cervix and lymph nodes in the pelvis (iliac, presacral and obturator group) [12]. This surgical technique corresponds to the Querleu-Morrow type C1 classification and includes resection of the paracervical tissues at the intersection with the internal iliac vessels, resection of the uterosacral ligaments to the rectum and vesicouterine to the bladder, complete mobilization of the ureter, and resection of 15 - 20 mm of the vagina from the tumor or cervix with nerve preservation [13].

Surgical treatment of endometrial cancer includes removal of the uterus, ovaries, and fallopian tubes; a sample of free fluid is taken for cytological analysis and regional lymph nodes of the iliac and obturator fossa to the level of the obturator nerve. Surgical treatment of ovarian cancer includes maximal surgical reduction of the tumor, sampling of free fluid aspirates for cytological analysis, hysterectomy with bilateral adnexectomy, omentectomy, and resection of all affected organs in the pelvis and abdomen [13]. Postoperative supervision was performed in the department by the doctor on duty and a nurse. The temperature list includes mostly 2 antibiotics (cephalosporins and aminoglycosides) in the period of 48 – 72 hours after surgery, analgesics (trodon – tramadol ampoules, and zodol – ketorolac, Hemofarm), antiemetics (ondasan – ondansetron ampoules, Slaviamed) and 3,000 ml of saline infusion. If the general condition of the patient required, like in hemodynamically unstable patients who underwent other interventions on the surrounding organs, the patient was placed in the surgical inten-

sive care unit. After surgery and arrival of the pathohistological findings, all patients were referred for a consultative examination to the Gynecologic Oncology Council of the Institute of Oncology of Vojvodina in Sremska Kamenica for a decision on additional therapy.

Results

In the period from 2011 – 2021, 1482 gynecological surgeries were performed at the Department of Obstetrics and Gynecology of the General Hospital "Dr. Radivoj Simonović" in Sombor, of which 50 (3.4%) were women suffering from various malignant tumors of the female genital tract. The age of the operated patients ranged from 28 - 75 years, with a mean age of 46 years. The distribution of patients in regard to the type of malignant tumors of genital organs as well as the basic characteristics of patients is shown in **Table 1**. Lymphovascular invasion (LVI) was present in 31 (62%) operated patients (vulva 1, cervix 9, endometrium 16 and ovary 5) and negative LVI was found in 19 (38%). The blood loss during surgery was 20 - 700 ml (average 230 ml) and the number of lymph nodes removed was 16 - 39 (x: 19). Positive lymph nodes with the presence of metastases were recorded in 11 (22%) operated patients, which required adjunctive therapy. The distribution of intra and postoperative complications is shown in **Table 2**. Recurrence occurred in 3 (6%) operated patients (vulva 1, endometrium 1, and ovary 1) and postoperative lethal outcome occurred in 4 (8%) patients (vulva 1, cervix 1, and ovary 2).

Discussion

In Serbia and Autonomous Province of Vojvodina, there is an evident increase in the incidence of malignant tumors of all localizations, including the organs of the female genital tract [3, 4, 14]. The diagnosis and treatment of these tumors are performed at 3 levels of health care, but also in the private health sector (private special gynecology hospitals) [6]. All new and diagnosed cases of malignant tumors need to be reported and referred to the multidisciplinary Gynecologic Oncology Council of the Institute of Oncology of Vojvodina in Sremska Kamenica. However, at all levels of health care, diagnostics and treatment are still performed by gynecologists-obstetricians of general professional orientation, including a small number of those who have a sub specialization in oncology or are exclusively engaged in gynecologic oncology, which is a trend in the European Union and United States. Although the Association of Gynecologists and Obstetricians of Serbia (UGOS) has been found to improve this process, by organizing an international congress for gynecological oncology under the auspices of European Society of Gynecologic Oncology (ESGO) in Belgrade in 2009, as well as numerous professional symposia and meetings, taking part in publishing textbooks on gynecologic oncology and so on, one gets the impression that the situation in Serbia has not changed significantly in the last 18 years [7, 12, 14]. There are still no precisely regulated legal frameworks regarding diagnostic protocols and referrals for treatment of patients with malignant tumors of the genital organs; there is a lack of well-conceived sub specialization in gynecologic oncology harmonized with the

Table 1. General patient characteristics: disease stage (FIGO), degree of cell differentiation, and histopathological classification
Tabela 1. *Opšte karakteristike pacijenata: stadijum bolesti (FIGO), stepen ćelijske diferencijacije i histopatološka klasifikacija*

Patient characteristics *Karakteristike pacijenata*	Localization of cancer/*Lokalizacija karcinoma*			
	Vulva/*Vulva*	Cervix/*Grlić materice*	Endometrium/*Endometrijum*	Ovary/*Jajnik*
FIGO Stage/*FIGO stadijum*				
I	3 (6%)	11 (22%)	20 (40%)	5 (10%)
II	1 (2%)	2 (4%)	2 (4%)	1 (2%)
III			2 (4%)	2 (4%)
IV				1 (2%)
Degree of cell differentiation *Stepen ćelijske diferencijacije*				
1	4 (8%)	8 (16%)	14 (28%)	5 (10%)
2		3 (6%)	7 (14%)	2 (4%)
3			1 (2%)	2 (4%)
Pathohistology/*Patohistologija*				
Planocellular type *Planocelularni tip*	3 (6%)	11 (22%)		
Adenocarcinoma *Adenokarcinom*		2 (4%)	22 (44%)	5 (10%)
Other types/*Ostali tipovi*	1 (2%)		2 (4%)	4 (8%)

Legenda: FIGO – Međunarodna federacija za ginekologiju i akušerstvo

Table 2. Intraoperative, postoperative complications and recurrences in operated gynecological and oncological patients in the period 2011 – 2021
Tabela 2. *Intraoperativne, postoperativne komplikacije i recidivi kod operisanih ginekološko-onkoloških pacijenata u periodu 2011–2021.*

Complications *Komplikacije*	Localization of cancer/*Lokalizacija karcinoma* Vulva/*Vulva* Cervix/*Grlić materice* Endometrium/*Endometrijum* Ovary/*Jajnik*		
Intraoperative/*Intraoperativne*			
Bleeding/*Krvarenje*			1
Ureter injury/*Povreda uretera*		1	
Postoperative/*Postoperativne*			
Wound infection/*Infekcija rane*			1
Wound dehiscence *Dehiscencija rane*	1		
Lymphocyst/*Limfocista*		3	1
Total complications *Ukupne komplikacije*	(2%)	4 (8%)	3 (6%)

ESGO program, and no precise results of treatment of gynecologic oncology patients in which representatives of various oncology centers would take part [16]. In the professional medical literature available to us, there are almost no cumulative results of the treatment of gynecological and oncological patients at the secondary health level in Serbia. The results of treatment can be compared exclusively with those at the tertiary health level, which is not adequate due to the different organization of work in these institutions [3, 11–15]. We explain this by the fact that only one specialist gynecologist-obstetrician, a full professor of gynecology and obstetrics, who has been employed at the tertiary health level for more than 3 decades (Clinic of Gynecology and Obstetrics of the Clinical Center of Vojvodina in Novi Sad) and also received education abroad, is in charge of the surgical techniques performed in the Sombor hospital.

In the presentation of results from Sombor hospital, most operated women had endometrial cancer 24 (48%), FIGO I stage 39 (78%) and the most common histological type was adenocarcinoma 31 (58%), which is similar to the published results in the tertiary health institutions [17–19]. We operated on 4 patients with vulvar cancer (3 with squamous cell carcinoma and 1 with Mb Paget). In all cases, radical surgical excision was applied, and in 2 (50%) patients the defect was covered with a local skin flap (V-Y bilateral flap and rhomboid flap), which is shown in **Figure 1** (C and D). Of the postoperative complications, one patient had a wound dehiscence, which healed per secundam with antibiotics and disinfectants, while one patient had a recurrence 15 months after surgery and radiation therapy with a lethal outcome due to dissemination of the disease. These results are similar to the previously published results of the Clinical Centre of Vojvodina [11, 20, 21] at the Clinic of Gynecology and Obstetrics in Novi Sad; there were 175 women with cervical cancer, 79.4% of patients were in FIGO I stage, the most common type was squamous cell carcinoma in 76.6% of operated patients, while 54.8% patients had a well-differentiated stage I tumor. During surgery, 32 lymph nodes were removed on average, the average blood loss was 300 ml, and various intra and postoperative complications were observed in 24.5% of patients [12]. This is similar to our results from Sombor, which refer to the surgical treatment of cervical cancer, where 84.6% of patients had FIGO I stage squamous cell carcinoma. The average number of 19 removed lymph nodes and the average blood loss of 230 ml is less than in the Novi Sad study [12, 22]. The total number of intraoperative complications of cervical cancer in Sombor is 8% less than in the Novi Sad study, where 24.5% of patients had intraoperative complications, which can be explained by a larger sample, different stages and more gynecologists who per-

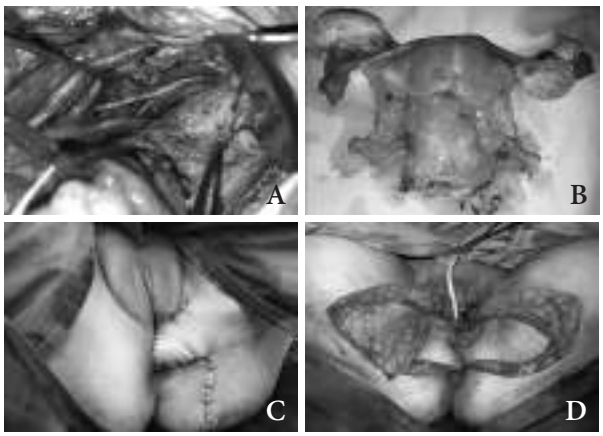

Figure 1. Various surgical techniques in the treatment of cervical and vulvar cancer: A - lymphadenectomy in the small pelvis; B - material after radical hysterectomy: uterus with parametrium; C - Rhomboid flap; D - V-Y skin flap
Slika 1. *Primena različitih hirurških tehnika u lečenju karcinoma grlića materice i vulve: A – limfadenektomija u maloj karlici; B – preparat nakon radikalne histerektomije: uterus sa parametrijumom; C – Romboidni režanj; D – V-Y kožni režanj*

formed these surgeries. There were 24 (48%) women with endometrial cancer, most of them with FIGO I stage; adenocarcinoma was present in 22 (91.6%) and well-differentiated stage 1 tumors were found in 14 (58.3%) women. In this group of patients there were 3 (6%) complications and in one patient with poorly differentiated stage 3 tumor recurrence was noted in the area of the anterior abdominal wall 9 months after postoperative radiation therapy and she was referred to the Institute of Oncology of Vojvodina. Vukomanović et al. examined the clinical and histological features of endometrial cancer in obese women [18]. Endometrial cancer in obese women is most often a well-differentiated FIGO stage I endometrioid adenocarcinoma, which is similar to our results. In our study, there were 9 patients with different types of ovarian cancer, of which 5 (55.6%) had an initial FIGO I stage. One patient with FIGO stage IV underwent exploratory laparotomy with cytoreduction and died 3 weeks after surgery, and 1 patient primarily operated with FIGO III C died due to disease progression 2.5 years later. No complications were noted during the surgeries. One of the published papers from the Clinic of Gynecology and Obstetrics of the Clinical Center of Vojvodina in Novi Sad from 2019, reported the highest number of patients with FIGO III stage (33.1%), the most common were epithelial histological types in 84.2%, the most common procedure was hysterectomy with bilateral adnexectomy and omentectomy and cytology (45.4%) while complications were noted in 4.3% of patients who underwent surgery [16]. In our study, the largest number of patients had FIGO I stage (55.6%), which is slightly higher and is related to the careful selection of cases and sending advanced stages to a higher tertiary level of healthcare. All our patients underwent hysterectomy with bilateral adnexectomy, omentectomy, and sampling for cytological analysis as a minimum procedure, and we did not have any complications related to patient selection, lower stage of the disease, and smaller sample.

Conclusion

With respect to all modern diagnostic-therapeutic principles of treatment, gynecologic oncology surgeries may be performed in secondary health care institutions, in gynecologic oncology departments of general hospitals. The essential condition for performing gynecologic oncology surgical procedures at a secondary level healthcare is a well-trained gynecology surgeon who has received complete training in gynecologic oncology at the tertiary level, as well as the optimal number of gynecologic oncology surgeries in accordance with recommendations of the European Society of Gynecological Oncology.

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TEN YEARS AFTER THE INTRODUCTION OF THE EUROPEAN SYSTEM FOR CARDIAC OPERATIVE RISK EVALUATION 2: A SINGLE CENTER VALIDATION

DESET GODINA OD UVOĐENJA EVROPSKOG SISTEMA ZA PROCENU KADIOHIRURŠKOG OPERATIVNOG RIZIKA 2: VALIDACIJA U JEDNOM CENTRU

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Summary

Introduction. The aim of this study was to evaluate the predictive value of the European System for Cardiac Operative Risk Evaluation II in adult patients with acquired heart diseases. **Material and Methods**. The research included a consecutive series of 6,031 patients who underwent coronary, valvular and combined cardiac surgical interventions in the period from January 15, 2015 to December 31, 2020. Model calibration was assessed by comparing the ratio of actual to expected postoperative mortality and using the Hosmer-Lemeshow test. The discriminative power was examined using the area under the receiver operating characteristic curve. **Results**. A total of 2,883 patients underwent isolated coronary surgery, 1,841 underwent valvular procedures, while a combined procedure was performed in 1,307 patients. The operative risk was moderately underestimated in the entire group, as well as in the group of patients who underwent surgical revascularization of the coronary arteries. In patients who underwent valvular surgery, the actual mortality rate was slightly overestimated, while in patients with combined procedures it was moderately underestimated. The European System for Cardiac Operative Risk Evaluation II showed excellent discriminative power in the whole group of patients undergoing surgery (area under the curve = 0.825, p < 0.0005). The cut-off value was 2.60, sensitivity 0.757 and specificity 0.750. The discriminative power of the model was excellent in the group of coronary patients (area under the curve = 0.810) as well as in the group with isolated valvular surgery (area under the curve = 0.815). In patients with combined procedures, the discriminatory power was very good (area under the curve = 0.775). **Conclusion.** The results of our single centre study show that European System for Cardiac Operative Risk Evaluation II predicts hospital mortality with satisfactory results in the entire group, but underestimates it when it comes to combined cardiac surgical procedures. The discriminative power of the model is excellent.

Key words: Cardiac Surgical Procedures; Hospital Mortality; Mortality; Adult; Risk Factors; Risk Assessment; Thoracic Surgery

Sažetak

Uvod. Cilj rada je da se proceni prediktivna moć Evropskog sistema za procenu operativnog rizika u kardiohirurgiji kod odraslih bolesnika sa stečenim oboljenjima srca. **Materijal i metode.** Istraživanje je obuhvatilo konsekutivnu seriju od 6.031 bolesnika operisanih u periodu od 15. januara do 31. decembra 2020. godine. Uključeni su bolesnici kojima su rađene koronarne, valvularne i kombinovane kardiohirurške intervencije. Kalibracija modela procenjena je poređenjem odnosa stvarnog i očekivanog postoperativnog mortaliteta i pomoću Hosmer-Lemešovog testa. Diskriminativna moć ispitana je pomoću *receiver operating characteristic curve*. **Rezultati.** Kod 2.883 bolesnika rađena je koronarna kardiohirurška intervencija, kod 1.841 valvularna, dok je kod njih 1.307 urađena kombinovana procedura. Za čitavu grupu, kao i za grupu bolesnika kod kojih je rađena hirurška revaskularizacija koronarnih arterija, operativni rizik bio je umereno potcenjen. Kod bolesnika kojima je rađena valvularna procedura stvarni mortalitet bio je blago precenjen, dok je kod bolesnika sa kombinovanim procedurama bio umereno potcenjen. Model Evropskog sistema pokazao je odličnu diskriminativnu moć u grupi svih operisanih bolesnika (*area under the curve* = 0,825, p < 0,0005). Granična vrednost bila je 2,60, senzitivnost 0,757, a specifičnost 0,750. Diskriminativna moć bila je odlična u grupi koronarnih bolesnika (*area under the curve* = 0,810), kao i u grupi sa izolovanom valvularnom hirurgijom (*area under the curve* = 0,815). Kod bolesnika sa kombinovanim procedurama, diskriminativna moć bila je vrlo dobra (*area under the curve* = 0,775). **Zaključak.** Rezultati istraživanja u našem centru pokazuju da Evropski sistem za procenu operativnog rizika u kardiohirurgiji zadovoljavajuće predviđa operativni rizik za čitavu grupu operisanih bolesnika, ali ga potcenjuje kada su u pitanju kombinovane kardiohirurške procedure. Diskriminativna moć je odlična.

Ključne reči: kardiohirurške procedure; bolnički mortalitet; mortalitet; odrasli; faktori rizika; procena rizika; grudna hirurgija

Introduction

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was developed in the period between 1995 and 1999 from a database of a multinational study performed in 8 European countries including 19,030 adult patients [1]. In the beginning, the system was additive and was quickly adopted, first in Europe and later in other countries [2, 3]. The logistic system was developed in

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Abbreviations

EuroSCORE	– European System for Cardiac Operative Risk Evaluation
AUC	– area under the curve
ICD	– Institute of Cardiovascular Diseases
O/E	– observed/expected
H-L	– Hosmer-Lemeshow
STS	– Society of Thoracic Surgeons
ACEF	– age, creatinine, ejection fraction

2003 and proved to be better, especially in the group of high-risk patients [4, 5].

The EuroSCORE model has been routinely used at the Institute of Cardiovascular Diseases (ICD) of Vojvodina since the beginning of 2001. The analysis of the results, two years later, showed that the model was accurate, and that there was no significant difference between expected (3.7%) and observed mortality (3.47%).

However, only a few years later, the accuracy of both additive and logistic EuroSCORE has been questioned, since many studies showed that the results were better than expected, especially in the low- and medium-risk groups, and worse than expected in high-risk groups [6, 7]. Similar results were obtained in our consecutive series of 4,675 operated coronary patients [8]. In other words, although it still managed to distinguish between low and high-risk patients, the model overestimated the risk in mild- and moderate-risk patients.

In order to improve the model, the latest model for evaluation of the results of operative risk in cardiac surgery, the EuroSCORE 2 was created. The model was based on the collected data of more than 22,000 operated patients (16,828 - group for creating a model and 5,553 - groups for its validation). The ICD Dedinje from Belgrade and ICD of Vojvodina from Sremska Kamenica contributed to the EuroSCORE 2 project with more than 800 patients [9, 10].

New relevant risk factors have been defined, and some old risk factors have been eliminated in line with the latest advances in cardiac surgery. After internal validation, the model showed very good power of discrimination [11]. The model was presented at the 25th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Lisbon, Portugal, in 2011, and introduced in routine use in 2012. The initial results of the EuroSCORE 2 showed better prediction than the previous model [12].

In our first study, including 1,247 patients undergoing surgery during a period of 14 months, starting from the beginning of 2012, we concluded that the EuroSCORE 2 showed a satisfactory predictive value of hospital mortality with solid discriminative power [13].

The aim of this study was to evaluate the predictive value of the EuroSCORE 2 in more than 6,000 operated patients, a group big enough for more precise analysis of results, not only for all patients, but also in coronary, valvular and combined cardiac procedures separately.

Material and Methods

All 6,031 consecutive patients who underwent coronary, valvular or combined (coronary and valvular) cardiac surgery, in the period from January 15, 2015 to December 31, 2020, were included in this study. The EuroSCORE 2 was calculated prospectively using the formulas available at the EuroSCORE website (www.euroscore.org).

Statistical analysis was performed using the statistical software package SPSS Version 19. The statistical significance of the difference between the mean EuroSCORE 2 and the mean mortality was determined using the Student's t-test. The Pearson chi-square test was used to assess the correlation between the numerical variables. The calibration of the EuroSCORE 2 was assessed by comparing the observed (O) and the expected (E) hospital mortality ratio and by the Hosmer-Lemeshow (H-L) test. The discriminative power of the EuroSCORE 2 was examined using area under the receiver operating characteristic curve (AUC), where cut-off, sensitivity and specificity were determined. Measures of descriptive statistics included frequencies and percentages. Differences were considered significant if $p < 0.05$.

Results

The total number of patients who underwent surgery in the period of 6 years was 6,031. There were 2,883 patients with isolated coronary surgery, 1,841 with valvular procedures and 1,307 patients with combined (coronary and valvular) interventions. The difference between the mean EuroSCORE 2 in all patients in the six-year period compared to the average observed mortality rate was statistically significant ($p < 0.0005$). This difference was also statistically significant ($p < 0.0005$) in combined surgeries, while in coronary surgery ($p = 0.895$) and valvular surgery ($p = 0.402$) it was not statistically significant.

The observed mortality rate in all patients was moderately underestimated. In coronary surgery the observed mortality rate was also moderately underestimated, while in valvular surgery it was slightly overestimated. In combined surgeries, the observed mortality rate was moderately underestimated. The calibration of the EuroSCORE 2 through types of cardiac surgeries is shown in **Table 1**.

Differences in the mean EuroSCORE 2 and types of surgery were statistically significant ($p < 0.0005$). The type of surgery and the observed mortality rate were related ($p < 0.0005$).

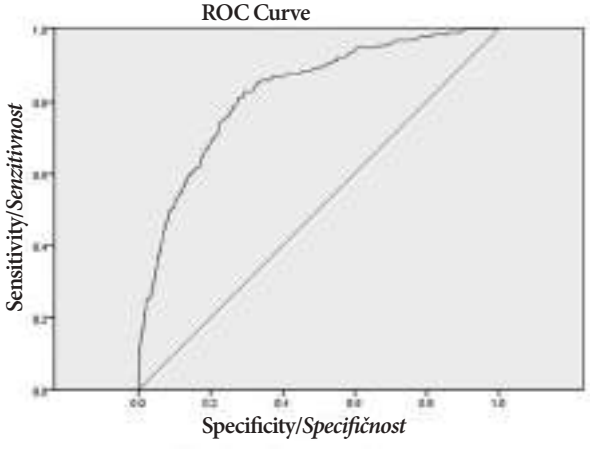
The calibration of the EuroSCORE 2 through the years, regarding, both H-L test and O/E mortality ratio, was good in 2016, 2017, 2018 and 2020, while in 2015 and 2019 the observed mortality ratio was higher than expected **(Table 2)**.

The EuroSCORE 2 showed an excellent discriminative power regarding the whole group of operated patients ($AUC = 0.825$, $p < 0.0005$). The

Table 1. Calibration of the EuroSCORE 2 in specific types of cardiac surgery
Tabela 1. *Kalibracija EvroSCORE 2 kroz tipove kardiohirurških procedura*

Type of surgery *Tip hirurške procedure*	Number of pts *Broj pacijenata*	EuroSCORE 2 (Expected mortality % *Očekivani mortalitet %*)	Observed mortality % *Stvarni mortalitet %*	O/E mortality ratio (95% confidence interval)/*Odnos očekivanog (E) i (O) stvarnog mortaliteta* (95% *interval poverenja*)	H-L test p value *Hosmer-Lemešov test, vrednost p*
Coronary *Koronarna*	2883	1.74	1.90	1.11 (1.08 – 1.17)	< 0.0005
Valvular *Valvularna*	1841	2.70	2.60	0.96 (0.89 – 1.05)	0.002
Combined *Kombinovana*	1307	5.05	6.50	1.29 (1.20 – 1.39)	0.009
Total/*Ukupno*	6031	2.75	3.13	1.14 (1.09 – 1.19)	< 0.0005

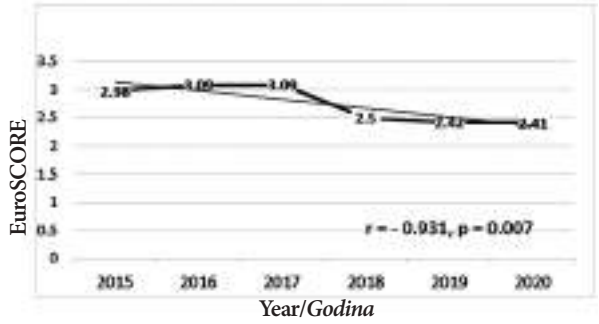
Legenda: EvroSCORE – Evropski sistem za procenu operativnog rizika u kardiohirurgiji



Graph 1. Discriminative power of the EuroSCORE 2
Grafikon 1. *Diskriminativna moć EvroSCORE 2 modela*

cut-off value was 2.60, sensitivity 0.757 and specificity 0.750 **(Graph 1)**.

The discriminative power of the EuroSCORE 2 **(Table 3)** was excellent in coronary surgery (AUC = 0.810) and valvular surgery (AUC = 0.815), but also very good in combined procedures (AUC = 0.775). The discriminative power of EuroSCORE in all three types of surgeries was very similar, while



Graph 2. The trend of the mean EuroSCORE 2 from 2015 to 2020
Grafikon 2. *Trend srednje vrednosti EvroSCORE 2 od 2015. do 2020.*

the difference in areas below the curves between valvular (maximum) and combined (minimum) surgery was not statistically significant (p = 0.409).

The discriminative power of the EuroSCORE 2 through the years, was excellent in the whole observed period **(Table 4)**, but only good in 2016 (AUC = 0.736).

The mean EuroSCORE 2 and observed years had a very strong negative correlation (r = - 0.928, p < 0.0005). The mean EuroSCORE 2 decreased from 2.98 in 2015 to 2.41 in 2020 (p < 0.0005). The

Table 2. The calibration abilities of the EuroSCORE 2 in the observed years
Tabela 2. *Moć kalibracije EvroSCORE 2 modela kroz godine*

Year *Godina*	Number of pts/*Broj pacijenata*	EuroSCORE 2 (Expected mortality % *Očekivani mortalitet %*)	Observed mortality % *Stvarni mortalitet*	O/E mortality ratio (95% confidence interval)/*Odnos očekivanog (E) i (O) stvarnog mortaliteta (95% interval poverenja)*	H-L test p value *Hosmer-Lemešov test, vrednost p*
2015	732	2.98	3.40	1.14 (1.04 – 1.15)	0.005
2016	1104	3.09	3.30	1.06 (0.97 – 1.15)	0.126
2017	1072	3.09	3.20	1.03 (0.93 – 1.14)	0.482
2018	1216	2.50	2.50	1.00 (0.91 – 1.14)	0.994
2019	1152	2.42	3.70	1.54 (1.40 – 1.72)	< 0.0005
2020	755	2.41	2.70	1.12 (0.97 – 1.27)	0.226
Total/*Ukupno*	6031	2.75	3.13	1.14 (1.09 – 1.19)	< 0.0005

Legenda: EvroSCORE – Evropski sistem za procenu operativnog rizika u kardiohirurgiji

Table 3. Discriminative power of the EuroSCORE 2 in specific types of cardiac surgery
Tabela 3. *Diskriminativna moć EvroSCORE 2 modela kroz tipove kardiohirurških procedura*

Type of surgery *Tip hirurške procedure*	AUC (95% confidence interval)/*Površina ispod krive (95% interval poverenja)*	Cut-off *Granična vrednost*	Sensitivity *Senzitivnost*	Specificity *Specifičnost*
Coronary/*Koronarna*	0.810 (0.752 - 0.869)	2.05	0.768	0.792
Valvular/*Valvularna*	0.815 (0.749 - 0.881)	2.45	0.750	0.755
Combined/*Kombinovana*	0.775 (0.726 - 0.825)	4.19	0.706	0.309

Legend: AUC - area under the receiver operating characteristic curve
Legenda: AUC – površina ispod krive, EvroSCORE – Evropski sistem za procenu operativnog rizika u kardiohirurgiji

Table 4. Discriminative power of the EuroSCORE 2 through the observed years
Tabela 4. *Diskriminativna moć EvroSCORE 2 modela kroz godine*

Year *Godina*	AUC (95% confidence interval)/*Površina ispod krive (95% interval poverenja)*	Cut-off *Granična vrednost*	Sensitivity *Senzitivnost*	Specificity *Specifičnos*t
2015	0.858 (0.792 -0.925)	3.77	0.840	0.813
2016	0.736 (0.658 – 0.813)	2.67	0.667	0.695
2017	0.823 (0.740 – 0.905)	3.00	0.765	0.769
2018	0.821 (0.749 – 0.892)	2.80	0.710	0.817
2019	0.863 (0.809 – 0.917)	2.75	0.791	0.821
2020	0.863 (782 – 0.944)	2.78	0.750	0,800
2015 - 2020	0.825 (0.795 – 0.855)	2,60	0.757	0.750

Legend: AUC - area under the receiver operating characteristic curve
Legenda: AUC – površina ispod krive, EvroSCORE – Evropski sistem za procenu operativnog rizika u kardiohirurgiji

trend of the mean EuroSCORE 2 from 2015 to 2020 is shown in **Graph 2.**

Discussion

According to the results of this study, the observed mortality rate in all patients was moderately underestimated, as well as in coronary and combined surgery subgroups. However, in valvular surgery the observed mortality rate was slightly overestimated. The calibration of the EuroSCORE 2 through years, regarding both H-L test and O/E mortality ratio, was good in 2016, 2017, 2018 and 2020, while in 2015 and 2019 the operative risk was underestimated. The EuroSCORE 2 showed excellent discriminative power regarding the whole group of operated patients in the period of six years, as well as in coronary surgery and valvular surgery, but very good in combined procedures. The discriminative power of the EuroSCORE 2 through the years was excellent in the whole observed period, but just good in 2016 year. The mean EuroSCORE 2 and observed years had a very strong negative correlation. The mean EuroSCORE 2 decreased from 2.98 in 2015 to 2.41 in 2020, but it was very good in combined procedures.

Similar results were published by Howell NJ et al., based on analysis of all three EuroSCORE models, in more than 12,000 operated patients from two European centers. Among those, there were 933 high-risk patients, whose logistic EuroSCORE was higher than 10. The conclusion was that the discriminative power of all three EuroSCORE models was good, but that in the group with increased risk, EuroSCORE 2 did not show better accuracy compared to the initial versions [14].

Paparella et al. presented an external validation of the EuroSCORE 2, based on the results of 6,293 operated coronary patients. According to their results, the discriminative power of EuroSCORE 2 was excellent (AUC = 0.830). Compared to calibration, in patients with lower and moderate risk, the model proved to be a good predictor of hospital mortality, while in those at increased risk, the operative risk was underestimated [15].

Similar results were published by Koszta et al. after the analysis of 2,287 operated patients in relation to the type of surgical intervention. In coronary surgeries, O/E ratio was 0.75 and the H-L test, p = 0.5789. In elective surgeries, O/E ratio was 1.1; H-L test, p = 0.139, and in emergency surgeries O/E ratio was 1.71; H-L test, p = 0.055. The conclusion was that the EuroSCORE 2 predicted better, compared to the initial models, but that it underestimated mortality in increased operative risk groups, related to emergency and combined surgery [16].

A preliminary research conducted at the ICD of Vojvodina in 2014, included 1,247 operated patients and showed good results in coronary and valvular surgery, but the results related to combined procedures, were not satisfactory [13].

A meta-analysis of Guida et al., that included 22 studies, including more than 145,000 cardiac surgical procedures, showed that the model had very good discriminative power (AUC = 0.792 and an O/E ratio: 1.019) for all procedures [17]. In isolated

coronary surgery, EuroSCORE 2 overestimated the risk (O/E ratio: 0.829). However, in the high-risk group, the model underestimated the mortality (O/E ratio: 1,253).

Nežic et al. from ICD Dedinje, Serbia, in a study of 1,864 patients, validated the EuroSCORE 2 [18]. The calibration was good for all groups, for coronary, valvular and combined surgeries. The discriminative power was acceptable only in combined surgeries (AUC = 0.72), but excellent in coronary surgery (AUC = 0.81), valvular surgery (AUC = 0.91), as well as in all patients (AUC = 0.85). In 2019, the authors from the same institution, reported performances of the EuroSCORE 2, including 10,048 operated patients [10]. The results were similar to those obtained in their previous study. Although H-L test did not perform well, O/E mortality ratio confirmed good calibration. The discriminative power for the whole group was excellent (AUC = 0.84), as well as in coronary surgery (AUC = 0.84) and valvular surgery (AUC = 0.86), while in combined surgeries it was very good (AUC = 0.78).

A multicenter study, conducted in 41 hospitals in Great Britain and Ireland, included 23,740 procedures, and Grant SW. et al. confirmed very good discriminative power (AUC = 0.808) and good calibration of the EuroSCORE 2. The results were better than predicted in coronary surgery, but the model failed the H-L test (p = 0.003), mainly due to overprediction in the highest and lowest-risk patients [19].

There are a large number of risk stratification models in cardiac surgery, which must be constantly revised and updated, because new risk factors must be considered. For any risk factor to be considered acceptable, it must, at a minimum, have an independent statistical relationship with the outcome and an advantage over the pre-existing predictors. An independent statistical correlation should be based on studies including large samples. The power of the model means that predictions of the outcome can be made as accurately as possible with as few parameters as possible. If there are a large number of variables in the model, multicollinearity may occur. The Society of Thoracic Surgeon (STS) model showed good accuracy in more than 138,000 subjects, but its disadvantage is that it considers a total of 33 risk factors [20, 21]. In contrast, the model proposed by Ranucci et al., created only for elective cardiac surgeries, has only 3 variables: age, serum creatinine level, and left ventricular ejection fraction (ACEF) [22].

The validation of a model is done based on its calibration (predictive power) and discriminative power. A good calibration means that the difference between the expected outcome and the observed outcome is small, ideally zero. The discriminative power of the model is the ability to distinguish between low and high-risk groups in relation to the outcome.

Numerous factors contributed to the fact that in the first decade of the 20th century there were significant changes in cardiac surgery. This refers to the continuous improvement of invasive cardiology procedures, preoperative preparation of patients, anesthesiological approach, surgical tactics and techniques, and postoperative treatment. The changes and advances in surgical treatment can serve as arguments to explain why the predictive power of the additive and logistic EuroSCORE has been decreased. This shows that overestimation of mortality rate was caused by improvements in peri-operative patient care. Apart from that, the expected mortality rate, given by the predictive model, is a standard that should at least be reached, but the aspiration is to be better. This effect, of increasing efficiency and improving quality due to the introduction of measurement results, is known as the Hawthorne effect [23, 24].

Barili et al. analyzed a consecutive series of 12,325 operated patients in Italy and compared all three EuroSCORE models. They concluded that the new model had good discriminative power, but was not more precise than the initial, additive, and logistic version [12].

Similar results were published by Howell NJ et al., based on the results of all three EuroSCORE models, in more than 12,000 operated patients from two European centers. Among those, there were 933 high-risk patients, whose logistic EuroSCORE was higher than 10. The conclusion was that the discriminative power of all three EuroSCORE models was good, but that in the group with increased risk EuroSCORE 2 did not show better accuracy compared to the initial versions [14].

Many authors have compared the two most well-known and widespread systems for evaluation of cardiac operative risk; the EuroSCORE 2 and the STS model. Kirmani et al. reported that both systems have similar discriminative power and good calibration in low-risk and moderate-risk patients [25]. Similar results were published by Sullivan PG. et al. in a meta analysis of differences in discriminative power of the EuroSCORE 2, STS and ACEF models. In conclusion, the EuroSCORE 2 and STS scores had similar discriminative power, better than ACEF score [26].

In our study, we analyzed not only the clinical performances of the EuroSCORE 2 for a total period of 6 years, but also the calibration and discrimination properties of the EuroSCORE 2 through the years. The discriminative power of the EuroSCORE 2 through the years was excellent in the whole observed period. It was found that the mean EuroSCORE 2 and observed years had a very strong negative correlation. The mean value of the EuroSCORE 2 decreased from 2.98 in 2015 year, to 2.41 in 2020. The mean value of the model has a declining trend. We could not find published studies evaluating the trend of the mean EuroSCORE 2 through the years. It would be interesting to assess this finding, 10 years after its introduction.

The limitation of our study is a relatively small sample size for more precise analysis, especially in subgroups of cardiac surgery patients. Furthermore, it is a single-center experience and the results may not represent national and international practice and

outcomes. More multicenter studies, including a greater number of patients, are necessary for more precise evaluation of the results.

Conclusion

In conclusion, the results of our single center study show that the European System for Cardiac Operative Risk Evaluation 2 predicts hospital mortality with satisfactory results concerning the whole group, but underestimates mortality in patients undergoing combined cardiac procedures. The discriminative power of the model is excellent.

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PREDICTORS OF VACCINATION AGAINST CORONAVIRUS DISEASE 2019 IN SERBIA

PREDIKTORI VAKCINACIJE PROTIV COVID-19 U SRBIJI

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Summary

Introduction. The main goal of vaccination against coronavirus disease 2019 is to significantly reduce the morbidity and mortality caused by severe acute respiratory syndrome coronavirus 2 infection. The free-of-charge recommended vaccination against coronavirus disease 2019 in Serbia started in December, 2020, and it is still ongoing. The aim of this study was to determine the main socio-demographic characteristics associated with the acceptance of vaccination against coronavirus disease 2019 among the Serbian population. **Material and Methods**. A cross-sectional survey was conducted among the participants aged ≥ 15 years in the general population of Serbia during September and October, 2021. Data were collected using an electronic questionnaire. **Results.** During the study period, a total of 1,418 participants were included in the survey. In general, vaccination against coronavirus disease 2019 was significantly ($p < 0.05$) more often accepted with increasing age of the participants, among females, those who were married and with higher education, among the university faculty members/health workers, employees in the government sector, those who had one child, and those with unspecified income. satisfaction compared to comparison groups. **Conclusion.** Taking into account all identified predictors, the main predictors of vaccination against coronavirus disease 2019 among our participants were family members/close friends or others who died from coronavirus disease 2019 and intention to get vaccinated against influenza in the future. There is an urgent need to conduct further studies that assess intentions, beliefs, and attitudes towards vaccines against coronavirus disease 2019 among the population throughout the Republic of Serbia.

Key words*:* Immunization; COVID-19 Vaccines; Serbia; Sociodemographic Factors; Health Knowledge, Attitudes, Practice; Surveys and Questionnaires; Vaccination Coverage

Sažetak

Uvod. Osnovni cilj vakcinacije protiv COVID-19 je značajno smanjenje morbiditeta i mortaliteta uzrokovanih infekcijom SARS-CoV-2. Preporučena, besplatna vakcinacija protiv COVID-19 u Republici Srbiji započeta je u decembru 2020. godine i još uvek traje. Cilj ove studije bio je da se utvrde glavne sociodemografske karakteristike u vezi sa prihvatanjem vakcinacije protiv COVID-19 među stanovništvom Republike Srbije. **Materijal i metode**. Sprovedena je studija preseka među učesnicima uzrasta ≥ 15 godina u opštoj populaciji Srbije tokom septembra i oktobra 2021. Podaci su prikupljeni korišćenjem elektronskog upitnika. **Rezultati**. Tokom posmatranog perioda, uključeno je ukupno 1.418 ispitanika. Uopšte posmatrano, vakcinacija protiv COVID-19 bila je značajno češće prihvaćena ($p < 0,05$) sa porastom uzrasta učesnika među ženama, onima koji su bili u braku i sa visokim obrazovanjem, kod nastavnika fakulteta/zdravstvenih radnika, onih koji su bili zaposleni u državnom sektoru, onih koji su imali jedno dete i ispitanika sa neodređenim zadovoljstvom u prihodima u poređenju sa poredbenim grupama. **Zaključak**. Uzimajući u obzir sve utvrđene prediktore, glavni prediktori vakcinacije protiv COVID-19 među našim učesnicima bili su podaci o postojanju članova porodice/bliskih prijatelja ili drugih koji su umrli od COVID-19 i namera da se ubuduće vakcinišu protiv gripa. Neodložno je potrebno sprovesti dalja istraživanja kojima se procenjuju namere, uverenja i stavovi prema vakcinama protiv COVID-19 među stanovništvom širom Republike Srbije.

Ključne reči: imunizacija; vakcine protiv COVID-19; Srbija; socio-demografski faktori; znanje o zdravlju, stavovi, praksa; ankete i upitnici; obuhvat vakcinacijom

Introduction

The global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared by the World Health Organization (WHO) on March 11, 2020 [1]. The SARS-CoV-2 has emerged as a major global concern, affecting not only the healthcare systems but also the economy, which sparked fear of a new worldwide economic downturn [2–4].

Elderly people and those with underlying medical conditions (e.g. cardiovascular disease, diabetes, chronic respiratory disease, or cancer) are at in-

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Abbreviations

COVID-19	– coronavirus disease 2019
SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
WHO	– World Health Organization
OR	– odds ratio
CI	– confidence interval
IQR	– interquartile range

creased risk of developing severe infection caused by SARS-CoV-2. However, people at any age, regardless of their medical conditions, may get COVID-19 and become seriously ill or die [5].

The main goal of COVID-19 vaccination is to significantly reduce the morbidity and mortality caused by SARS-CoV-2 [3, 6].

The success of vaccination campaign can be undermined by vaccine hesitancy worldwide [2, 6]. Even before COVID-19 pandemic, WHO declared vaccine hesitancy as one of the ten challenges to global health [7], and this problem has grown throughout the ongoing COVID-19 pandemic [3, 8, 9].

In Serbia, the COVID-19 vaccination campaign using Pfizer-BioNTech BNT162b2 (Comirnaty®) started on December 24, 2020. The recommended immunization program was implemented (and it is still ongoing), and all COVID-19 vaccines were offered free of charge. Until the end of the study period, the Medicines and Medical Devices Agency of Serbia approved four vaccines for countrywide vaccination, namely Pfizer-BioNTech BNT162b2 (Comirnaty®), Gamaleya Research Institute Gam-COVID-Vac (Sputnik V®), Sinopharm BBIBP-CorV (Vero Cell®), and Oxford/AstraZeneca ChAdOx1-S/nCoV-19 AZD1222 (Vaxzevria®) [10], and everyone has the possibility to choose a vaccine among those four available. These vaccines are based on different platforms and have diverse mechanisms of action, which were previously described elsewhere [11–14]. According to available data (report of the Institute of Public Health of Serbia), during the first 10 months of 2021, a total of 6.172.015 doses of COVID-19 vaccines were given in Serbia (one dose was received by 2.870.046, two doses by 2.749.410, and three doses by 552.559 persons). Coverage of at least one dose of COVID-19 vaccine in adult population (over 18 years of age) of Serbia until October 31, 2021 was 49.8% [15]. The majority of citizens of Serbia (3.861.745 or 62.6%) were vaccinated with Sinopharm BBIBP-CorV.

The aim of our study was to evaluate the main socio-demographic characteristics as well as certain vulnerability factors for the acceptance of COVID-19 vaccines among Serbian population.

This study was public health surveillance and no clearance by Ethics Committee for this response is required in Serbia. Personal and confidential information were removed, except for demographic, socioeconomic, and vulnerability factors, as well as participants' COVID-19 vaccination status, and the data were anonymized before the authors could access them.

Material and Methods

The survey recruitment was performed from September 1 to October 31, 2021. Study participants were recruited from different parts of Serbia, including major cities, namely Belgrade, the capital city with approximately 1.7 million inhabitants, and Novi Sad, the main administrative Center of Vojvodina with a population of 362.675 citizens, as well as a number of smaller cities across Serbia. Data were collected using an electronic questionnaire. This cross-sectional survey was designed using Google forms® platform and used a snowball sampling strategy. At the beginning of the research, the study investigators shared the survey link in social media (Twitter, Instagram, Facebook), on the website of the Institute of Public Health of Vojvodina, Novi Sad) and through emails to their primary social contacts (aged ≥ 15 years). In the primary communication, respondents were requested to share the link of the survey.

On receiving and clicking the link, participants were auto-directed to the informed consent page, followed by the survey questionnaire. Once they filled out the questionnaire, the system would not allow them to sign up again. The inclusion criteria were as follows: (1) age of 15 years and over; (2) ability to read and complete the self-administered questionnaire independently; (3) voluntary agreement to participate in this study; and (4) knowledge of Serbian language. People who fulfilled these criteria and answered the questionnaire within the specified period were included in the study.

We used an anonymous, population-based, structured questionnaire in Serbian language. The questionnaire was developed based on relevant research on this topic after a thorough literature review [16–20]. We designed a questionnaire which consisted of several sections that covered demographic, socioeconomic, as well as various vulnerability factors. A history of vaccination against COVID-19 (vaccinated with at least one dose of COVID-19 vaccine or unvaccinated) was also included in the questionnaire. Detailed instructions to participants were also provided in order to inform them to select one or more given options from the list of answers, depending on the question they were referring to. A small survey that preceded the investigation was performed with the aim to further improve the quality of the questionnaire. The draft questionnaire was pilot tested in 200 participants. Based on these data and a feedback from these participants, a refined version of the questionnaire was prepared and included in the final study.

The primary group of the survey included those who were "vaccinated with at least one dose of COVID-19 vaccines" (we presumed that this classification potentially means that these participants intended to complete immunization against COVID-19 in the near future), and they were compared with those that did not receive any vaccine and were assigned to the "unvaccinated group". Categorical

variables were compared using chi-square or Fisher's exact test. Fisher's exact test was used to determine whether or not there is a significant association between two categorical variables. Multivariable logistic regressions were used to assess the association between selected vulnerabilities of participants and COVID-19 vaccination status. The multivariable model was adjusted for potential confounders, including age, gender, marital status, having children, employment, and income satisfaction. Logistic regression models were employed using a priori hypothesis to tabulate odds ratios (OR) and their 95% confidence interval (CI) All analyses were performed using SPSS software tool (version 22) MedCalc for Windows, version 12.3.0 (MedCalc Software, Mariakerke, Belgium). A two-tailed p-value < 0.05 was considered statistically significant.

Results

General socio-demographic characteristics

During the study period, a total of 1,418 participants were enrolled. The mean age of the participants was 44 years (median age 44 years; interquartile range (IQR) 37 - 53). Out of the total number of respondents, 1,065 (75.1%) were vaccinated with at least one dose of COVID-19 vaccine, and 353 (24.9%) subjects were not vaccinated against COVID-19. The mean age of vaccinated and unvaccinated persons was 46 years (median age 45 years; IQR 39 - 53) and 39.3 years (median age 40 years; IQR 30 - 48), respectively.

Most of the study participants were aged 40 - 49 years (496/1418; 35.0%), females (854/1,418; 60.2%), married (909/1,418; 64.1%), graduate award holders (644/1,418; 45.4%), service holders (649/1,418; 45.8%), employed in the government sector (641/1,418; 45.2%), without children (531/1,418; 37.4%), and with undefined income satisfaction (800/1,418; 56.4%). Out of all participants, there were respondents from the City of Novi Sad, other cities in Vojvodina, City of Belgrade, and other cities of Serbia, 918 (64.7%), 316 (22.3%), 113 (8%), and 71 (5%), respectively.

Socio-demographic characteristics

In general, vaccination against COVID-19 significantly ($p < 0.05$) increased with the age of participants, among females, among married participants, those with higher education level, among the university faculty members/health workers, those who were employed in the government sector, those who had one child, and those with undefined income satisfaction compared to comparison groups. Similar results were obtained when these characteristics were compared with the uptake of COVID-19 vaccines in four different settlement areas covered in our research separately, although few exceptions have been observed as follows: vaccination against COVID-19 was not significantly associated with the age of participants in other cities in Serbia ($p = 0.4698$), with gender in other cities in Vojvodina ($p = 0.1320$) and other regions in Serbia ($p = 0.9128$), with marital status in Novi Sad ($p = 0.2207$), in Belgrade ($p = 0.3474$) and other regions in Serbia ($p = 0.0985$), with education level in Belgrade ($p = 0.1930$) and other regions in Serbia ($p = 0.0914$), with the number of children in other regions in Serbia ($p = 0.8576$), and income satisfaction in Belgrade ($p = 0.2958$) and other regions in Serbia ($p = 0.4143$) **(Table 1)**.

Vulnerabilities of the participants

The **Table 2** shows the associations between certain vulnerabilities of the participants and COVID-19 vaccination status. Thus, multiple logistic regression models revealed that those who previously had laboratory-confirmed COVID-19, those who had family members affected by COVID-19, those who had family members/close friends or others who died due to COVID-19, those who were previously vaccinated against influenza, those who were planning to get the seasonal flu vaccine in the future, and respondents who received all childhood vaccines, were more likely ($p < 0.05$) to receive a vaccine against COVID-19. Surprisingly, presumably an important vulnerability factor of participants, namely "having any chronic disease" was not significantly associated (OR (95% CI): 1.24 (0.92 - 1.67)) with vaccination against COVID-19.

Discussion

To the best of our knowledge, this study is the first one to examine the association of certain demographic, socioeconomic and vulnerability factors of participants and their decision to receive COVID-19 vaccine after their implementation in the national immunization programme, using an online self-reported questionnaire.

This study was conducted in different locations of Serbia during the largest (fifth) wave of COVID-19 outbreak.

Public attitudes towards COVID-19 vaccination vary around the world [3, 21–26].

In our survey, as many as ¾ out of the total number of respondents were vaccinated with at least one dose of COVID-19 vaccine, and such a high uptake could be ascribed to a specific method design of our study (self-selected online voluntary survey), which may predominantly recruit persons that are more prone to be vaccinated. Indeed, the proportion of vaccinated individuals in our study was considerably higher compared to COVID-19 vaccine coverage in Serbia that was below 50% at the time when the study was carried out [15]. However, vaccination status of COVID-19 was different in four settlement areas where our participants lived. Namely, participants from the City of Novi Sad, other cities of Vojvodina, City of Belgrade, and other cities in Serbia received at least one dose of COVID-19 (80.5%, 70.3%, 61.1%, and 49.3%, respectively). A similar example of different prevalence of COVID-19 vaccine acceptance in different

Table 1. Demographic and socioeconomic factors and attitudes in relation to vaccination status against COVID-19 and respondents' place of residence

Tabela 1. *Demografski i socioekonomski faktori i stavovi u odnosu na vakcinalni status protiv COVID-19 i mestu prebivališta ispitanika*

Variables/*Varijable*	City of Novi Sad *Grad Novi Sad* (N/*B*=918)						Other cities in Vojvodina/*Ostali gradovi u Autonomnoj Pokrajini Vojvodina* (N/*B*=316)					
	Total Ukupno	Vaccinated *Vakcinisani* (N/*B*=739)		Unvaccinated *Nevakcinisani* (N/*B*=179)		p/*p*	Total *Ukupno*	Vaccinated *Vakcinisani* (N/*B*=222)		Unvaccinated *Nevakcinisani* (N/*B*=94)		p/*p*
	n	n	%	n	%		n	n	%	n	%	
Did you previously have laboratory-confirmed COVID-19?/*Da li ste prethodno imali potvrđen COVID-19?*												
No/*Ne*	667	565	84.71	102	15.29	<0.001	202	155	76.73	47	23.27	0.0008
Yes/*Da*	251	174	69.32	77	30.68		114	67	58.77	47	41.23	
Were any of your family members affected by COVID-19?/*Da li je bilo ko od članova Vaše porodice obolelo od COVID-19?*												
No/*Ne*	537	452	84.17	85	15.83	**0.0010**	161	120	74.53	41	25.47	0.0898
Yes/*Da*	381	287	75.33	94	24.67		155	102	65.81	53	34.19	
Did any of your family members/close friends or others die due to COVID-19? *Da li je bilo ko od članova Vaše porodice/bliskih prijatelja imao fatalni ishod zbog COVID-19?*												
No/*Ne*	185	101	54.59	84	45.41		59	27	45.76	32	54.24	
Yes, family member/close friend	223	197	88.34	26	11.66	<0.001	49	37	75.51	12	24.49	<0.001
Yes, other/*Da, drugi*	510	441	86.47	69	13.53		208	158	75.96	50	24.04	
Do you have any chronic disease (e.g. Diabetes mellitus, hypertension, chronic cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, malignancy or any other chronic diseases)?/*Da li imate neko hronično oboljenje (dijabetes melitus, arterijsku hipertenziju, hronično kardiovaskularno oboljenje, bubrežno oboljenje, hroničnu opstruktivnu bolest pluća, malignitet ili dr.)?*												
No/*Ne*	621	492	79.23	129	20.77	0.1589	217	140	64.52	77	35.48	0.0010
Yes/*Da*	297	247	83.16	50	16.84		99	82	82.83	17	17.17	
Did you ever get the seasonal flu vaccine?/*Da li ste ikada vakcinisani sezonskom vakcinom protiv gripa?*												
No/*Ne*	630	478	75.87	152	24.13	<0.001	209	133	63.64	76	36.36	0.0003
Yes/*Da*	288	261	90.63	27	9.38		107	89	83.18	18	16.82	
Do you plan to get seasonal flu vaccine in the future?/*Da li planirate da se vakcinišete protiv gripa u budućnosti?*												
No/*Ne*	336	203	60.42	133	39.58		130	69	53.08	61	46.92	
Yes/*Da*	299	276	92.31	23	7.69	<0.001	99	89	89.90	10	10.10	<0.001
Unsure/*Nisam siguran*	283	260	91.87	23	8.13		87	64	73.56	23	26.44	
Did you get all vaccines in a childhood?/*Da li ste vakcinisani svim vakcinama u dečjem uzrastu?*												
No/*Ne*	15	9	60.00	6	40.00	0.0433	6	1	16.67	5	83.33	0.0099
Yes/*Da*	903	730	80.84	173	19.16		310	221	71.29	89	28.71	
Vaccines against COVID-19 available in Serbia are safe/*Vakcine protiv COVID-19 u Srbiji su bezbedne*												
No/*Ne*	117	23	19.66	94	80.34		50	4	8.00	46	92.00	
Yes/*Da*	697	650	93.26	47	6.74	<0.001	205	186	90.73	19	9.27	<0.001
Don't Know/*Ne znam*	104	66	63.46	38	36.54		61	32	52.46	29	47.54	
It is true that in our country there were not registered life-threatening reactions after immunization against COVID-19? *Da li je istina da u našoj državi nisu registrovane ozbiljne neželjene reakcije nakon vakcinacije protiv COVID-19?*												
No/*Ne*	258	147	56.98	111	43.02		108	50	46.30	58	53.70	
Yes/*Da*	471	433	91.93	38	8.07	<0.001	99	91	91.92	8	8.08	<0.001
Don't Know/*Ne znam*	189	159	84.13	30	15.87		109	81	74.31	28	25.69	
Do you think that vaccines against COVID-19 can provoke autoimmune disease? *Da li mislite da vakcine protiv COVID-19 izazivaju autoimune bolesti?*												
No/*Ne*	236	140	59.32	96	40.68		70	29	41.43	41	58.57	
Yes/*Da*	476	434	91.18	42	8.82	<0.001	123	104	84.55	19	15.45	<0.001
Don't Know/*Ne znam*	206	165	80.10	41	19.90		123	89	72.36	34	27.64	
Do you think that vaccines against COVID-19 can provoke infertility? Da li mislite da vakcine protiv COVID-19 izazivaju sterilitet?												
No/*Ne*	594	539	90.74	55	9.26		141	130	92.20	11	7.80	
Yes/*Da*	159	84	52.83	75	47.17	<0.001	78	30	38.46	48	61.54	<0.001
Don't Know/*Ne znam*	165	116	70.30	49	29.70		97	62	63.92	35	36.08	
Adverse events after vaccination against COVID-19 are most commonly local (i.e. pain, swelling, redness) *Neželjene reakcije nakon vakcinacje protiv COVID-19 su najčešće lokalne (npr. bol, otok, crvenilo)*												
No/*Ne*	69	23	33.33	46	66.67		26	6	23.08	20	76.92	
Yes/*Da*	796	690	86.68	106	13.32	<0.001	241	192	79.67	49	20.33	<0.001
Don't Know/*Ne znam*	53	26	49.06	27	50.94		49	24	48.98	25	51.02	
Do you think that vaccines against COVID-19 can protect you against severe clinical forms of disease and lethal outcome? *Da li mislite da vakcine protiv COVID-19 štite protiv teških formi oboljenja i smrtnog ishoda?*												
No/*Ne*	141	38	26.95	103	73.05		63	9	14.29	54	85.71	
Yes/*Da*	711	661	92.97	50	7.03	<0.001	201	183	91.04	19	9.45	<0.001
Don't Know/*Ne znam*	66	40	60.61	26	39.39		52	30	57.69	22	42.31	

Variables *Varijable*	Belgrade/*Beograd* (N/*B*=113)						Other regions of Serbia/*Ostali regioni u Srbiji* (N/*B*=71)					
	Total *Ukupno*	Vaccinated *Vakcinisani* (N/*B*=69)		Unvaccinated *Nevakcinisani* (N/*B*=44)		p/*p*	Total *Ukupno*	Vaccinated *Vakcinisani* (N/*B*=35)		Unvaccinated *Nevakcinisani* (N/*B*=36)		p/*p*
	n	n	%	n	%		n	n	%	n	%	
Did you previously have laboratory-confirmed COVID-19?/*Da li ste prethodno imali potvrđen COVID-19?*												
No/*Ne*	80	54	67.50	26	32.50	0.0289	48	22	45.83	26	54.17	0.3991
Yes/*Da*	33	15	45.45	18	54.55		23	13	56.52	10	43.48	
Were any of your family members affected by COVID-19?/*Da li je bilo ko od članova Vaše porodice oboleo od COVID-19?*												
No/*Ne*	63	45	71.43	18	28.57	**0.0112**	37	18	48.65	19	51.35	0.9092
Yes/*Da*	50	24	48.00	26	52.00		34	17	50.00	17	50.00	
Did any of your family members/close friends or others die due to COVID-19? *Da li je bilo ko od članova Vaše porodice/bliskih prijatelja imao fatalni ishod zbog COVID-19?*												
No/*Ne*	27	6	22.22	21	77.78		25	4	16.00	21	84.00	
Yes, family member/close friend *Da, član porodice/blizak prijatelj*	29	20	68.97	9	31.03	<0.001	13	8	61.54	5	38.46	<0.001
Yes, other/*Da, drugi*	57	43	75.44	14	24.56		33	23	69.70	10	30.30	
Do you have any chronic disease (e.g. Diabetes mellitus, hypertension, chronic cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, malignancy or any other chronic diseases)?/*Da li imate neko hroničnо oboljenje (dijabetes melitus, arterijsku hipertenziju, hronično kardiovaskularno oboljenje, bubrežno oboljenje, hroničnu opstruktivnu bolest pluća, malignitet ili dr.)?*												
No/*Ne*	79	45	56.96	34	43.04	0.1731	55	25	45.45	30	54.55	0.2300
Yes/*Da*	34	24	70.59	10	29.41		16	10	62.50	6	37.50	
Did you ever get the seasonal flu vaccine?/*Da li ste ikada vakcinisani sezonskom vakcinom protiv gripa?*												
No/*Ne*	71	32	45.07	39	54.93	<0.001	56	24	42.86	32	57.14	0.0451
Yes/*Da*	42	37	88.10	5	11.90		15	11	73.33	4	26.67	
Do you plan to get seasonal flu vaccine in the future?/*Da li planirate da se vakcinišete protiv gripa u budućnosti?*												
No/*Ne*	58	20	34.48	38	65.52		49	15	30.61	34	69.39	
Yes/*Da*	35	34	97.14	1	2.86	<0.001	9	9	100.00	0	0.00	<0.001
Unsure/*Nisam siguran*	20	15	75.00	5	25.00		13	11	84.62	2	15.38	
Did you get all vaccines in a childhood?/*Da li ste vakcinisani svim vakcinama u dečjem uzrastu?*												
No/*Ne*	4	0	0.00	4	100.00	0.0211	3	0	0.00	3	100.00	0.2394
Yes/*Da*	109	69	63.30	40	36.70		68	35	51.47	33	48.53	
Vaccines against COVID-19 available in Serbia are safe/*Vakcine protiv COVID-19 u Srbiji su bezbedne*												
No/*Ne*	40	4	10.00	36	90.00		37	5	13.51	32	86.49	
Yes/*Da*	63	59	93.65	4	6.35	<0.001	28	26	92.86	2	7.14	<0.001
Don't Know/*Ne znam*	10	6	60.00	4	40.00		6	4	66.67	2	33.33	
It is true that in our country there were not registered life-threatening reactions after immunization against COVID-19? *Da li je istina da u našoj državi nisu registrovane ozbiljne neželjene reakcije nakon vakcinacije protiv COVID-19?*												
No/*Ne*	53	13	24.53	40	75.47		41	9	21.95	32	78.05	
Yes/*Da*	39	37	94.87	2	5.13	<0.001	19	17	89.47	2	10.53	<0.001
Don't Know/*Ne znam*	21	19	90.48	2	9.52		11	9	81.82	2	18.18	
Do you think that vaccines against COVID-19 can provoke autoimmune disease? *Da li mislite da vakcine protiv COVID-19 izazivaju autoimune bolesti?*												
No/*Ne*	48	13	27.08	35	72.92		38	7	18.42	31	81.58	
Yes/*Da*	49	43	87.76	6	12.24	<0.001	20	19	95.00	1	5.00	<0.001
Don't Know/*Ne znam*	16	13	81.25	3	18.75		13	9	69.23	4	30.77	
Do you think that vaccines against COVID-19 can provoke infertility? *Da li mislite da vakcine protiv COVID-19 izazivaju sterilitet?*												
No/*Ne*	60	52	86.67	8	13.33		28	23	82.14	5	17.86	
Yes/*Da*	37	5	13.51	32	86.49	<0.001	34	6	17.65	28	82.35	<0.001
Don't Know/*Ne znam*	16	12	75.00	4	25.00		9	6	66.67	3	33.33	
Adverse events after vaccination against COVID-19 are most commonly local (i.e. pain, swelling, redness) *Neželjene reakcije nakon vakcinacije protiv COVID-19 su najčešće lokalne (npr. bol, otok, crvenilo)*												
No/*Ne*	21	1	4.76	20	95.24		27	6	22.22	21	77.78	
Yes/*Da*	86	65	75.58	21	24.42	<0.001	41	29	70.73	12	29.27	<0.001
Don't Know/*Ne znam*	6	3	50.00	3	50.00		3	0	0.00	3	100.00	
Do you think that vaccines against COVID-19 can protect you against severe clinical forms of disease and lethal outcome? *Da li mislite da vakcine protiv COVID-19 štite protiv teških formi oboljenja i smrtnog ishoda?*												
No/*Ne*	42	4	9.52	38	90.48		36	4	11.11	32	88.89	
Yes/*Da*	65	62	95.38	3	4.62	<0.001	28	27	96.43	1	3.57	<0.001
Don't Know/*Ne znam*	6	3	50.00	3	50.00		7	4	57.14	3	42.86	

Table 2. Predictors of vaccination against COVID-19 according to certain characteristics of respondents – multivariate logistic regression model
Tabela 2*. Prediktori vakcinacije protiv COVID-19 prema određenim karakteristikama ispitanika – multivarijantni logistički regresioni model*

Logistic regression variables *Varijable logističke regresije*	OR [a]	(95% CI/*Interval poverenja*)	p/*p*
Previously having laboratory-confirmed COVID-19/*Prethodna laboratorijska potvrda COVID-19*	2.15	1.64 – 2.80	**< 0.001**
Having family members affected by COVID-19/*Postojanje obolelih od COVID-19 u porodici*	1.60	1.24 – 2.07	**0.0003**
Having family members/close friends or others who died due to COVID-19 *Postojanje smrtnog ishoda među članovima porodice/bliskim prijateljima*	4.75	3.56 – 6.34	**< 0.001**
Having any chronic disease (e.g. Diabetes mellitus, hypertension, chronic cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, malignancy or any other chronic diseases)/*Postojanje bilo kog hroničnog oboljenja (dijabetes melitus, hipertenzija, hronično kardiovaskularno oboljenje, bubrežno oboljenje, hroničnu opstruktivnu bolest pluća, malignitet ili dr.)*	1.24	0.92 – 1.67	0.1605
Previous vaccination against influenza/*Vakcinisan sezonskom vakcinom protiv gripa ranije*	2.98	2.14 – 4.13	**< 0.001**
Planning to get vaccinated against seasonal flu in the future *U planu vakcinacija protiv sezonskog gripa u budućnosti*	8.06	6.00 – 10.83	**< 0.001**
Received all vaccines in a childhood/*Dobijene sve vakcine u dečjem uzrastu*	5.17	2.29 – 11.67	**0.0001**

[a] Adjusted for the following variables: age, gender, marital status, having children, employment, and income satisfaction.
[a] *Prilagođeno za sledeće varijable: godine, pol, bračni status, broj dece, zaposlenje i zadovoljstvo prihodima.* Numbers in bold indicate statistical significance/*Boldovani brojevi su statistički značajni*.

countries within the same region of South Asia has previously been published [6].

Regarding the age distribution and vaccine acceptance in our study, except for other regions of Serbia with no significant difference of received COVID-19 vaccine in terms of age groups, in all other three locations a higher incidence of vaccination was found among older compared to younger participants. This phenomenon may result from the fact that the older adults are at a higher risk of morbidity, hospitalization and mortality than the young ones [3].

Males are more willing to accept the vaccine against COVID-19 than females, and reasons for this gender inequality are not clearly defined [3]. One of the possible reasons for willingness to accept COVID-19 vaccines may lie in the higher fatality rate of COVID-19 among males [27]. However, at least based on our study, since vaccination was more frequent among females than males (79.3% vs. 68.8%, respectively), but only in two biggest cities in Serbia (Novi Sad and Belgrade), it is possible that the female population can be more easily convinced than males to get vaccinated for herd immunity, as it has already been suggested [28]. Furthermore, results of some studies showed that married individuals were more prone to get vaccinated than the unmarried ones [21, 29, 30]. With exception of other cities in Vojvodina, where married status was positively associated with vaccination, in all other three locations marital status was not an independent variable for receiving the COVID-19 vaccine.

Results of numerous studies worldwide strongly indicate that high education level and high-income status were associated with positive attitudes toward vaccination against COVID-19 [22, 23, 25, 28]. One of the probable reasons for this finding may be the fact that people with higher-level of education may have a better understanding of both COVID-19 and immunization than those with less formal education [29]. Previously published data also showed that employed people, especially in professional and managerial occupations [25, 30] were more willing to accept COVID-19 vaccine. As expected, our results showed that respondents with higher level of education were more likely to be vaccinated than their counterparts. The present study also showed that health care workers, university faculty members, and those employed in the government sector were more likely to get vaccinated than their counterparts in all four investigated locations. Considering the fact that health care workers perceived a greater risk to get infected, as well as their high level of understanding all aspects of COVID-19, it is expectable that health care workers are more likely to be vaccinated than the others [31]. Indeed, we found that 83% of enrolled health care workers were vaccinated with at least one dose of COVID-19 vaccine.

We found that the participants who had family members/close friends or others who died due to COVID-19 and those planning for future seasonal influenza vaccination, were five and eight times, respectively, more likely to receive a vaccine than those in comparing groups. In contrast to other vulnerability factors, in our study the presence of chronic diseases was not significantly associated with the higher probability of getting vaccinated against COVID-19. Similar findings had been published before [6], and this was explained by the uncertainty about vaccine effectiveness, potential side effects and fear of disease deterioration and a lack of trust in vaccines that might have contributed to hesitancy. Fortunately, there are also findings which strongly indicate that participants with chronic disease, who may have severe health problems if they are diagnosed with COVID-19, are more willing to

get vaccinated than those belonging to other groups they were compared with [32].

It is well known that the spread of the SARS-CoV-2 virus is the perfect storm for conspiracy theories, and that the situation has significantly worsened since the COVID-19 pandemic included lockdowns [33]. This is especially important considering the inadequate knowledge about COVID-19 vaccination in particular, as well as existence of strong anti-vaccination movement in our region with their noticeable negative influence and destructive messages towards vaccination in general [34].

Our study has some limitations. First, it was a cross-sectional study, so our results primarily present a picture of the public response at the time point of this research. Second, our data were obtained by online self-administered questionnaire that may lead to biases due to limited participation of some members of the community, such as illiterate and those from rural settlements who did not have access to the internet. Third, there were only 3% of respondents aged 15 – 19 years (37 out of total 1,418). It should be also mentioned that, in accordance with National recommendation [15], subjects of this age group were vaccinated only with Pfizer-BioNTech BNT162b2 vaccine and therefore we cannot include their counterparts of the same age who would potentially prefer to get other available COVID-19 vaccines in Serbia. Fourth, although our online questionnaire was available across Serbia, it limits the generalizability of our results because they were not proportionally available in all regions of our country, i.e. our recruited sample was not statistically representative of the Serbian population as a whole. Taking into account that the participation in our study was voluntary, this study has a potential for self-selection bias by the predominant participation of the subjects being previously vaccinated against COVID-19. Finally, there is a possibility that not every participant fully understood the connotations of the questions or that some of them answered questions based on what they considered to be expected from them, which all may influence the quality of our data, and therefore, our results should be interpreted with some caution.

Conclusion

In conclusion, dissemination of information on coronavirus disease 2019 vaccines, tailored to specific community needs across Serbia, may provide wider acceptance and increase the coverage of vaccination against coronavirus disease 2019. According to our findings, the main predictors of vaccination against coronavirus disease 2019 among our participants were information about having family members/close friends or others who died from coronavirus disease 2019 and intention to get vaccinated against influenza in the future. There is an urgent need to conduct further studies that assess intentions, beliefs, and attitudes towards vaccines against coronavirus disease 2019 among the population throughout the Republic of Serbia.

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QUALITY OF LIFE OF FAMILIES OF PREMATURE CHILDREN

KVALITET ŽIVOTA PORODICA PREVREMENO ROĐENE DECE

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Summary

Introduction. The quality of family life is defined as the well-being of a family in which the individual and family needs constantly interact. Families are continually adapting to various changes in the course of life, until they reach a balance in functioning. Premature birth is a challenge for parents. Many parents develop symptoms of depression or anxiety, and impaired family functioning continues to manifest years after the premature birth itself. All this significantly affects the quality of life of these families. **Material and Methods.** This research included 101 families of premature children in the territory of Autonomous Province of Vojvodina. The following assessment instruments were used: a general questionnaire and the Beach Center Family Quality of Life Scale. **Results.** The primary family is the most common living environment. More than half (61.5%) of children spend the most of their time with their primary family. The majority of parents included in this research are satisfied with family interactions. The emotional component of this category was rated as "very satisfied" by most of the parents (61.5%). A large percentage of parents (86.5%) are involved in the Association of Parents of Premature Children and this is an important factor in improving their quality of life and making transitions easier. **Conclusion.** Premature birth of a child significantly affects the family quality of life. A clinical approach to these families is not sufficient. A holistic, family-oriented approach could potentially be very useful in working with these families. Addressing both the physical and psychological needs of these families can provide very useful information and guidelines for further work in improving their quality of life.

Key words: Quality of Life; Family; Parenting; Infant, Premature; Psychosocial Support Systems; Personal Satisfaction; Child

Sažetak

Uvod. Kvalitet života porodica je definisan kao dobrobit porodice u kojem su potrebe pojedinca i porodice u konstantnoj interakciji. Porodice se konstantno prilagođavaju različitim promenama u životnom toku, sve dok ne postignu ravnotežu u funkcionisanju. Prevremeni porođaj predstavlja izazov za roditelje. Mnogi roditelji razviju depresivne simptome ili anksioznost, a narušeno porodično funkcionisanje ispoljavaju i godinama nakon samog prevremenog porođaja. Sve ovo značajno utiče na kvalitet života ovih porodica. **Materijal i metode.** Istraživanjem je obuhvaćena 101 porodica sa prevremeno rođenim detetom na teritoriji Autonomne Pokrajine Vojvodine. Korišćeni su sledeći instrumenti procene: Opšti upitnik i Skala porodičnog kvaliteta života (engl. *Beach Center Family Quality of Life Scale − Beach FQOL Scale*). **Rezultati.** Primarna porodica predstavlja najučestaliji ambijent življenja. Više od polovine dece, tačnije 61,3% najveći procenat vremena provode u krugu svoje primarne porodice. Zadovoljstvo porodičnim interakcijama je prisutno kod najvećeg broja roditelja uključenih u ovo istraživanje. Emocionalna komponenta ove kategorije je kod većine roditelja (61,5%) označena kao „veoma zadovoljan". Veliki procenat roditelja, odnosno 86,6% je uključeno u Udruženje roditelja prevremeno rođene dece, te ovo predstavlja bitnu kariku u poboljšanju njihovog kvaliteta života i lakši prolazak kroz tranzicije. **Zaključak.** Prevremeno rođenje deteta značajno utiče na kvalitet života porodice. Klinički pristup u radu sa ovim porodicama nije dovoljan. Holistički pristup, orijentisan na porodicu, potencijalno bi mogao da bude veoma koristan u radu sa ovim porodicama. Sagledavanje kako fizičkih, tako i psihičkih potreba ovih porodica može nam dati veoma korisne podatke i smernice za dalji rad u oblasti poboljšanja njihovog kvaliteta života.

Ključne reči: kvalitet života; porodica; roditeljstvo; prevremeno rođeno dete; sistemi psihosocijalne podrške; personalna satisfakcija; dete

Introduction

The quality of family life is defined as the well-being of the family in which the individual and the family needs interact [1]. According to the family systems theory, the relationship between family members may significantly affect the psychosocial well-being of the child [2]. In the period when the family is the greatest source of support, hope, and strength for a child, as a consequence, the sensitivity of the child to the psychological state of the parents increases [2].

The construct of the quality of family life is greater than both the needs of a single family member and the mother-child dyad, emphasizing the family unity and the needs and strengths of all the family members [3].

In Serbia, around 4,000 babies are born prematurely [4]. According to the World Health Organization (WHO), the rate of preterm births ranges from 5% to 18% and it is highest in developing countries. Also, the WHO points to even higher rate of prematurity in the following period [4]. Premature birth, and conse-

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Abbreviations
FQOL – family quality of life
WHO – World Health Organization

quentially low birth weight are the primary problems in healthcare throughout the world [5]. Today, the survival rate of premature children rises, especially among newborns of extremely low birth weight, but it may cause higher risk of cognitive, motor, and social impairment, as well as psychiatric conditions [5].

Premature birth is a challenge for parents, who unexpectedly find themselves in a new situation, in which they face many new questions. In an ecological sense, the family and its surroundings have the greatest influence on the child's development [6]. There is evidence that premature babies with poor general health show better outcomes if they are surrounded by warm family affection [6]. The parental mental health is an important link in the chain of developmental encouragement. The first link which endangers this aspect of functioning is hospitalization. The interaction between a mother and her child, their physical contact is of great importance to a newborn child and the development of its identity and security [7]. This precious contact can be lost during hospitalization. The United Nations Children's Fund in Serbia has, exactly for this reason, carried out a series of programs intended to raise donations for the purpose of acquiring the necessary equipment for skin-to-skin contact between mother and child, nursing chairs for comfortable experience of mother and child during contact, as well as devices intended for breastfeeding and storage of mother's milk, the best food for a newborn [7].

The main goal of this research is to determine the specificity of the quality of family life of families of premature children.

Based on the set goals, the following hypotheses were evaluated:

1. There is a delay in the premature child's psychomotor development and the parents feel the need for stimulation programs, primarily in the domain of motor and speech-language development.
2. In over 50% of cases the parents involve experts of various profiles in establishing the psychomotor status of premature children.
3. A satisfaction with family interactions exists within families of premature children.
4. There is a satisfaction with parenting in families of premature children.
5. There is a physical/material satisfaction in families of premature children.
6. There is a satisfactory level of support for families of premature children.

Material and Methods

This research was conducted in the territory of the Autonomous Province of Vojvodina from April to August of 2020. Due to the epidemiological situation, the research was conducted over the internet (online questionnaire). Parents who were members of the Association of Parents of Premature Children "Optimistic" were sent questionnaires by email with consent forms and instructions on how to fill them out. The research included 101 families of premature children.

For the purpose of data collection, the following instruments were used:

1. General questionnaire

The questionnaire was designed for the purpose of this research.

It consists of three parts complementing each other and providing a holistic view of the families. The first part of the questionnaire deals with sociodemographic characteristics of families: parental age, degree of education, economic status, housing conditions, number of children, and others.

The second part of the questionnaire deals with the premature child, parental age at childbirth, as well as determinants of the child development (Apgar score), newborn weight, whether it was a twin pregnancy, who the child spent most of the time with, and others.

The third part of the questionnaire consists of closed-ended questions where the parents were asked to describe their parenting, to rate the significance of information received on regular appointments, whether they were involved in support programs, and others.

2. Beach Center Family Quality of Life (FQOL) Scale by Hoffman, Marquis, Poston, Summers, and Turnbull from 2006, was the second instrument [8]. The scale was translated into Serbian [9] and a consent for its use in this research was obtained.

The scale is intended for families with children from birth to the age of 21.

The scale includes 25 items assessing family perception of satisfaction with various aspects of family life. The parents' satisfaction was rated on a 5-point scale (1 - very dissatisfied and 5 - very satisfied). In the end, a score demonstrating the average value of given answers in every domain is calculated.

The instrument has good psychometric characteristics [9]. According to the author, a very good internal consistency of the FQOL scale exists in the scale as a whole ($\alpha = 0.930$), as well as a good internal consistency with the lowest recorded value being 0.743 in the domain of Emotional well-being, and the highest in Family interaction ($\alpha = 0.875$). The authors of the scale report the following psychometric characteristics: the Cronbach α of 0.88 for the scale as a whole, and 0.90 in the domain of Family interaction, 0.86 in the domain of Parenting, 0.84 for Emotional well-being, 0.74 in the domain of Physical/Material well-being, and 0.85 in the domain of Disability-related support [8].

The recorded data was analyzed using the descriptive method of statistical analysis.

Results

The primary family is the most common living environment in the analyzed sample. A smaller part (31.4%) lives with extended family, and just 3% of children live only with their mother. The highest percentage of the respondents lives in their own housing (80.4%).

Table 1. Gestational week (GW) at birth
Tabela 1*. Gestacijska nedelja rođenja deteta*

To 26 GW *do 26. nedelje*	27 - 29 GW *27–29. nedelja*	30 - 32 GW *30–32. nedelja*	33 - 35 GW *33–35. nedelja*	36 - 37 GW *36–37 nedelja*
10 (10%)	12 (12%)	33 (32.7%)	43 (42.3%)	4 (3.9%)

Table 2. Aspects of the development of premature children where parents noticed a delay or a need for stimulation
Tabela 2. *Aspekti razvoja prevremeno rođenog deteta u kojima roditelji uočavaju kašnjenje ili potrebu za stimulacijom*

Gross motor skills/*Gruba motorika*	18 (22.5%)
Fine motor skills/*Fina motorika*	23 (28.7%)
Speech-language development/*Govorno-jezički razvoj*	27 (33.8%)
Cognitive development/*Kognitivni razvoj*	12 (15%)
Socio-emotional development/*Socio-emocionalni razvoj*	15 (18.8%)
Other (hyperactivity and the like)/*Ostalo (hiperaktivnost i slično)*	3 (3.9%)
No deviations in the development/*Nije prisutno odstupanje u razvoju*	22 (28.2%)

There were 42.2% of two-children families and 40.2% were one-child families. One-third of the study sample has premature children from twin pregnancies. Fifteen children (14.7%) were conceived in vitro, and 87 (85.3%) were conceived naturally.

Table 1 shows that premature birth commonly occurs at 33 to 35 week of gestation in the analyzed children. Extremely premature children account for 10% of the sample.

Forty four (43.1%) children had a birth weight less than 1,500 grams. A birth weight of less than 2,500 grams was found somewhat more frequently, in 54 cases (52.9%). Only 4 (3.9%) newborns had a birth weight over 2,500 grams.

Table 2 shows that the largest percentage of parents noticed a deviation in their child's speech-language development, followed by difficulties in gross and fine motor skills. This result confirms the hypothesis number 1. It is important to note that some children required additional stimulation in multiple areas.

More than half of parents reported that they visited experts of various profiles for the purpose of child's psychomotor status evaluation (67 parents/66.3% of the sample). Most visited pediatricians, neurologists, pulmonologists, and cardiologists. This confirms the hypothesis number 2. However, 70 (69.3%) children were not involved in a program of early childhood intervention focusing on the family and the child, but programs of medical model-based response to challenges that arose during the development.

Table 3. Percentage of satisfaction with family interactions
Tabela 3. *Procenat zadovoljstva porodičnim interakcjama*

	Very satisfied *Veoma zadovoljan*	Satisfied *Zadovoljan*	Neither *Ni zadovoljan ni nezadovoljan*	Dissatisfied *Nezadovoljan*	Very dissatisfied *Veoma nezadovoljan*
My family enjoys spending time together. *Moja porodica uživa u vremenu koje provodimo zajedno.*	51 (49.5%)	47 (45.6%)	5 (4.9%)		
My family members talk openly with each other. *Članovi moje porodice otvoreno razgovaraju jedni sa drugima.*	40 (38.5%)	53 (51%)	9 (8.7%)	2 (1.9%)	
Our family solves problems together. *Naša porodica zajednički rešava probleme*	40 (38.5%)	49 (47.1%)	12 (11.5%)	3 (2.9%)	
My family members support each other to accomplish their goals./*Članovi moje porodice podržavaju jedni druge u ostvarenju ciljeva.*	41 (39.4%)	53 (51%)	7 (6.7%)	2 (1.9%)	1 (1%)
My family members show that they love and care for each other./*Članovi moje porodice pokazuju da vole i da brinu jedno za drugo.*	64 (61.5%)	32 (30.8%)	5 (4.8%)	2 (1.9%)	1 (1%)
My family is able to handle life's ups and downs. *Moja porodica se snalazi u životnim usponima i padovima.*	41 (39.8%)	53 (51.5%)	8 (7.8%)	1 (1%)	

Table 4. Overview of the "parenting" subcategory
Tabela 4. *Prikaz potkategorije „roditeljstva"*

	Very Satisfied *Veoma zadovoljan*	Satisfied *Zadovoljan*	Neither *Ni zadovoljan ni nezadovoljan*	Dissatisfied *Nezadovoljan*	Very Dissatisfied *Veoma nezadovoljan*
My family members teach the children how to be independent./*Članovi moje porodice pomažu deci da budu samostalna.*	42 (40.4%)	49 (47.1%)	9 (8.7%)	4 (3.8%)	
My family members help the children with their schoolwork./*Članovi moje porodice pomažu deci oko školskih zadataka.*	30 (30.9%)	50 (51.5%)	12 (12.4%)	4 (4.1%)	1 (1%)
My family members teach the children how to get along with others./*Članovi moje porodice uče decu kako da se slažu sa drugima.*	55 (53.4%)	44 (42.7%)	3 (2.9%)	1 (1%)	
Adults in our family teach the children to make good decisions./*Odrasli u našoj porodici uče decu da donose dobre odluke.*	47 (45.2%)	49 (47.1%)	6 (5.8%)	2 (1.9%)	
Adults in my family know other people in the children's lives (friends, teachers, etc.). *Odrasli u mojoj porodici poznaju druge osobe u životima dece (prijatelje, nastavnike, itd.)*	33 (33%)	56 (56%)	9 (9%)	1 (1%)	1 (1%)
Adults in my family have time to take care of the individual needs of every child. *Odrasli u mojoj porodici imaju vremena da se brinu o individualnim potrebama deteta.*	41 (40.2%)	47 (46.1%)	12 (11.8%)	1 (1%)	1 (1%)

Table 3 shows the percentage of satisfaction with family interactions. The quality of family interactions has a basic role in child development. The items related to the emotional component of family interaction ("My family members show that they love and care for each other") take the first place in this category. These results confirm the hypothesis number 3.

Table 4 shows the degree of satisfaction with parenting. A large number of parents are very satisfied with activities inside the family related to the child's ability to cooperate. A small percentage is dissatisfied with the activities of the family regarding schoolwork. This confirms the hypothesis number 4.

Table 5 shows the degree of satisfaction of parents with their physical/material well-being, which speaks in favor of the hypothesis number 5.

Table 5. Overview of the subcategory "physical/material well-being"
Tabela 5. *Prikaz potkategorije „fizičko/materijalno blagostanje"*

	Very Satisfied *Veoma zadovoljan*	Satisfied *Zadovoljan*	Neither *Ni zadovoljan ni nezadovoljan*	Dissatisfied *Nezadovoljan*	Very Dissatisfied *Veoma nezadovoljan*
My family members have transportation to get to the places they need to be./*Članovi moje porodice imaju prevoz da stignu tamo gde treba.*	47 (45.2%)	47 (45.2%)	6 (5.8%)	3 (2.9%)	1 (1%)
My family gets medical care when needed. *Moja porodica dobija medicinsku negu kada je potrebna.*	39 (37.5%)	49 (47.1%)	13 (12.5%)	3 (2.9%)	
My family has a way to take care of our expenses. *Moja porodica ima načina da vodi računa o našim troškovima.*	27 (26%)	57 (54.8%)	16 (15.4%)	4 (3.8%)	
My family gets dental care when needed. *Moja porodica ima stomatološku zaštitu kada je potrebno.*	41 (39.4%)	47 (45.2%)	12 (11.5%)	4 (3.8%)	
My family feels safe at home, work, school, and in our neighborhood./*Moja porodica se oseća bezbedno u kući, na poslu, u školi i u našem naselju.*	39 (37.5%)	53 (51%)	11 (10.6%)	1 (1%)	

Table 6. Overview of the "emotional well-being" subcategory
Tabela 6. *Prikaz potkategorije „Emocionalno blagostanje"*

	Very Satisfied *Veoma zadovoljan*	Satisfied *Zadovoljan*	Neither *Ni zadovoljan ni nezadovoljan*	Dissatisfied *Nezadovoljan*	Very Dissatisfied *Veoma nezadovoljan*
My family has the support we need to relieve stress./*Moja porodica ima podršku koja nam je potrebna da ublažimo stres.*	33 (31.7%)	48 (46.2%)	18 (17.3%)	4 (3.8%)	1 (1%)
My family members have friends or others who provide support./*Članovi moje porodice imaju prijatelja ili nekoga ko ih podržava.*	35 (34%)	54 (52.4%)	13 (12.6%)		1 (1%)
My family members have enough time to pursue our own interests./*Članovi moje porodice imaju vremena za naša zajednička interesovanja.*	36 (35%)	48 (46.6%)	14 (13.6%)	5 (4.9%)	
My family has outside help available to us to take care of special needs of all family members. *Mojoj porodici stoji na raspolaganju pomoć spolja kako bismo se pobrinuli za posebne potrebe svih članova.*	32 (31.7%)	37 (36.6%)	24 (23.8%)	6 (5.9%)	2 (2%)

Table 6 shows that the majority of parents have a friend or someone else who supports them. These results confirm the hypothesis number 6.

Discussion

Premature birth is a source of stress for both parents [10]. Mothers and fathers of newborns have increased levels of depression, anxiety and posttraumatic stress when compared to parents of full-term children. The study showed that around 40% of mothers and fathers reported symptoms of depression and half reported symptoms of anxiety soon after the premature birth of a child. These symptoms are significantly more notable with parents of premature children and during the child's development [10].

The quality of life of any family, including one of a premature child, cannot be observed isolated from social factors. Generally, parents who report a greater need for social support, tend to have lower levels of life satisfaction, consequentially bringing on more parental stress [1]. It is very important to mention that the premature birth itself presents a risk factor for the parental mental health [10]. Taking this into account, a systematic and integrated response is needed to promote well-being, monitor mental health and ease access to evidence-based early childhood intervention for families of premature children. Parents, as well as their babies, spend months at a time in the hospital, opening up the possibility for screening and support in the intensive care unit. At the same time, parents need help with contacting external services, to be informed of their rights and available possibilities [10]. A research conducted in our country [11] found that the most common obstacle regarding services is the lack of awareness that they exist. More than half of the interviewed parents did not know which services were available to them [11].

Intervention after premature birth should be [10] adaptive, individualized and multilayered, with mandatory direct psychological support for the parents. The support should be provided for the parents after learning about the health condition of the child, in order to face and overcome stress in the long run and adapt to their new life circumstances [12]. All of the experts involved should work toward a common goal, which is encouragement of the development of the child and support for the parent-baby relationship [10].

To evaluate the physical status of the newborn and the need for reanimation, the well known Apgar score was developed [13]. The research [14] that included premature children born at the Institute for Neonatology, reported that 22.4% of children had an Apgar score of 4 at 1 minute, while 20% of children had an Apgar score less than 6 at 5 minute. This data significantly matches the data obtained in our study. More recent researches [15] report a 75 - 80% greater risk of an autism specter disorder in children with a low or medium Apgar score at birth.

While progress in the neonatal care brought on a greater survival rate of these children, the developmental consequences persist. A research [16] analyzing 4,122 premature children showed results in line with ours. This research also showed that a large percentage of children exhibited difficulties in speech-language development.

When looking at things as a whole, our research showed positive results. When interpreting the data, it is very important to take into account that the parents involved in this research are active members of the Association of Parents of Premature Children. They may get additional support which undoubtedly affects their positive outlook. Expanding the sample by including parents who are not members of the Association would provide more complete understanding of the situation.

Conclusion

Parenting comes with many responsibilities. Being a parent of a premature child comes with additional difficulties and challenges. Based on the data of our research, we can conclude that lives of these families depend on a multitude of factors. A clinical approach to both the child and the family is not sufficient when approaching families of premature children. A holistic approach to both their physical and emotional needs is necessary.

Early support for families of premature children is important, in order to use the sensitive period of early development, because it affects the quality of their life in a positive manner. Supporting families in the aim of improving their quality of life consists of considering their strengths and resources, advisory work, as well as connecting them to other people and associations.

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ASSESSMENT OF THE QUALITY OF LIFE IN PATIENTS WITH KNEE OSTEOARTHRITIS

PROCENA KVALITETA ŽIVOTA OSOBA OBOLELIH OD OSTEOARTROZE KOLENA

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Summary

Introduction. Osteoarthritis is a degenerative rheumatic disease of the peripheral joints. It mostly affects one joint, usually the hip and knee joints, as well as the distal interphalangeal joints of the wrist and thumb carpometacarpal joint. The clinical symptoms include pain, swelling, stiffness, crepitus, muscle atrophy, subluxation, as well as reduced joint mobility, greatly affecting the quality of life of patients. The aim of this study was to assess the quality of life of patients with knee osteoarthritis and determine whether there is a difference in the quality of life of patients with unilateral and patients with bilateral knee osteoarthritis. **Material and Methods**. The study was designed as a retrospective study including 60 patients, 30 patients with unilateral gonarthrosis and 30 patients with bilateral gonarthrosis. The EuroQoL five dimensions questionnaire was used to assess the quality of life. **Results.** There is no statistically significant difference in the quality of life between individuals with unilateral and bilateral knee osteoarthritis, but there is a significant positive correlation between the pain intensity and difficulties in the domains of quality of life. **Conclusion.** People with osteoarthritis of the knee mostly take painkillers and have a good or excellent response to therapy. There is no statistically significant difference in the quality of life among people with unilateral and bilateral knee osteoarthritis. There is a significant positive correlation between the pain intensity and difficulties in the domains of quality of life. There is a significant negative correlation between the perception of general health and all five domains of quality of life.

Key words: Quality of Life; Osteoarthritis, Knee; Pain; Knee; Correlation of Data; Surveys and Questionnaires

Sažetak

Osteoartroza predstavlja degenerativno reumatsko oboljenje perifernih zglobova. Uglavnom je zahvaćen jedan zglob, najčešće zglobovi kuka i kolena, kao i distalni interfalangealni zglobovi i karpometakarpalni zglob palca ruke. U kliničkoj slici dominira bol, otok, ukočenost, krepitacije pri pokretima, mišićna atrofija, subluksacije kao i smanjenje pokretljivosti zgloba, što veoma utiče na kvalitet života obolele osobe. Cilj ove studije je da se proceni kvalitet života osoba obolelih od osteoartroze kolena i utvrdi da li postoji razlika u kvalitetu života osoba koje imaju zahvaćen jedan zglob kolena u odnosu na osobe kod kojih su zahvaćena oba kolena zgloba. **Materijal i metode.** Studija je koncipirana kao retrospektivna studija u koju je uključeno 60 ispitanika starosti od 37 do 82 godine, od kojih 30 ispitanika ima jednostranu gonartrozu i 30 ispitanika obostranu gonartrozu. Za procenu kvaliteta života korišćen je *EuroQoL five dimensions* upitnik. **Rezultati.** Ne postoji statistički značajna razlika u proceni kvaliteta života između osoba sa jednostranom i obostranom osteoartrozom kolena, ali postoji značajna pozitivna korelacija procene intenziteta bola i teškoća u domenima kvaliteta života. **Zaključak.** Osobe sa osteoartrozom kolena u većini slučajeva piju lekove protiv bolova i imaju dobar ili odličan odgovor na terapiju. Ne postoji statistički značajna razlika u proceni kvaliteta života između osoba sa jednostranom i obostranom osteoartrozom kolena. Postoji značajna pozitivna korelacija procene intenziteta bola i teškoća u domenima kvaliteta života. Postoji značajna negativna korelacija percepcije opšteg zdravlja i svih pet domena kvaliteta života.

Ključne reči: kvalitet života; osteoartritis kolena; bol; koleno; korelacija; ankete i uptinici

Introduction

Osteoarthritis (OA) is a degenerative rheumatic disease of the peripheral joints. In addition to the fact that degenerative rheumatic diseases are primarily diseases affecting the cartilage, early symptoms of the disease also involve the synovium and subchondral part of the bone. It mostly affects one joint, usually the hip and knee joints, as well as the distal interphalangeal joints and the carpometacarpal joint of the thumb [1]. The incidence of hip OA is higher in men, while hand and knee OA is more common in women. The etiology is not completely elucidated, but it is assumed that it causes damage to the cartilage and it mostly affects the weight-bearing joints. The clinical symptoms include pain, swelling, stiffness (lasting less than 20 minutes), and crepitus during movement, muscle atrophy (especially in the quadriceps region), subluxation and reduced joint mobility. The course of the disease is individual; it may stop at a certain stage, and regression of certain problems is possible [2].

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Abbreviations
OA – osteoarthritis
EQ-5D – EuroQoL five dimensions
BMI – body mass index
NSAIDs – non-steroidal anti-inflammatory drugs

The diagnosis is based on a clinical examination which includes: palpation, measuring the joint range of motion, joint circumference, manual muscle testing, measuring the local temperature, and pain provocation tests. Laboratory findings are within normal limits [1].

The knee OA (gonarthrosis) may involve the medial or lateral tibiofemoral compartments of the knee joint and/or the patellofemoral compartment [3].

The OA can be divided into two categories: primary OA, often idiopathic, with abnormality of joint biomaterials and mechanical changes in the joint structure, while the external stimuli are normal; and secondary OA that results from superimposed risk factors (e.g., joint injury), while the cartilage is normal [4]. The most common way of developing OA is increased or irregular mechanical load on the joint. It is more common after surgical removal of the meniscus, as well as after previous knee disease or injury [5]. Severe trauma and repeated joint movements contribute to the development of OA. Also, obesity increases the risk of OA by two to three times compared to people of normal weight [6].

The OA is a slowly progressive disease. The main symptom is pain that is worse during activity and is relieved by rest [6]. Pain is located deep in the joint and since the cartilage of the joint is without nerve endings, pain in OA originates from periarticular structures (nerve endings in the periosteum, microfractures in the subchondral bone, medullary hypertension, joint capsule or muscle spasm) [7].

Patients with OA suffer from morning stiffness that lasts about 20 - 30 minutes, as well as stiffness at the beginning of the movement, e.g., during the first few steps after getting up [8].

Physical examination may reveal swelling and painful tenderness localized above the bone or in the soft tissue area. Crepitus during joint movements may be located by palpation [2]. It can also be felt when performing passive movements, sometimes it is heard during active movements of the joint.

Varus and valgus deformities of the knee joint mostly occur in advanced OA [8]. The OA of the medial space is responsible for the formation of varus deformities, while in the lateral section OA leads to valgus deformities [2].

Early-stage OA is rarely accompanied by symptoms, so radiologically advanced OA may exist without symptoms [8]. The course of the disease is individual and it may be stopped in certain cases.

The diagnosis of OA is made based on the symptoms, i.e., the clinical picture. The most common diagnostic procedures are radiography in the anteroposterior and lateral profile. The cartilage image shows cartilage loss and the cartilage damage is indicated by narrowing of the joint space, appearance of osteophytes and calcium deposits inside the joint [9]. The severity of OA may be radiologically assessed by Kellgren and Lawrence score [10]:

Grade 0 - none;

Grade 1 - initial osteophytes;

Grade 2 - moderate joint space narrowing, moderate subchondral sclerosis;

Grade 3 - more than 50% joint space narrowing, round femoral condyles, advanced subchondral sclerosis, advanced osteophytes;

Grade 4 - joint destruction, joint space narrowing, subchondral cysts of the tibial and femoral condyles, subluxation of the joint.

There are no laboratory findings that are specific to OA. People with OA mostly have normal erythrocyte sedimentation rate, normal values of complete blood count, and synovial fluid shows very mild leukocytosis [2].

The three main goals for OA treatment are to reduce pain, maintain joint mobility and slow down the progression of the pathological process. Treatment of OA of the knee may be divided into pharmacological treatment, non-pharmacological conservative treatment, and surgical treatment.

The aim of this study was to assess the quality of life of people with OA of the knee and determine whether there is a difference in the quality of life of patients with unilateral and patients with bilateral knee OA.

Material and Methods

The retrospective study was conducted at the Special Hospital for Rheumatic Diseases in Novi Sad. It included 60 people with OA of the knee, of which 6 were male and 54 female, aged 37 to 82 years. The patients were divided into two groups. The first group included 30 patients with unilateral gonarthrosis, and the second included 30 patients with bilateral gonarthrosis. Participation was voluntary and all participants signed an informed consent.

EuroQoL five dimensions (EQ-5D), Likert scale, and numeric pain scale were used in the research and demographic data were also collected. The patients were interviewed and informed about the goal and protocol of the research. After signing the informed consent, they filled out the questionnaires. This research was approved by the Ethics Committee of the Special Hospital for Rheumatic Diseases in Novi Sad.

The EQ-5D quality of life scale, the Likert scale and the numeric rating scale were used to assess the patients' quality of life. The EQ-5D questionnaire is a questionnaire which evaluates the generic quality of life and measures health.

The EQ-5D quality of life questionnaire comprises the following 5 dimensions:

1. Mobility
2. Self-care
3. Everyday activities (e.g., work, study, household chores, family or leisure activities)
4. Pain/Discomfort
5. Anxiety/Depression.

Each dimension of the questionnaire has three response levels of severity: 1. no problems; 2. some problems; 3. extreme problems.

The questionnaire also has a vertical visual analogue scale for assessing one's own health condition, where patients grade their health status from 0 (worst conceivable health condition) to 100 (best conceivable health condition).

Patients also reported which non-steroidal anti-inflammatory drugs (NSAIDs) they were taking. Having in mind the effects of the drugs on the symptoms of OA, the responses on Likert scale were ranked: 0 (none), 1 (bad), 2 (weak), 3 (good), 4 (excellent).

Pain is more precisely rated using a numerical rating scale (from 0 to 10), where score of 0 means no pain, and score of 10 means the worst possible pain. Body mass index (BMI) was calculated for each participant.

Results

The average age of examinees was 66.45 years; the average age of participants with unilateral gonarthrosis was 66.47 years, and in those with bilateral gonarthrosis it was 66.43 years. Women predominated in the whole sample and in both subgroups, and there were only 6 men and 54 women. The largest number of participants (about 50%) completed secondary school education, while about 25% of participants completed primary school, college or university. The described differences were tested by c^2 test. The obtained results showed that there were no significant differences between the two groups of examinees in relation to sociodemographic characteristics.

Most of the examinees were taking painkillers, while 25 had hypertension, mostly those with bilateral gonarthrosis.

There was only one severely obese subject, while the number of malnourished and mildly obese subjects was equal (N = 10). Most of the examinees had an ideal or increased body weight (obesity).

Most of the examinees reported that they had a good or excellent response to therapy. The number of respondents with a poor response was equal to the number of those who had no response to therapy.

Regarding the pain intensity and the perception of general health, we found that patients with unilateral gonarthrosis perceived their health better and reported a lower degree of pain.

These differences were also tested by the c^2 test. The results showed that there were no statistically significant differences in any of the observed medical aspects between subjects with unilateral and bilateral gonarthrosis.

The **Table 1** shows the scores of the examinees in the whole sample and in two subgroups on the quality-of-life scales. The results of the t-test showed that there were no significant differences in the estimated quality of life of patients with unilateral and bilateral gonarthrosis on any quality of life scales.

Table 1. Quality of life of patients
Tabela 1. *Kvalitet života pacijenata*

Quality of life scales *Skale kvaliteta života*	All *Svi*	Unilateral OA *Unilateralna OA*	Bilateral OA *Bilateralna OA*	Test *Test*	p *p*
Mobility/*Mobilnost*					
	12	5	7	1.525	.465
	47	25	22		
	1	0	1		
Self-care/*Briga o sebi*					
	38	21	17	3.474	.176
	19	9	10		
	3	0	3		
Everyday activities/*Uobičajene aktivnosti*					
	22	12	10	.357	.837
	31	15	16		
	7	3	4		
Pain/Discomfort/*Bol/nelagodnost*					
	3	2	1	.912	.634
	38	20	18		
	19	8	11		
Anxiety/Depression/*Anksioznost/depresija*					
	26	14	12	2.070	.355
	15	9	6		
	19	7	12		

Legenda: OA – osteoartoza

Table 2. Relationship between pain and quality of life
Tabela 2. *Odnos bola i kvaliteta života*

Quality-of-life scales/pain *Skale kvaliteta života/bol*	All *Svi*		Unilateral gonarthrisis *Unilateralna gonartroza*		Bilateral gonarthrosis *Bilateralna gonartroza*	
	r	p	r	p	r	p
Mobility/*Mobilnost*	**.443**	**.000**	.248	.187	**.565**	**.001**
Self-care/*Briga o sebi*	**.483**	**.000**	**.509**	**.004**	**.464**	**.010**
Everyday activities/*Uobičajene aktivnosti*	**.620**	**.000**	**.592**	**.001**	**.646**	**.000**
Pain/Discomfort/*Bol/nelagodnost*	**.588**	**.000**	**.512**	**.004**	**.651**	**.000**
Anxiety/Depression/*Anksioznost/depresija*	**.425**	**.000**	.248	.186	**.538**	**.002**

Table 3. Relationship between age and quality of life
Tabela 3. *Odnos starosti i kvaliteta života*

Quality-of-life scales/Age *Skale kvaliteta života/Starost*	All *Sve*		Unilateral gonarthrosis *Unilateralna gonartroza*		Bilateral gonarthrosis *Bilateralna gonartroza*	
	r	p	r	p	r	p
Mobility/*Mobilnost*	.242	.063	.323	.082	.184	.329
Self-care/*Briga o sebi*	.186	.156	.300	.107	.123	.518
Everyday activities/*Uobičajene aktivnosti*	**.336**	**.009**	**.433**	**.017**	.249	.184
Pain/Discomfort/*Bol/nelagodnost*	.149	.256	.221	.240	.084	.658
Anxiety/Depression/*Anksioznost/depresija*	.218	.094	**.398**	**.029**	.072	.706

The descriptive analysis showed that most of the respondents had no problems taking care of themselves, but pain and mobility were a problem in most of them. Half of the respondents had a problem with anxiety and depression.

The **Table 2** shows the relationship between the perception of pain intensity and the quality-of-life dimension. This correlation was tested by Pearson's correlation coefficient and the bolded values are significant.

In the overall sample, there was a significant positive correlation between the pain intensity and difficulties in the domains of quality of life. The respondents with a higher intensity of pain reported greater difficulties in the domains of mobility, self-care, normal activities, pain and care. The findings were the same in the examinees with bilateral gonarthrosis.

Subjects with unilateral gonarthrosis reported an association only between pain intensity and self-care, normal activities and pain, while mobility and care were not significantly correlated with pain in this subgroup of subjects.

The results of this study showed that there was a significant positive correlation between age and problems with everyday activities in the whole sample and the subgroup of examinees with unilateral gonarthrosis **(Table 3)**. This subgroup presented with significant correlation between age and care and depression. Older examinees reported greater difficulties in this domain.

In the subgroup of examinees with bilateral gonarthrosis, age did not show a significant correlation with the quality of life.

In regard to the relationship between BMI and quality of life, analysis was performed in the whole sample and in two individual groups of examinees. The results showed that there was no significant correlation between BMI and any domain of quality of life **(Table 4)**.

In regard to the relationship between the general health and quality of life, the results showed that there was a significant negative correlation between the perception of general health and all domains of quality of life in the overall sample. The examinees with better general health reported fewer difficulties in all five

Table 4. Relationship between body mass index (BMI) and quality of life
Tabela 4. *Odnos indeksa telesne mase (ITM) i kvaliteta života*

Quality of life/BMI *Kvalitet života/ITM*	All *Svi*		Unilateral gonarthrosis *Unilateralna gonartroza*		Bilateral gonarthrosis *Bilateralna gonartroza*	
	r	p	r	p	r	p
Mobility/*Mobilnost*	.065	.621	.027	.888	.096	.614
Self-care/*Briga o sebi*	.054	.681	-.132	.488	.064	.735
Everyday activities/*Uobičajene aktivnosti*	.197	.130	.330	.075	.070	.713
Pain/Discomfort/*Bol/nelagodnost*	.174	.183	.290	.063	-.047	.804
Anxiety/Depression/*Anksioznost/depresija*	.224	.084	.175	.355	.341	.065

Table 5. Relationship between the general health and quality of life
Tabela 5. *Odnos procene opšteg zdravlja i kvaliteta života*

Quality of life/General health *Skale kvaliteta života/Opšte zdravlje*	All *Svi*		Unilateral gonarthrosis *Unilateralna gonartroza*		Bilateral gonarthrosis *Bilateralna gonartroza*	
	r	p	r	p	r	p
Mobility/*Mobilnost*	**-.350**	**.006**	**-.423**	**.020**	-.331	.074
Self-care/*Briga o sebi*	**-.350**	**.006**	-.326	.079	-.323	.082
Everyday activities/*Uobičajene aktivnosti*	**-.469**	**.000**	**-.500**	**.005**	**-.433**	**.017**
Pain/Discomfort/*Bol/nelagodnost*	**-.271**	**.036**	-.137	.470	-.358	.052
Anxiety/Depression/*Anksioznost/depresija*	**-.308**	**.017**	-.326	.079	-.257	.170

domains of quality of life. A significant negative correlation between general health and quality of life was also found in the sample of examinees with unilateral gonarthrosis. Negative correlation was found in the dimensions of quality of life: mobility and everyday activities. Examinees with unilateral gonarthrosis with more problems with mobility and everyday activities assessed their general health as worse.

In the sample of examinees with bilateral gonarthrosis, the only significant correlation with general health were everyday activities and the examinees with greater difficulties in everyday activities rated their general health as worse **(Table 5)**.

Discussion

The most common form of arthritis is OA that causes pain, functional limitations and disability. The prevalence is higher among women (25.4%) compared to men (17.6%). Older people (50% of people over the age of 65 and 29.3% of people between the ages of 45 - 64) are more likely to get OA than younger population (7.9% of people between the ages of 18 and 44) [11].

Our study included 60 patients, most of whom were women (90%). The average age was 66.45 years. Most patients completed secondary school education (about 50%), while an equal number completed primary and tertiary education. The largest number of examinees had ideal (N = 21) or increased body weight, i.e., pre-obesity (N = 18).

A study conducted by Seokhan et al. found that age (≥ 65 years), female gender, obesity, and lower education were among the most important risk factors for OA of the knee [12]. However, Lawrence et al. found that severe forms of OA are not related to old age, but that there is a significant increase after the age of 50 [13–15].

A study conducted by Grotle et al. followed 1,854 people aged 24 to 74 over 10 years and found that obesity significantly affects the development of OA of the knee [16]. Szoeke et al. found that every 5 kg increase in body weight doubles the risk for OA of the knee [17].

In our study, the majority of examinees (90%) was taking NSAIDs and reported good or excellent response to therapy.

Comparing two groups of patients with OA of the knee (unilateral and bilateral gonarthrosis), we found that there were no statistically significant differences in quality of life between these two groups of patients, but many patients reported problems with pain and mobility, as well as anxiety and depression. Patients completed the recommended EQ-5D-3L questionnaire, although the EQ-5D-5L questionnaire is increasingly used as it offers the possibility of additional responses and exceeds the limits of the EQ-5D-3L questionnaire [18, 19].

In a study including 2,481 patients (1,130 with bilateral knee pain, 646 with unilateral knee pain, and 705 without knee pain) a short form-12 item questionnaire was used and showed that patients with bilateral knee pain had a lower quality of life and general health in relation to the other two groups of patients [20].

A significant correlation between age and problems with everyday activities was found in the whole sample of examinees and the subgroup with unilateral gonarthrosis. We may conclude that older examinees have greater difficulties in this domain. Also, in the sample of examinees with unilateral gonarthrosis, there is an association between age and anxiety and depression.

A study conducted by Bobić Lucić and Grazio found that older people with OA of the knee who lack security in performing daily activities have more physical difficulties and a greater impact of pain on everyday activities, so improving balance would lead to better functioning of the elderly and to improving of their quality of life in general [21].

The results of this study show that there is a significant negative correlation between the perception of general health and all domains of quality of life in the whole sample. This means that those examinees that have better general health report fewer difficulties in all five domains of quality of life. Examinees with unilateral gonarthrosis have more problems with mobility and everyday activities, while examinees with bilateral gonarthrosis only report issues with everyday activities.

Conclusion

People with osteoarthritis of the knee mostly take painkillers and have a good or excellent response to therapy. There is a significant positive correlation between the pain intensity and difficulties in the domains of quality of life. There is a significant negative correlation between the perception of general health and all five domains of quality of life.

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DIFFERENCES IN THE PREVALENCE OF MUSCULOSKELETAL PAIN BETWEEN HEALTH CARE STUDENTS AND STUDENTS OF SPORTS AND PHYSICAL EDUCATION

RAZLIKE U PREVALENCIJI MIŠIĆNO-SKELETNOG BOLA IZMEĐU STUDENATA ZDRAVSTVENE NEGE I STUDENATA SPORTA I FIZIČKOG VASPITANJA

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Summary

Introduction. Musculoskeletal pain is one of the most common types of pain affecting muscles, bones, joints, ligaments and tendons. The aim of this study was to determine the differences in the prevalence of musculoskeletal pain between students of sports and physical education and health care students. **Material and Methods.** The cross-sectional study included a total of 50 students, of whom 25 (50%) were students of sports and physical education, and 25 (50%) were students of health care. Data on the musculoskeletal system of students were collected through a questionnaire for the analysis of musculoskeletal symptoms. **Results.** The results showed that the neck and upper back pain was not negligible (14 respondents, 28%) as well as the lower back pain (27, 54%). Based on the Chi-square test, it was concluded that low back pain was significantly more common in students of health care ($\chi^2 = 3.945$; $p = 0.047 < 0.05$) than in students of sports and physical education. Also, neck pain was significantly more common in health care students ($\chi^2 = 6.349$; $p = 0.012 < 0.05$). **Conclusion.** Based on the obtained results, it can be concluded that students mostly presented with low back pain, followed by the neck and upper back pain. Engaging in proper exercises on weekly basis and excess weight reduction can prevent low back pain.

Key words: Musculoskeletal Pain; Prevalence; Students; Neck Pain; Back Pain; Low Back Pain; Surveys and Questionnaires

Sažetak

Uvod. Mišićno-skeletni bol je jedan od najčešćih tipova bola koji zahvata mišiće, kosti, zglobove, ligamente i tetive. Cilj ovog rada bio je utvrđivanje razlike u prevalenciji mišićno-skeletnog bola između studenata Sporta i fizičkog vaspitanja i studenata Zdravstvene nege. **Materijal i metode.** Studija preseka obuhvatila je uzorak od ukupno 50 studenata, od kojih je bilo 25 (50%) studenata Sporta i fizičkog vaspitanja, a 25 (50%) studenata Zdravstvene nege. Podaci o stanju mišićno-skeletnog sistema studenata prikupljeni su upitnikom za analizu mišićno-skeletnih simptoma. **Rezultati.** Rezultati su pokazali da prisustvo bola u vratu i gornjem delu leđa nije bilo zanemarljivo (14 ispitanika, što čini njih 28%), ali i u donjem delu leđa (27, što čini 54% ispitanika). Na osnovu Hi-kvadrat testa zaključeno je da je bol u donjem delu leđa bio značajno više zastupljen kod studenata Zdravstvene nege ($\chi^2 = 3,945$; $p = 0,047 < 0,05$), nego kod studenata Sporta i fizičkog vaspitanja. Takođe, i bol u vratu je bio značajno češći kod studenata Zdravstvene nege ($\chi^2 = 6,349$; $p = 0,012 < 0,05$). **Zaključak.** Na osnovu dobijenih rezultata može se zaključiti da je među studentima najviše bio prisutan bol u donjem delu leđa, zatim u vratu i gornjem delu leđa. Pravilno vežbanje svake nedelje i smanjenje prekomerne težine može sprečiti bol u donjem delu leđa.

Ključne reči: muskuloskeletni bol; prevalenca; studenti; bol u vratu; bol u leđima; lumbalni bol; ankete i upitnici

Introduction

Musculoskeletal pain is one of the most common types of pain that affects muscles, bones, joints, ligaments and tendons, and it can be acute or chronic. Acute musculoskeletal pain may be strong in intensity, but it is usually short-lived and most often caused by fractures, sprains, dislocations and infections. In contrast, chronic musculoskeletal pain is persistent over an extended period of time and is probably related to other factors [1].

Low back pain has become a serious problem, since it has a high incidence in the working population, but also in adolescents and children [2]. The prevalence of low back pain in children is similar to that in adult population [3]. A longitudinal study of 12- to 15-year-

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olds showed that the annual incidence of musculoskeletal pain in the spine was 21.5% [4]. Risk factors for the development of low back pain in students are numerous, such as gender, height and weight, reduced muscle flexibility and mobility, hypermobility, obesity, psychosocial factors, participation in competitive sports, weight, type and manner of carrying a backpack, bad posture habits, sedentary lifestyle that includes spending a lot of time in front of a TV and computer, as well as low levels of physical activities [5, 6].

Apart from low back pain, it was found that neck and shoulder pain are the most common [7] and pain in the neck, shoulders and arms may also affect the students' quality of life [8]. It has been established that female students present with significantly more pain in the neck, shoulders, wrists, hands and upper and lower back compared to male students [9].

Health care students are generally less physically active than students in other fields, such as sports and physical education, due to the relatively more demanding curriculum, which is associated with the sedentary behavior. Thus, the increased incidence of musculoskeletal pain in these students can be explained in this way, because students of sports and physical education are mostly more physically active [10].

Having all this in mind, the main aim of this paper was to determine the differences in the prevalence of musculoskeletal pain between students of sports and physical education and students of health care.

Material and Methods

This research was conducted as a cross-sectional study from November 1 to 15, 2021 in Serbia. The sample included 50 students, of whom 25 were students of sports and physical education and 25 were students of health care at the State University in Novi Pazar. In this study, the standardized Nordic questionnaire for the analysis of musculoskeletal symptoms [11] was used to collect data on the prevalence of musculoskeletal symptoms in students. In addition to this questionnaire, the participants were asked several questions related to: gender, age, duration and frequency of physical activities, body position in which they spend most of the day, the existence of musculoskeletal pain and the history of these problems.

The objectives of the study were explained to potential participants at the very beginning of the research. Participation in the study was voluntary and with informed consent, and confidentiality and anonymity of the data obtained was guaranteed. All data were protected and were available only to the research team.

The research was approved by the Institutional Ethics Committee of the State University of Novi Pazar. The procedures of this study were in line with the provisions of the Declaration of Helsinki on Medical Research Involving Human Subjects [12].

A special database was created, and the collected data were processed using the statistical software IBM SPSS statistics, version 25 (SPSS Inc., Chicago, IL, USA). The statistical data processing included the basic measures of central tendency and variability of descriptive statistics, frequency analysis to show the participation of certain modalities (groups or characteristics) of a variable in relation to the total sample size, Chi-square independence test to examine the significance of the representation of a particular characteristic in groups of respondents that are of importance. In addition, the Shapiro-Wilk test was used to analyze the normality of distribution of variables of interest, and the post-hoc tests. The p value is a number describing how likely it is that our data would have occurred by random chance. For $p < 0.05$ it is concluded that there is a significant difference or deviation from the expected theoretical model.

Results

The gender distribution of respondents is shown in **Table 1**, while the results of descriptive statistics for the students' body weight and body height are shown in **Table 2**.

Table 3 shows the incidence of pain in a particular part of the body in the last 12 months.

The results of questionnaire showed that 54% of all respondents presented with low back pain. We

Table 1. Gender distribution of respondents
Tabela 1. *Polna struktura ispitanika*

	No./*Br.*	%
Male/*Muški*	19	38.0
Female/*Ženski*	31	62.0
Total/*Ukupno*	50	100.0

Table 2. Descriptive statistics for students' body weight and body height
Tabela 2. *Rezultati deskriptivne statistike za telesnu masu i visinu studenata*

	Mean *Aritmetička sredina*	Standard deviation *Standardna devijacija*	Minimum *Minimum*	Maximum *Maksimum*
BW/*TM*	69.42	10.742	48	92
BH/*TV*	174.24	9.942	152	199

Legend/*Legenda:* BW/*TM* – Body weigth/*Telesna masa (kg),* BH/*TV* – Body height/*Telesna visina (cm)*

Table 3. The incidence of pain in a particular part of the body
Tabela 3. *Učestalost prisustva bola u određenom delu tela*

	Pain/*Bol*	No./*Br*	%
Neck *Vrat*	No/*Ne*	36	72
	Yes/*Da*	14	28
	Total/*Ukupno*	50	100
Upper back *Gornji deo leđa*	No/*Ne*	36	72
	Yes/*Da*	14	28
	Total/*Ukupno*	50	100
Lower back *Donji deo leđa*	No/*Ne*	23	46
	Yes/*Da*	27	54
	Total/*Ukupno*	50	100

Table 4. The pain prevalence in different body regions and statistical difference between health care students and students of sports and physical education
Tabela 4. *Zastupljenost bola u različitim delovima tela i statistička razlika između studenata Zdravstvene nege i studenata Sporta i fizičkog vaspitanja*

	With pain/*Sa bolom*		Without pain/*Bez bola*			
	No./*Br.*	%	No./*Br.*	%	χ^2	p
Upper back/*Gornji deo leđa*	14	28	36	72	0.397	0.529
Knee joints/*Zglobovi kolena*	10	20	40	80	2.000	0.157
Ankles/*Skočni zglobovi*	10	20	40	80	0.000	1.000
Shoulders/*Ramena*	10	20	40	80	2.000	0.157
Wrists/*Ručni zglobovi*	9	18	41	82	3.388	0.066
Hips/*Kukovi*	5	10	45	90	0.222	0.637
Elbows/*Laktovi*	1	2	49	98	1.020	0.312

Legend/*Legenda:* χ^2 – Chi-square/*Hi-kvadrat;* p – Statistical significance/*Nivo statističke značajnosti*

investigated if gender distribution and the study program affected the incidence of low back pain.

It should be noted that pain in the neck and upper back was not negligible (14 respondents, 28%), followed by pain in the knee joints and ankles (20%), in the shoulders (20% had pain in at least one shoulder), and in the wrists (18% had pain in at least one wrist). Pain in the hips (10%) and elbows (2%) was less common. **Table 4** shows the pain prevalence in different body regions.

Lower back pain

When it comes to the curricula, it was found that in the last 12 months low back pain was more prevalent among health care students (17, 68% of surveyed students), while among students of sports and physical education this problem was less reported (15, 60%). Based on the Chi-square test, it was concluded that low back pain was significantly more prevalent in health care students in the last 12 months ($\chi^2 = 3.945$; $p = 0.047 < 0.05$).

Table 5 shows the difference in the prevalence of low back pain between health care students and students of sports and physical education.

There were more male respondents who did not report pain in the low back (12, 63.2%) while most respondents with low back pain were female (20, 64.5%). The Chi-square test showed that the prevalence of low back pain in the last 12 months did not differ significantly between male and female students ($\chi^2 = 3.632$; $p = 0.057 > 0.05$).

All students (12) who spent most of the day standing claimed that they did not have low back pain. A total of 75% of students who spent their day mostly in a sitting position reported low back pain, while in students who spent their day in variable positions, the difference was not significant, i.e. 15 of them (53.6%) reported low back pain and 13 (46.4%) claimed that they did not have low back pain. The prevalence of low back pain in students who spent most or great part of the day in a sitting position was statistically significant ($\chi^2 = 9.886$; $p = 0.007 < 0.05$)

In the last 7 days, low back pain was reported by fewer students. A total of 15 (30%) students claimed to have felt pain. It turned out that the data did not give reliable results depending on other variables, so for that reason we considered them to be a consequence of chance or individual characteristics, as well as the habits of the respondents.

Neck pain

Among other parts of the body, significant differences in the prevalence of neck pain were found for some variables. Namely, 14 (56%) students of health care and 22 (88%) students of sports and physical education reported no neck pain. Although in both cur-

Table 5. Differences in the prevalence of low back pain in health care students and students of sports and physical education
Tabela 5. *Razlika u prevalenciji bola u donjem delu leđa između studenata Zdravstvene nege i studenata Sporta i fizičkog vaspitanja*

	Pain/*Bol*	Low back/*Donji deo leđa*	
		No./*Br.*	%
Health care *Zdravstvena nega*	No/*Ne*	8	32
	Yes/*Da*	17	68
	Total/*Ukupno*	25	100
Sports and physical education *Sport i fizičko vaspitanje*	No/*Ne*	15	60
	Yes/*Da*	10	40
	Total/*Ukupno*	25	100

Table 6. Differences in the prevalence of neck pain in health care students and students of sports and physical education
Tabela 6. *Razlika u prevalenciji bola u vratu između studenata Zdravstvene nege i studenata Sporta i fizičkog vaspitanja*

	Pain/*Bol*	Neck/*Vrat*	
		No./*Br.*	%
Health care *Zdravstvena nega*	No/*Ne*	14	56
	Yes/*Da*	11	44
	Total/*Ukupno*	25	100
Sports and physical education *Sport i fizičko vaspitanje*	No/*Ne*	22	88
	Yes/*Da*	3	12
	Total/*Ukupno*	25	100

ricula more students had no neck pain, the number was statistically significantly lower among students of sports and physical education. Neck pain was significantly more common in health care students (χ^2 = 6.349; p = 0.012 < 0.05). Differences in the prevalence of neck pain between health care students and students of sports and physical education are shown in **Table 6.**

Also, 17 (89.5%) male students and 19 (61.3%) female students claimed that they had no neck pain. The prevalence of neck problems in the last 12 months was significantly lower among male students (χ^2 = 4.641; p = 0.031 < 0.05). It has been proven that neck pain does not depend on the position in which the student spends most of the day (χ^2 = 0.471; p = 0.790 > 0.05).

In the last 7 days, the prevalence of neck pain has decreased so much that it could not be associated with any other variables, i.e. it was considered to be a consequence of individual characteristics and habits of the subjects.

In regard to other parts of the body, the prevalence of problems was insignificant (20% or less) to draw reliable conclusions and they were considered to be a consequence of chance, individual characteristics and habits of individual respondents. This is especially pronounced due to a small number of respondents.

Discussion

The study suggests that musculoskeletal pain is common in the educational environment and that it is a significant risk factor affecting health and quality of life of students, requiring special health services, and thus significantly burdening the health system. An additional concern is the fact that back pain during adolescence may have health consequences in later adulthood. Our study examined differences in the prevalence of musculoskeletal pain between students of sports and physical education and students of health care.

A study that investigated the prevalence, pattern, and possible risk factors for musculoskeletal pain over 12 months in a sample of 145 students of occupational therapy and physiotherapy found that the prevalence of musculoskeletal pain among students was 89.7%. The neck pain was most common (66.2%), followed by low back pain (64.4%) [13]. The findings are not in line with the results of our study, because in our sample low back pain was the most common, followed by neck and upper back pain. The duration of daily commutes and participation in regular exercises are significantly related to the prevalence of musculoskeletal pain. Also, in the mentioned study, students who exercised regularly had a 9.47 times lower chance of developing musculoskeletal pain [13]. Our findings show that in the last 12 months, 60% of health care students had problems in the lower back, while among students of sports and physical education this problem was much less present. This can be explained by the fact that students of sports and physical education are generally more physically active [10, 13].

Alshagga et al. [14] studied the prevalence of musculoskeletal pain among Malaysian medical students

and found that 45.7% of respondents had musculoskeletal pain in at least one part of the body during the past seven days and 65.1% of all students during the past year [14]. It is in line with our study in which the prevalence of respondents who experienced low back pain in the last year was 54%, while in the past seven days it was significantly lower, 30% of all students.

Algarni et al. [15] reported that the prevalence of musculoskeletal pain among medical students in Saudi Arabia was also high. They found that 85.3% of all subjects had musculoskeletal pain in at least one part of the body at any given time, 54.4% in the past week, and 81.9% in the past year [15]. These values are significantly higher than those obtained in our study, but also in the study conducted in medical students of the University of Belgrade, where the prevalence of low back pain was 17.2% [16]. This can be related to similar academic curricula at all medical schools in Serbia, and differences in relation to the curricula around the world. In contrast to these national studies, low back pain was less present among Brazilian medical students, with a prevalence of 9.2% [17].

Kompal et al. [18] reported a high prevalence of neck and low back pain (54%) that occurs regularly in medical students in Pakistan, while Hayes et al. [19] and Lorusso et al. [20] concluded that low back pain was more common than shoulder and neck pain. The results of their research are in line with the findings of our study.

Contrary to our findings, Cho et al. [21] concluded that in a sample of high school students, neck and shoulder pain (56%, 45%, respectively) were more common compared to low back pain (37%).

In the literature, studies including student population reported different estimates of the prevalence of musculoskeletal pain, with varying degrees of severity. These variations can be explained by different populations and methodologies used in different studies. A meta-analysis of 25 relevant studies examining risk factors of musculoskeletal pain, with a focus on the prevalence of low back pain among nurses, showed that the prevalence rate of low back pain varied among different studies conducted in Italy, ranging from 33% to 86%. Previous studies also suggest that female gender, physical factors, and psychosocial factors are important risk factors for low back pain [20]. Our study also showed that gender is an important risk factor of musculoskeletal pain, because a significantly higher number of students who had both low back pain and neck pain were female. This finding is also consistent with the results of research conducted by Wijnhoven, De Vet and Picavet [9].

In addition to physical, some psychological factors, such as depression and psychosomatic symptoms, may also be risk factors of musculoskeletal pain, and are therefore associated with reduced quality of life [22].

Neck and lower back pain are the main sources of morbidity and the main symptoms that patients complain about to their general practitioners in all countries and in all segments of the population [23]. Low back pain is a common occurrence among health care students, with serious consequences for their private life and work. Engaging in proper exercises on weekly basis and excess weight reduction can prevent lower back pain and reduce the use of analgesics. The competent authorities of medical schools should be aware of this health problem and undertake preventive measures, because we assume that short educational support could improve knowledge, attitudes and beliefs of health students on musculoskeletal pain (such as pain in the neck, shoulders and low back). The burden of low back pain is increasing in low- and middle-income countries, such as Serbia, and it negatively affects the health system by increasing health care costs.

Strengths and limitations of the study

To the best of our knowledge, our study was among the first in Serbia to examine differences in the prevalence of different types of musculoskeletal pain in students of health care and students of sports and physical education in Serbia. Although the practical implications of the results of this study can be very important for health interventions that lead to a better quality of life for students, this study has some limitations that should be mentioned. Namely, based on the design of the cross-sectional study, it was not possible to detect cause-and-effect relationships [24]. Also, the use of self-assessment questionnaires can lead to systematic bias in answering. These findings are limited, among other things, due to sample size and non-representative sample.

Conclusion

Based on the obtained results, it can be concluded that students mostly presented with low back pain, followed by the neck and upper back pain. Musculoskeletal pain is very common among healthcare students and is significantly associated with sedentary postures and low levels of physical activities.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
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UNDERSTANDING THE STATE OF CONFUSION IN PATIENTS WITH PSYCHOSIS DURING COVID-2019 PANDEMIC – A REPORT OF TWO CASES

KAKO RAZUMETI KONFUZNO STANJE KOD PACIJENTA SA PSIHOZOM U VREME PANDEMIJE COVID-19 – PRIKAZ DVA SLUČAJA

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Summary

Introduction. There is a lot of evidence that coronavirus disease 2019 has various manifestations. This paper presents a report of two cases with the aim to indicate the multifactorial etiology of confusional states in patients with mental disorders at the time coronavirus disease 2019 pandemic. The severe acute respiratory syndrome coronavirus-2 affects not only the respiratory and cardiovascular systems, but also the brain, kidneys and other organ systems. One of the first manifestations of this infection can be mental confusion. **Case Study.** The first patient, a woman diagnosed with schizoaffective psychosis, suddenly presented with confusion, followed by hypersedation which was at first attributed to overmedication. In another patient, with the diagnosis of bipolar affective disorder, sudden confusion (delirium) was initially recognized as an element of mental disorder deterioration. A more detailed observation revealed that the confused state in both patients was caused by severe acute respiratory syndrome coronavirus-2 infection. **Discussion.** It is common for the manifestations of severe acute respiratory syndrome coronavirus-2 infection to include respiratory and cardiovascular syimptoms. However, symptoms related to other organs and organ systems, including changes in neurological and psychological status, should not be ignored. **Conclusion**. It was noticed that confusion and delirium-like states are quite common early symptoms of coronavirus disease 2019. In psychiatric patients, it is always necessary to rule out the organic etiology of the consciousness disorder and immediately proceed with the diagnostic procedures. One should certainly keep in mind that diagnostic errors are possible, not only due to various manifestations of the infection, but also due to the stigmatization of mental illness, which must be overcome in order to provide the best possible treatment effects.

Key words: Psychotic Disorders; Confusion; Delirium; COVID-19; Pandemics; Signs and Symptoms

Sažetak

Uvod. Postoji mnogo dokaza da infekcija virusom korona ima različite manifestacije. U radu su predstavljene studije dva slučaja kako bi se ukazalo na multifaktorsku etiologiju konfuznih stanja kod pacijenata sa mentalnim poremećajima u vreme infekcije. Virus SARS-CoV-2 utiče ne samo na respiratorni i kardiovaskularni sistem, već aficira i mozak, bubrege i druge organske sisteme. Jedna od prvih manifestacija ove infekcije može biti konfuzno stanje svesti. **Prikaz slučajeva.** Prva pacijentkinja se lečila zbog shizoafektivne psihoze. Kod nje se iznenada ispoljila konfuznost, praćena hipersedacijom, što je u prvi mah delovalo kao intoksikacija psihofarmacima. Kod pacijenta sa dijagnozom bipolarnog afektivnog poremećaja, konfuzno-delirantna klinička slika je u prvi mah prepoznata kao element pogoršanja mentalnog poremećaja. Detaljnijom opservacijom utvrđeno je da je konfuzno stanje kod oba pacijenta uzrokovano infekcijom SARS-CoV-2. **Diskusija.** Uobičajeno je da manifestacije infekcije SARS-Cov-2 obuhvataju simptome respiratornih i kardiovaskularnih organa. Međutim, ne treba zanemariti simptome koji se odnose na druge organe i organske sisteme, između ostalih i promene u neurološkom i psihičkom statusu. **Zaključak.** Konfuzno-delirantna stanja svesti neretko su rani simptomi COVID-19. Kod psihijatrijskih pacijenata uvek je neophodno isključiti organsku etiologiju poremećaja svesti te odmah pristupiti potrebnim dijagnostičkim procedurama. Svakako treba imati u vidu da su dijagnostičke greške moguće, ne samo zbog različitih manifestacija infekcije, već i zbog stigmatizacije mentalnih bolesti, koju je neophodno prevazići radi najboljeg mogućeg efekta lečenja.

Ključne reči: psihoze; konfuzija; delirijum; COVID-19; pandemija; znaci i simptomi

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Abbreviations

COVID-19 – coronavirus disease 2019
SARS-CoV-2 – severe acute respiratory syndrome coronavirus-2
PCR – polymerase chain reaction
CT – computed tomography

Introduction

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a major health problem for the World Health Organization nowadays. For nearly two years, the whole world has been fighting a battle against COVID-19 infection. Health workers in primary, secondary and tertiary health care institutions, have learned a lot about clinical features of COVID-19 and a lot of information has been published worldwide [1–3]. All the medical staff has become familiar with COVID-19 symptoms, diagnosis and treatment options [4–7]. However, it is interesting that one common symptom, mental confusion, is underestimated and sometimes hard to recognize, especially in psychiatric patients who were previously psychotic and then were infected with SARS-CoV-2 [7–13]. Although almost 30% of patients with moderate to severe SARS-CoV-2 infection develop psychiatric symptoms, including confusion, agitation, auditory hallucinations and speech dysfunction, there still persists the diagnostic problem of these symptoms in psychiatric patients [14–16]. Nevertheless, psychiatric patients with COVID-19 infection belong to a vulnerable category and there is a diagnostic dilemma about the etiology of confusion. Presently, there is limited source of literature discussing the possible pathophysiology and risk factors for developing confussion in COVID-19 [16–20]. In psychiatric patients, medical professionals need to identify if confusion is a manifestation of psychiatric exacerbation, a result of psychotropic overmedication, or it is a result of SARS-CoV-2 infection. Here, we present two patients with psychosis and SARS-CoV-2 infection. In both patients the leading symptom of COVID-19 infection was mental confusion.

Case 1

We present a 57-year-old female patient (N. M.), divorced, lives alone, has a 16-year-old daughter who lives with the patient's former husband. The patient has a long psychiatric history. Thirty years ago, her disorder started as a generalized anxiety disorder. Later on, depressive episodes appeared, followed by a few suicidal attempts by medication overdose.

Several years ago, the clinical picture deteriorated with psychotic elements and the patient was treated in a psychiatric hospital several times.

On admission, she was confused, presenting with auditory hallucinations, hypomanic and depressive symptoms. Due to such symptoms, the diagnosis was changed to schizoaffective disorder. The patient showed non-compliance and spent a few months in the hospital, whereas the symptoms gradually improved. Satisfying remission with a limited functionality has been accomplished and the patient was discharged with a therapy including lithium, antipsychotics and benzodiazepine.

Several days later, the patient visited an emergency psychiatric clinic. She was pale, and presented with somnolence, weakness, bradypsychia, confusion, and dehydration. The rapid antigen test for SARS-CoV-2 was negative. An intoxication with psychiatric medications was suspected and the patient was admitted to the Psychiatry Clinic. A biochemistry test showed that lithium levels were within therapeutic range, but inflammatory markers were elevated, C-reactive protein was 79.9 mg/L, D-dimer was 10 mg/l, erythrocyte sedimentation rate was 102, while the white blood cells count was normal. The urine test result was normal. Ultrasound of the abdomen and urinary tract was unremarkable. Internal medicine specialist suggested a computed tomography (CT) of the abdomen. The abdominal CT showed ground glass opacity like changes in the basal pulmonary parts. Antibiotic therapy was initiated. Polymerase chain reaction (PCR) test for SARS-CoV-2 was done and the result showed that our patient had SARS-CoV-2 infection.

The patient was transferred to the Clinic for Infectious Diseases. Her general condition was good, oxygen saturation in room air was 98% all the time, she did not have fever, and soon after beginning the therapy with two antibiotics (ciprofloxacin and erythromycin) she was feeling well and inflammatory markers were not out of range. Ten days after the admission, the PCR was negative, and she was transferred back to the psychiatry unit. She became conscious, coherent, without psychotic symptoms, though she felt fatigue for some time. Lithium was started again, as part of her therapeutic regimen, as well as other psychopharmaceuticals and the patient was discharged in psychiatric remission.

Case 2

A 62-year-old male patient (M. M.), married, with bipolar affective disorder, received psychiatric treatment for more than 20 years. Over two years, he was in complete remission, taking psychiatric medications all the time (valproate 1000 mg/day, lithium carbonate 600 mg/day and clonazepam 0.5 mg/day). The patient presented with comorbidities, including hypertension and benign prostate hypetrophy under medical control.

The symptoms occured suddenly, after several sleepless nights. One night the patient developed psychomotor agitation and confusion (he did not recognise his wife and his home), became incoherent, with optic and auditory hallucinations. He was taken to the hospital, where a brain CT was done, followed by wide spectrum of blood tests. The rapid antigen test for SARS-CoV-2 was negative, as well as the PCR test. There was a diagnostic dilemma, if this was a new psychotic episode, since in the past he presented with fully disorganized behavior symptoms. On the other hand, organic etiology could not be excluded. The patient was observed and his labo-

ratory test results showed very high levels of C-reactive protein - 335 mg/L, D-dimer of almost 8 mg/L, and leukopenia - $2,5x10^9$/l. The PCR for COVID-19 was repeated and this time the PCR test was positive. The CT scan of thorax showed initial pneumonia in both basic segments of the lungs. Due to the protocol for treating COVID-19 infections, all necessary medications were initiated together with antipsychotics and benzodiazepins to treat his acute delirious state. Lithium was excluded and valproate dose was reduced. After three days of therapy, his mental confusion resolved, and in the following period the patient had no phychiatric symptoms. During hospitalization, the patient was in psychiatric remission. After three weeks, the patient was negative for SARS-CoV-2 on two PCR tests, and all blood parmeters were normal. The pneumonia was in regression, and patient was discharged. In the next few weeks, he completely recovered, without symptoms of mental disorder.

Discussion

Confusion was the leading symptom of COVID-19 infection in the presented cases. During the first few days, other symptoms were mild or absent. The first SARS-CoV-2 rapid antigen SARS-CoV-2 tests were negative in both patients, but followed by positive PCR tests. Infection was suspected due to elevated inflammatory parameters and ground-glass opacity changes seen on thorax CT scans.

The very beginning of symptoms could have been attributed to psychotic relapse or overdose of psychiatric medications (which was not the first episode of these symptoms in neither of these patients). It has been noticed that both the confusion and delirium-like state are quite common early symptoms of COVID-19 disease [1, 2, 4–6]. In fact, these symptoms are among the six most common symptoms of SARS-CoV-2 infection [7–12, 17–20]. According to the present literature, the evidence of acute confusional state is found in about 15 - 35% during the acute phase of COVID-19 infection [8, 21–23]. Pathophysiology of such state is usually multifactorial. Almost 30% of such patients have hypoxemia, [6, 8, 24], older patients frequently have various comorbidities, including dementia and psychiatric illness [4, 7, 14, 15]. Also, therapy with glucocorticoids, part of the therapy protocol for COVID-19 infection may also exacerbate inflammation-associated neural damage [8, 23, 24]. In patients who need sedation, confusion or fluctuating alertness, with delayed awakening after stopping sedation was described [6, 14, 17]. These two cases were presented in order to refresh the knowledge of medical professionals and to remind that confusion and delirious states, due to stigmatization and overgeneralization, can be easily attributed to psychiatric manifestations only. Medical professionals must keep in mind that COVID-19 has many clinical forms and manifestations [7–11]. Also, patients with comorbidities, including psychiatric illness, are at greater risk for confusion and delirious symptoms [8, 12–15]. It is very important to bear in mind that, when de novo confusion appears in psychiatric patients, physicians should consider COVID-19 as a possible cause of such symptoms as well as other possible medical causes [8, 9, 12, 13].

Conclusion

It is certain that misdiagnosed coronavirus disease 2019, presenting with delirium, may only cause failure to start adequate therapy in timely manner. Confusion, as a symptom of coronavirus disease 2019, affects usually older people, without fever and other symptoms of infection, but it can also happen to young people, particularly with comorbidities, including psychitric disorders. In clinical practice, misdiagnosis of confusion as the main symptom of severe acute respiratory syndrome coronavirus-2 infection is a serious problem. This happens beacuse the family members as well as medical staff do not recognize confusion as an important symptom, or attribute it to the psychiatric disease, which is, in many cases, due to the stigmatization of mental illness. Thus, in patients with mental problems, the focus should be on the physical etiology of these symptoms.

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ILIOPSOAS ABSCESS IN INFANTS – A CASE REPORT

APSCES ILIOPSOASA KOD ODOJČADI – PRIKAZ SLUČAJA

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Summary

Introduction. Iliopsoas abscess is a rare condition, which may be categorized as primary or secondary. Primary iliopsoas abscess is caused by lymphohematogenous spread of infectious agents from a distant site, unlike secondary iliopsoas abscess that is a result of direct spread of a nearby infectious or inflammatory process. The diagnosis and treatment of primary iliopsoas abscess are often prolonged, due to the rarity of the disease and the nonspecific signs and symptoms. **Case Report.** This study presents a case of a one-month old infant with a left-sided iliopsoas abscess. The physical examination revealed a swelling with a pronounced vascular pattern in the area of the left groin. Laboratory findings showed leukocytosis and increased inflammatory markers. An abscess within the left hemiabdomen and inguinofemoral region was diagnosed by ultrasonography and computerized tomography. The main therapeutic approach included antibiotic therapy, as well as surgical drainage of the abscess. Staphylococcus aureus was isolated from a 100 ml sample of the drained abscess. The treatment outcome was good. **Conclusion.** Given the frequency of iliopsoas abscess in infants, which is far less common than other primary diseases, greater attention must be paid to symptoms and signs during clinical examination, along with the appropriate choice of diagnostic procedures. Timely diagnosis, as well as adequate treatment of iliopsoas muscle abscess, is imperative in order to prevent the development of complications, such as systemic inflammation and sepsis.

Key words: Psoas Abscess; Infant; Groin; Tomography, X-Ray Computed; Ultrasonography; Drainage; Diagnosis; Signs and Symptoms; Treatment Outcome

Sažetak

Uvod. Apsces iliopsoasa je retko oboljenje koje može biti primarno i sekundarno. Primarni apsces iliopsoasa je uzrokovan limfohematogenim širenjem infektivnih agensa sa udaljenog mesta, za razliku od sekundarnog apscesa koji se formira direktnim širenjem susednog infektivnog ili inflamatornog oboljenja. **Prikaz slučaja.** Prikazujemo slučaj odojčeta starog mesec dana sa razvijenim levostranim iliopsoasnim apscesom. U fizikalnom pregledu je uočen otok i naglašena vaskularna šara u predelu leve prepone. U laboratorijskim nalazima registovana je leukocitoza, kao i povećanje inflamatornih markera. Apscesna kolekcija u levom hemiabdomenu i ingvinofemoralnoj regiji dijagnostikovana je ultrasonografijom i kompjuterizovanom tomografijom. Glavni terapijski pristup obuhvatio je antibiotsku terapiju, kao i hiruršku drenažu apscesa. Iz 100 ml uzorka drenirane apscesne kolekcije izolovan je *Staphylococcus aureus*. Ishod lečenja je bio dobar. **Zaključak.** S obzirom na učestalost ovakve vrste patologije kod odojčeta, koja je ređa u odnosu na ostale primarne bolesti, mora se obratiti veća pažnja na simptome i znakove pri kliničkom pregledu, kao i na odgovarajući izbor dijagnostičke procedure. Pravovremeno postavljanje dijagnoze, kao i adekvatno lečenje apscesa mišića iliopsoasa neophodno je kako bi se sprečio razvoj komplikacija, poput sistemske inflamacije i sepse.

Ključne reči: iliopsoasni apsces; odojče; prepone; CT; ultrasonografija; drenaža; dijagnoza; znaci i simptomi; ishod lečenja

Introduction

An abscess is a localized purulent process, which can have an acute or chronic course. A chronic abscess, unlike an acute one, is surrounded by a pseudocapsule made of inflammatory cells. Chronic localized purulent infections most often affect organs from which drainage of pus is difficult, such as bone marrow or brain [1, 2]. Acute abscesses may occur in muscle tissue, in which case they most commonly affect the muscles around the hip, including the iliopsoas, piriformis, obturators, adductors, gluteus, and quadriceps [3, 4].

Iliopsoas abscess (IPA) is a rare condition with an unknown incidence. Depending on the etiology, it is classified as primary or secondary. Primary IPA is caused by lymphohematogenous spread of infectious agents, which is facilitated by a rich iliopsoas muscle vascularity. The main sources of pathogens are the respiratory system, gastrointestinal tract, as well as the urinary tract. The predisposing factor is a not fully developed immune system [5]. Secondary IPA is caused by direct spread of an adjacent infectious or inflammatory condition and it can be associated with trauma and instrumentation in the lumbar spine, inguinal region or hip region [6]. The diagnosis of primary IPA is usually

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Abbreviations

IPA – iliopsoas abscess
US – ultrasonography
LL – laterolateral
AP – anteroposterior
CC – craniocaudal
CT – computed tomography
MRI – magnetic resonance imaging

prolonged, and the treatment is often delayed due to the rarity of the disease and the lack of specific clinical signs [3–6]. This study presents a case of a one-month-old infant with a left-sided IPA.

Case Report

A 30-day-old infant was admitted to the Department of Neonatal Surgery of a regional hospital with a swelling and erythema of the left groin and thigh noticed by the parents the night before. The infant was conscious, eupneic, normocardial, afebrile, well-nourished, with normal tonicity and musculature. The physical examination revealed swelling and a pronounced vascular pattern in the area of the left groin. The infant's mother claimed that the child was moving his left leg less than the right since birth. Laboratory tests showed increased inflammatory factors (white blood cells - 26.73 x 10^9/L, C-reactive protein - 111.50 mg/L). The first Doppler ultrasonography (US) was performed after admission and showed a clearly limited paravesical lesion in the left hemiabdomen, 36 x 33 x 70 mm (laterolateral (LL) x anteroposterior (AP) x craniocaudal (CC)) in size, filled with dense fluid, with signs of marginal hyperemia on color Doppler. The described lesion cranially reached the lower half of the left kidney, and caudally it followed through the inguinal canal into the anterior femoral region. Differential diagnosis pointed to an abscess and/or hematoma. Empiric parenteral antibiotic therapy was immediately initiated with vancomycin and meropenem. The patient was referred for computed tomography (CT), with and without intravenous contrast. The CT examination revealed that the left iliopsoas muscle from the lower half of the left kidney was extremely voluminous, with disturbed architectonics, postcontrast with evident irregular, dense multiseptated fluid collection, with approximate dimensions 33 x 32 x 74 mm (AP x LL x CC) **(Figures 1 and 2)**. The lesion showed postcontrast intensive marginal staining and an increase in the density of retroperitoneal fat along the inferior pole of the left kidney. The described lesion extended through the inguinal canal into the femoral region, where an anterior and medial increase in the density of subcutaneous adipose tissue and reactively altered lymph nodes were observed. The lesion was in close contact with the iliac blood vessels, and rested directly on the inner surface of the iliac bone, without affecting the bone tissue itself. The CT scan of the abdomen did not show any additional changes. The lesion corresponded to IPA.

Based on the patient history, as well as clinical, US and CT findings, an abscess collection in the left hemiabdomen and inguinofemoral region was diagnosed. On the fifth day of hospitalization, under ultrasonography control, an incision was made in the lower left quadrant of the abdomen, and the ab-

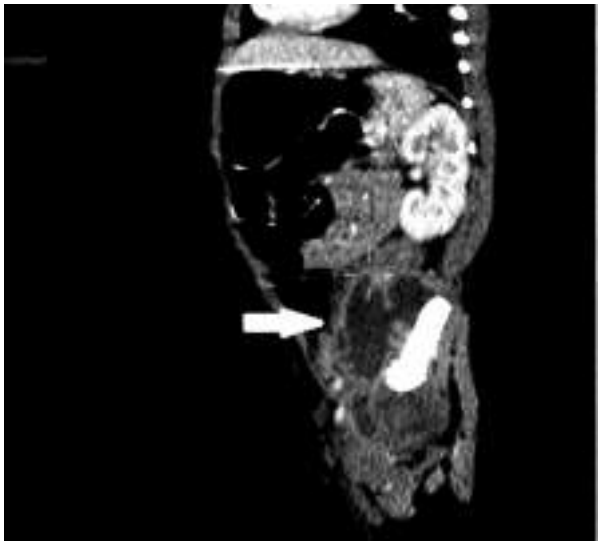

Figure 1. Contrast-enhanced CT of the abdomen and pelvis (sagittal section): irregular hyperdense fluid collection extending to inguinum, with marginal staining of the left iliopsoas muscle

Slika 1. *Kompjuterizovana tomografija abdomena i male karlice (sagitalni presek): postkontrastna slika pokazuje nepravilnu hiperdenznu tečnu kolekciju koja se proteže do ingvinuma i rubno se boji u levom iliopsoasnom mišiću*

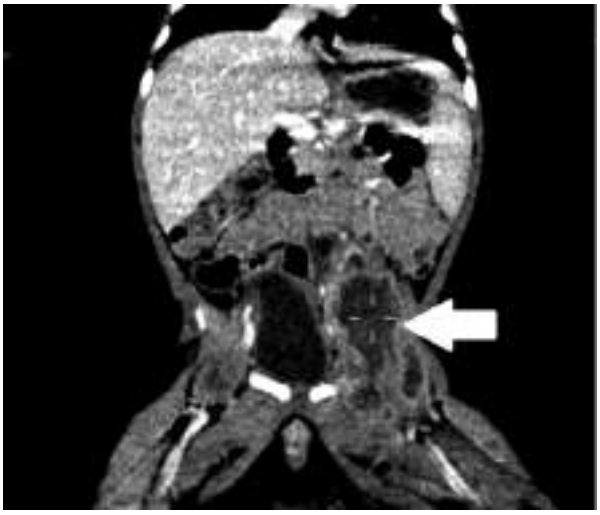

Figure 2. Contrast-enhanced CT of the abdomen and pelvis (coronal section): irregular multilocular lesion in the left iliopsoas muscle and inguinum

Slika 2. *Kompjuterizovana tomografija abdomena i male karlice (koronalni presek): postkontrastna slika pokazuje nepravilnu multilokuliranu promenu u levom iliopsoasnom mišiću i ingvinumu*

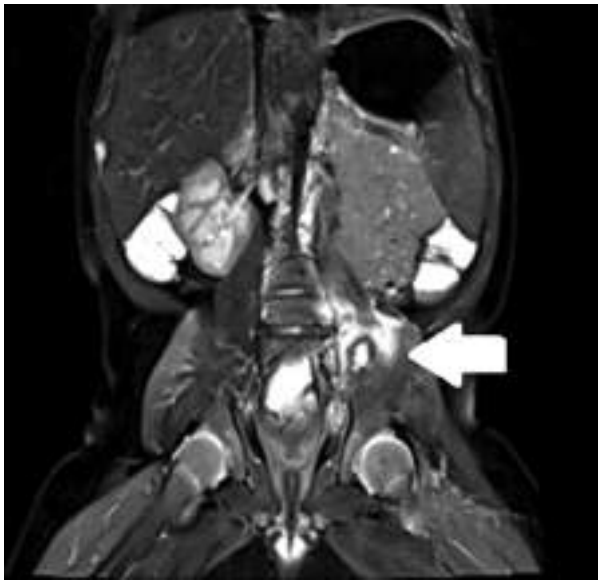

Figure 3. Magnetic resonance imaging of the abdomen and pelvis: T2W TSE FS COR native image showing encapsulated fluid collection located in the left iliopsoas muscle, hypointense capsule and perilesional edema
Slika 3. *Magnetna rezonancija abdomena i karlice: T2W TSE FS COR nativni snimak pokazuje inkapsuliranu tečnu kolekciju u levom iliopsoasnom mišiću, hipointenznu kapsulu i perilezioni edem*

scess collection was approached by a pneumocath, and about 100 ml of purulent contents was evacuated, and the sample was sent for microbiological examination. In the immediate postoperative period, a fall of red blood cells was observed, and the child received a blood transfusion. The postoperative course continued favorably. Subsequent stabilization of the patient's general condition, improvement of local clinical findings, and decrease of inflammatory parameters continued from the seventh postintervention day. Parenteral antibiotic therapy was carried out for 17 days, after which oral antibiotics were introduced (amoxicillin/clavulanic acid and moxifloxacin). After the intervention, magnetic resonance imaging (MRI) of the abdomen was performed and compared with the previous CT findings **(Figures 3 and 4).** Volume reduction was predominantly at the expense of fluid/detrital component of the formation. The lesion showed a discrete restricted diffusion, and in postcontrast sequences there was a high signal intensity of the solid component, which mainly consisted of muscle fibers of disturbed structure. Between the muscle fibers, a larger complex/detrital collection was detected, partly limited by a 3 mm thick wall and partly in bands with impregnated intermediary fibers. More cranially, there was a smaller round collection with a centrally positioned fluid/detrital component 13 mm in diameter, and a 3 mm thick wall. The MRI showed significant reduction in dimensions of the left iliopsoas muscle, predominantly due to the partial regression of the fluid/detrital component, with persistence of gross

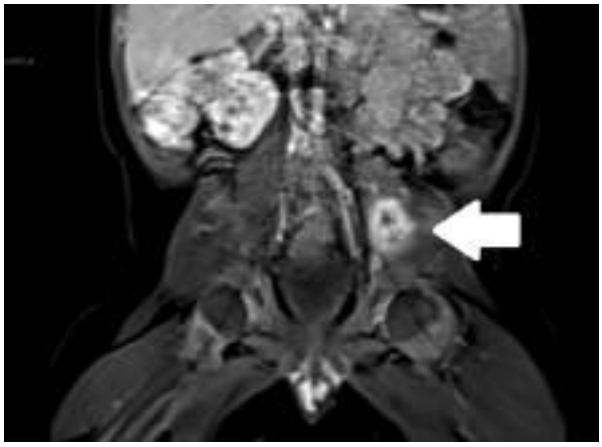

Figure 4. Magnetic resonance imaging of the abdomen and pelvis (coronal section): T1 Dixon-VIBE postcontrast image showing hyperintense round lesion in the left iliopsoas muscle (a wide peripheral postcontrast enhancement of the encapsulated fluid collection)
Slika 4. *Magnetna rezonancija abdomena i karlice (koronalni presek): T1 Dixon-VIBE postkontrastni snimak pokazuje hiperintenznu okruglastu leziju u levom iliopsoasnom mišiću (uočava se široko rubno prebojavanje inkapsulirane tečne kolekcije)*

disturbance of muscle fibers. In the further course of hospitalization, the infant was afebrile, in good general condition, with normal vital parameters and satisfactory clinical findings. The follow-up laboratory report showed that the inflammatory parameters were within the reference range. A follow up US was performed before discharge and it showed almost complete regression in comparison to the initial US. The muscle was significantly less distended, with just a small fluid component. The infant was discharged on the 28th day from admission in good general physical condition for further home treatment.

Discussion

Primary muscle abscess is more common in the younger population than in adults, although it is most common in infants. It is mostly seen in tropical areas [7]. Staphylococcus aureus is the most common cause of the primary, while Escherichia coli is the main cause of the secondary IPA [6]. Predisposing factors for the development of abscesses of this type are immunodeficiency and diabetes mellitus [8]. In neonates, the crucial thing is to make an accurate and timely diagnosis, since the diagnosis of muscle abscess in the hip region may have symptoms similar to other diseases, such as septic arthritis of the hip joint, due to a very similar clinical presentation [7, 9]. The clinical picture is dominated by fever, loss of appetite, anxiety of the child, as well as leg or groin swelling, cellulitis, limitation of leg motion, and pain [8–10]. The IPA cases in infants are sporadic in the literature [6–11]. What these cases have in common with ours is that the clinical

picture describes the swelling of the region where the abscess is located and the impossibility of extension, internal rotation, and abduction as of the upper leg on the side where the lesion is present, as well as leukocytosis and increase of inflammatory parameters in laboratory test results. In addition, in all cases the children were born without any musculoskeletal anomaly, and were normally gaining weight and height. The initial diagnostic method was US, whose advantages are easy availability, lack of radiation, as well as no need for intravenous contrast medium. However, US can be nonspecific, and therefore other diagnostic procedures should be considered [10]. Further diagnostic methods include CT and MRI, providing a definitive diagnosis. The treatment of IPA depends on its size, as well as on clinical parameters of patients. The most common treatment is conservative, and it includes appropriate antibiotic therapy covering Staphylococcus aureus and also any other possible source of the abscess, or percutaneous puncture under ultrasound control followed by a full course of appropriate antibiotic therapy [9–11]. In these cases, initial empirical antibiotic therapy was later changed according to antibiogram reports if required. Fatal outcome has been described in the literature as a consequence of sepsis due to delayed diagnosis because of nonspecific nature of the illness [7].

Conclusion

Iliopsoas muscle abscess is a very rare pathological entity in infants. Therefore, attention must be paid to the symptoms and signs during clinical examination, along with the appropriate choice of diagnostic procedures. Timely diagnosis, as well as adequate treatment is imperative in order to prevent the development of complications, such as systemic inflammation and sepsis.

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FOLIE À DEUX – A CASE REPORT

FOLIE À DEUX – PRIKAZ SLUČAJA

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Summary

Introduction. Shared psychotic disorder, or folie à deux, is a rare entity characterized by the transmission of psychotic symptoms from one patient (the inducer) to another (the induced). Delusional disorder is a type of mental illness (International Classification of Diseases, Tenth Revision, Clinical Modification, diagnosis code F24; it was moved from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, to Other Specified Schizophrenia Spectrum and Other Psychotic Disorders). Only one person (the inducer) suffers from a real psychotic disorder, and the other/s is/are induced, and most often recover/s after separation from the inducer. **Case Report.** Based on the medical records and available literature on this condition, we present a case of a mother and son with this disorder, where the son with a paranoid psychosis transfers it to his mother. They lived alone in the same household for years, socially isolated from the others. **Conclusion.** In general, the research has shown that there are no uniform opinions among authors regarding the incidence of the disorder in males and females, at younger and older age, as well as in relationships between partners, siblings, and between parents and children. Most agree that long-term social isolation is among the most common risk factors, as well as dominance and strong power of suggestion in one partner, and passivity and tendency to suggestion in the other.

Key words: Shared Paranoid Disorder; Risk Factors; Mental Disorders; Social Isolation; Delusions; Interpersonal Relations; Suggestion; Mother-Child Relations; Treatment Outcome

Sažetak

Uvod. Udvojeni psihotični poremećaj je retka pojava koju karakteriše transmisija psihotičnih simptoma sa jednog pacijenta (*induktor*) na drugog (*indukovani* partner). Ovaj poremćaj je tip mentalne bolesti (šifra u ICD-10 sistemu klasifikacije je F24, a u DSM-V je premešten pod: „drugi specifični shizofreni spektar i drugi psihotični poremećaji"). Jedna osoba (induktor) boluje od pravog psihotičnog poremećaja, a drug(e)a je(su) indukovan(e)a, i najčešće ozdrav(e) i kada dođe do separacije od induktora. **Prikaz slučaja.** Koristeći medicinsku dokumentaciju, kao i literaturu dostupnu za temu, prikaz slučaja opisuje sina i majku sa ovim poremećajem, pri čemu sin boluje od paranoidne psihoze, koju „prenosi" na majku. Oni dugi niz godina žive sami u domaćinstvu, socijalno izolovani od okoline. **Zaključak.** U osnovi, istraživanja su pokazala da ne postoje ujednačena mišljenja među autorima u pogledu broja poremećaja uočenih kod muškaraca i žena, u mlađem i starijem uzrastu, kao i u odnosu partnera, braće i sestara, odnosu roditelj−dete. Većina se slaže da je najznačajniji faktor dugotrajna socijalna izolacija, kao i dominacija i jaka moć sugestije kod jednog, a pasivnost i sklonost sugestiji kod drugog partnera.

Ključne reči: udvojeni psihotički poremećaj; faktori rizika; mentalni poremećaji; socijalna izolacija; zablude; međuljudski odnosi; sugestija; odnosi majke i deteta; ishod lečenja

Introduction

”Folie à Deux is a rare syndrome that has attracted much clinical attention. There is increasing doubt over the essence of the condition and the validity of the original description, such that it remains an elusive entity difficult to define” [1]. According to Shimizu M. et al., shared psychotic disorder (SPD) was first discovered and described by Jules Baillarger as “folie a communique” in 1860 [2]. In 1877, Lasegue and Falret coined the name “folie à deux” or “insanity or psychosis of two” in their paper “La folie a deux” (also called “Lasègue-Falret syndrome”) [3] **(Table 1).** In his paper from 1942, Gralnick defined SPD as the transfer of delusional ideas, and/or abnormal behavior from one person to another, or one person to several others, related or unrelated, who have been in close association with the primary affected person [4]. If the disorder is shared with more than two people, it may be called folie à trois, folie à quatre, folie à famille… [5]. The number of reported and recognized cases of SPD is relatively small [6]. According to Schoenhals and his 14-year-experience, only four cases on SPD (around 0.028% of the total number of his patients) were admitted to the hospital [7]. In addition, an extensive review of the literature showed that many cases of folie à deux were not reported and remained unrecognized, so our impression of a low incidence of the illness is false. Specifically, Dušan Kovačević’s movie “Balkan Spy” is a popular dramatization of this subject matter. The main character transmits his

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Abbreviations
SPD – shared psychotic disorder

paranoid psychosis on his inmates. It is common knowledge that under normal circumstances, psychotic symptoms are not transmissible, and do not affect neither healthy nor mentally disturbed individuals. Accordingly, transmission may occur in specific cases: if people have lived together in isolated environments for a long time, spending most of their lives dependent on each other, if the "primary" patient or an inducer is a dominant partner, and if the "secondary" partner is a passive and a susceptible person, or possibly if delusion-like ideas are closely related to a potential turn of events in their environment [8].

The most common risk factors for SPS are 1) length of a relationship plays a significant role in the development of this disorder, 2) intimacy of the relationship (usually in family members or married couples), 3) social isolation, an individual in conditions of lack of social interaction may be confused and under the strong influence of another person from the environment, 4) comorbid personality disorder (such as neurotic or introvert persons with emotional immaturity), 5) mental disorder (usually untreated) in the nuclear family (untreated person with a mental disorder may have an influence on the other members), 6) cognitive disability and impairment, that disrupts rational reasoning, 7) stressful life events can influence the judgment of the individual, 8) age (usually elderly being a dominant while the young being submissive), 9) gender (more common in females) [9–13]. A paper found that 98% of cases reported between 1993 and 2005, occurred within the nuclear family, usually between married or common-law couples (52%) or sisters (24%), 50% of them in sister-sister and mother-daughter relationships and 8% in non-consanguineous patients or friends [14]. Some clinical characteristics arise, such as frequent mother-daughter associations and diagnosis of schizophrenia in inducing subject [15]. Scharfetter reported that the most common age range of the dominant partner is 16 to 82 years (average 38.5 years) and that of the submissive partner is 4 to 79 years (average, 36.2 years) [16]. Some cases of Ekbom syndrome, also known as delusional parasitosis (in which an individual harboring the delusion of being infested with insects or parasites), are described with the combination of folie à deux [17]. The first case was described by Skott in 1978. Patients may present with skin excoriations and crusting in an attempt to eliminate the underlying pathogens [18]. Also, there are a few reports on Incubus syndrome known as demonic lover, which is a dissociative disorder like dissociative hyperventilation, trance and demonic possession disorder, and dissociative amnesia [19] and Fregoli syndrome (a rare delusional belief that one or more familiar persons, usually persecutors following the patient, repeatedly change their appearance) can be found within folie à deux psychosis [20].

According to Guirvach et al. homicides may arise from all forms of folie à deux and they are most often committed with great violence. Two types of homicide are mainly described: manslaughter (no intent to kill, but death happens due to delusions and hallucinations) and intentional homicide. Research shows that a combination of mystical and persecutory delusions in SPD is associated with a high risk of homicide [21]. Delusional disorders can be induced by dopaminergic agents like psychoactive substances (PAS). Studies show that the most common PAS that cause delusional disorders are cannabis, cocaine, and amphetamines [22]. There are a few reports on the use of cannabis and amphetamines in folie à deux, which can also be combined with delusional infestations in some cases [23]. In his paper: "Folie à deux - the psychosis of association" Gralnick suggested a classification of four types of folie à deux: 1) Folie impose, 2) Folie simultanee, 3) Folie communique – a communicated insanity, 4) Folie induite [4].

Case Report

A single 39-year-old male, currently unemployed, tradesman by profession, without children, has been

Table 1. Terminology and definition of folie à deux
Tabela 1. *Terminologija i definicija folie à deux*

Serbian	Indukovano sumanuto duševno oboljenje
French	Folie á deux
English (DSM-V)	Induced delusional disorder DSM-5 does not consider Shared Psychotic Disorder as a separate entity, but rather, the physicians should classify it as a "Delusional Disorder" or "Other Specified Schizophrenia Spectrum and Other Psychotic Disorders". *Indukovani psihotični poremećaj* *DSM-5 ne smatra udvojeni psihotični poremećaj zasebnim entitetom, već bi lekari trebalo da ga klasifikuju kao Psihotični poremećaj ili kao Specifični poremećaj iz spektra shizofrenije ili drugi psihotični poremećaj.*
Latin	Psychosis paranoides inducta

Legend/*Legenda:* DSM-5 - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition/*Dijagnostički i statistički priručnik za mentalne poremećaje, peto izdanje*

living with his 66-year-old mother in the same household for many years. He had type 1 diabetes and hypothyroidism since his childhood and there was no evidence of genetic mental illness in the family. The mother is divorced, has no more children, has a primary education and works at the market. There is no information if she was treated by a psychiatrist. The young man was treated at the Psychiatry Clinic on multiple occasions. The first hospitalization was in 1999, when he was diagnosed with opioid addiction. He underwent abstinence treatment more than once and enrolled in short-term methadone treatment. Before the end of 2017, he visited the Outpatient Clinic of the Clinical Center, accompanied by his mother, and upon his arrival complained of several somatic symptoms which were the main reason for his visit. They both looked decent and were well dressed. During the conversation, he revealed a dissociative disorder characterized by a wide range of alterations in the flow of thinking and presented with a series of non-systematized delusions. Accordingly, besides exhibiting megalomaniacal ideas and opinions (e.g. he said that he was engaged in the world's music star production, that he was the founder of a children's foundation which has raised millions of dollars to support children, and among other things he was going to marry the princess of England and he was in the Federal Bureau of Investigation witness protection program...), he demonstrated paranoid delusional ideation (he reported that some people from the casino want to hurt him because he has a children's foundation and that his mobile phone was tapped and cameras were set up to monitor him in his house...), as well as delusional ideas of reference (when passing by someone he always heard the sound of coins and messages communicated to him through the TV and radio station...). Among sensory delusions, he experienced cenesthopathic hallucinations (such as a built-in chip in his head that controls him, mobile applications which regulate the work of his heart...). At the same time, he did not affectively communicate his ideas. Instead, he was accompanied by his mother who fully confirmed the delusional ideas of her son (she said that she was recorded and followed whenever she left the house and that her son was controlled by someone who entered his head through the computer... that the phone rings strangely at night as someone was recording them...). She had a defensive attitude, and showed mood-congruent delusions (she was irreplaceable). Initially, the disorder was recognized as an induced delusional mental illness, where the young man agrees to be admitted to hospital, but his mother refuses it, as well as being prescribed any drugs, claiming that she is not crazy and that the only reason she agreed to let her son be treated is to regulate his blood sugar levels.

An antipsychotic therapy (fluphenazine) was administered to the young man. Satisfactory response to the therapy was reflected in gradual disappearance of psychotic symptoms, and ultimately by complete dissociation from the delusions present on admission to hospital. Conversations were held with his mother almost on daily basis and she regularly visited her son. At first she was still suspicious and did not trust the doctors (she said she thought doctors were involved), but there was a gradual reduction in delusions after separation from her son. After some time, when the son's discharge was planned, his mother said that she may have overstated and exaggerated things a bit and that she supported the fantasies of her son.

In our case, a young man and his mother have lived together for many years, and most of the time they depended on each other, living relatively socially isolated and without employment. During the treatment, on the grounds of paranoid psychosis, the son underwent treatment with antipsychotic medication. After the disappearance of symptoms, psychotherapeutic treatment was recommended to both of them, which they both accepted. The young man was recommended to take prescribed antipsychotic medications regularly, checking the status of mental health regularly, as well as finding a job, if possible a part-time job, to prevent further social isolation. So far, no recurrence of the disease has been recorded. We may conclude that this is the case of a folie impose - imposed psychosis, which is also supported by the fact that after separation from her son, the mother's symptoms disappeared.

Discussion

There is limited research examining SPD. One of the reasons is that SPD may be a rare condition. Another possibility is that patients with shared psychotic disorder rarely seek psychiatric treatment on their own, because of the lack of insight. They become visible if they commit a crime or if their strange behavior is noticed by others [24]. Etiologically, folie à deux has been proposed to underlie either psychogenic, sociogenic or biogenic genesis [25]. Most studies, explaining the psychopathology of this disorder, have mentioned the role of genetic susceptibility, but the occurrence of the disorder in friends and spouses also suggests an additional environmental factor as an exogenous factor [26]. Gender differences in the prevalence of folie à deux differ in the observations of several authors. Few authors believe that this disorder is more prevalent among females due to a subordinate social status, while the others think that there is equal prevalence in both genders, as well as at a younger and older age. It is considered to be evenly distributed among married couples, siblings, as well as in parent-child relationships (long-term relationships). Also, it seems that the most important factor is social isolation of the couple; it involves the transfer of delusions from the dominant (primary) partner to the second, because they usually have identical content of the delusional system and evidence that they share [27–29]. If the second person is exposed to the primary, it may be a trigger for a transient psychotic phenomenon, and the secondary subject will develop a psychotic episode (the young man's mother confirmed that she supported the fan-

tasies of her son) [30]. Usually, the secondary patient sees the primary patient as credible and trustworthy [31]. Association is found between psychosis and adverse childhood experiences such as neglect by parents or other caregivers or traumatic personal experiences (physical abuse, suicidal attempts, alcohol abuse in the family or close environment) [32]. In our case, we do not have substantial data, with the exception of an absent father.

Folie à deux seems to include a syndrome including such disorders as schizophrenia, paranoid/delusional disorder, and reactive psychosis [2]. Folie à deux, in most cases involves delusional beliefs, there is no evidence of psychomotor disturbances, flattened affect, or formal thought disorder, and it is transmitted to the secondary patient. Similary, except for the belief in her son's delusions (she spontaneously produced only the paranoid and interpretative ones) [33]. The basic therapeutic principle in psychiatry, as well as in other areas of physical medicine, claims that it is necessary to diagnose the disorder as early as possible and start treatment, use a proper dosage of the medication, and apply the medical treatment for the required amount of time [34]. Fortunately, the contact with a psychiatrist, although accidental in our case, was established early and the outcome was fairly positive. Treatment depends on the severity of the case. Old data suggest that separation is the primary method, but new data show that it may be insufficient or may aggravate the psychosis. In our case, however, separation proved to be a very helpful intervention. Drug treatment alone or combined with other types of treatments may improve the condition. If the disorder is treatable with medications only, it indicates the severity of the clinical case. Psychotherapy, as a way of treatment, can be done as mono-therapy, or both can be used. It is very difficult to predict the prognosis of this disorder. The adherence to the management plan in both partners may provide a better outcome than being untreated [9]. In our case, the psychotic symptoms in the induced penitent, inducers mother, were significantly reduced by separation from the primary patient, whereas the primary patient was treated with antipsychotics in our clinic, which led to the remission of the disorder. The young man was recommended to take prescribed antipsychotic medication regularly, checking the status of mental health regularly, as well as finding a job, if possible a part-time job to prevent social isolation.

Conclusion

In general, the research has shown that there are no uniform opinions among authors regarding the incidence of the disorder in males and females, at younger and older age, as well as in relationships between partners, siblings, and between parents and children. Most authors agree that long-term social isolation is among the most common risk factors, as well as dominance and strong power of suggestion in one partner, and passivity and tendency to suggestion in the other. We can conclude that this case was "folie impose" psychosis, supported by the fact that mother's symptoms disappeared after separation from her son.

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Case report
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CONGENITAL PULMONARY AIRWAY MALFORMATION IN ADULTS – A CASE SERIES

KONGENITALNA MALFORMACIJA PLUĆNIH DISAJNIH PUTEVA KOD ODRASNIH – PRIKAZ SERIJE SLUČAJEVA

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Summary

Introduction. Two-thirds of patients with congenital pulmonary airway malformation are asymptomatic at birth, but during life they may develop symptoms such as recurrent respiratory infections. The purpose of this paper is to present three cases of adult patients in whom congenital pulmonary airway malformation was diagnosed and treated at the Institute for Lung Diseases of Vojvodina, along with the clinical course of the disease and the therapeutic procedure. **Case Report 1.** A 24-year-old female with a medical history of asthma and recurrent signs of lower respiratory tract infections was referred to a thoracic surgeon. Computed tomography of the chest and clinical features were consistent with a congenital lung disease. A left lower video-assisted thoracoscopic lobectomy was performed. Histopathological analysis confirmed type II congenital pulmonary airway malformation with pulmonary sequestration. **Case Report 2.** A 41-year-old male with a history of left-sided spontaneous pneumothorax at the age of 16 was referred to a thoracic surgeon due to moderate hemoptysis, one month after hospital treatment of left-sided bronchopneumonia. On chest computed tomography, multiple cystic lesions were found in the left lower lung lobe. Thoracotomy and left lower lobectomy were performed. Histopathological analysis confirmed type I congenital pulmonary airway malformation. **Case Report 3.** The third patient was a 16-year-old male with a history of juvenile asthma and recurrent right-sided bronchopneumonia. Sings of necrotizing pneumonia, lung abscess, and mediastinal lymphadenomegaly were found in the affected lobe. Thoracotomy and right lower lobectomy were performed. Histopathological analysis confirmed type II congenital pulmonary airway malformation. **Conclusion.** In children and young adults with recurrent small airway inflammation, congenital lung malformation should be considered in the differential diagnosis.

Key words: Respiratory System Abnormalities; Congenital Abnormalities; Adult; Cystic Adenomatoid Malformation of Lung, Congenital; Thoracic Surgery

Sažetak

Uvod. Dve trećine pacijenata sa kongenitalnom malformacijom plućnih disajnih puteva su asimptomatski pri rođenju, ali tokom života mogu razviti simptome u vidu rekurentnih respiratornih infekcija. Svrha ovog rada je da prikaže tri slučaja odraslih pacijenata, kod kojih je dijagnostikovana i lečena kongenitalna malformacija disajnih puteva u Institutu za plućne bolesti Vojvodine, uz prikazan klinički tok bolesti i terapijski postupak. **Prikaz slučaja 1.** Žena starosti 24 godine, sa anamnezom astme i ponavljajućim znacima infekcije donjih disajnih puteva, upućena je torakalnom hirurgu. Kompjuterizovana tomografija grudnog koša i klinička slika ukazali su na kongenitalnu bolest pluća. Načinjena je leva donja video-asistirana torakoskopska lobektomija. Patohistološkom analizom potvrđena je kongenitalna malformacija disajnih puteva pluća tip II sa plućnim sekvestrom. **Prikaz slučaja 2.** Muškarac starosti 41 godine sa istorijom levostranog spontanog pneumotoraksa u uzrastu od 16 godina, upućen je torakalnom hirurgu zbog učestalih hemoptizija, mesec dana nakon hospitalnog lečenja levostrane bronhopneumonije. Na kompjuterizovanoj tomografiji grudnog koša su opisane multiple cistične lezije, locirane u levom donjem plućnom režnju. Načinjena je torakotomija i leva donja lobektomija. Histopatološki izveštaj: kongenitalna malformacija disajnih puteva pluća tip I. **Prikaz slučaja 3.** Muškarac star 16 godina, sa istorijom juvenilne astme i ponavljajuće desne bronhopneumonije. U zahvaćenom režnju opisani su znaci nekrotizirajuće pneumonije, apscesa pluća uz medijastinalnu limfadenomegaliju. Načinjena je torakotomija i desna donja lobektomija. Histopatološkom analizom potvrđena je kongenitalna malformacija disajnih puteva pluća tip II. **Zaključak.** Kod dece i odraslih u mlađem životnom dobu sa rekurentnim zapaljenjem malih disajnih puteva, treba misliti na urođene malformacije pluća, u okviru diferencijalne dijagnoze.

Ključne reči: anomalije respiratornog sistema; kongenitalne anomalije; odrasli; urođena cistična adenomatozna anomalija pluća; grudna hirurgija

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Abbreviations

CPAM – congenital pulmonary airway malformation
CT – computed tomography
VATS – video-assisted thoracoscopic surgery

Introduction

Congenital pulmonary airway malformation (CPAM), formerly known as congenital cystic adenomatoid malformation is a rare developmental disorder of the fetal tracheobronchial tree [1]. Two-thirds of these patients are asymptomatic at birth, but during life they may develop symptoms such as recurrent respiratory infections and are often treated for bronchitis or asthma for years [2].

The purpose of this paper is to present three cases of adult patients in whom CPAM was diagnosed and treated at the Institute for Lung Diseases of Vojvodina in the last five years along with the clinical course of the disease and the therapeutic procedure.

Case report 1

The first patient, a 24-year-old female with a medical history of asthma and recurrent lower respiratory tract infections was referred to a thoracic surgeon after four episodes of pneumonia in the last five months. Chest computed tomography (CT) showed clustered central and peripheral cystic bronchogenic lesions of different sizes and shapes with thin or imperceptible cystic walls. The entire S8, S9, and S10 left lung segments were affected, S6 was completely spared as well as parts of S7. The largest lesion was described as a subpleural bulla in the S9/S10 measuring 9 x 4.6 cm and there was no communication with the tracheobronchial tree **(Figure 1)**. The CT imaging and clinical features were consistent with congenital lung disease. Due to recurrent respiratory infections and the lung cystic lesion, a left lower video-assisted thoracoscopic surgery (VATS) lobectomy was performed. During the VATS procedure, apart from the described bulla, the affected segments were pale and overinflated. The incidental finding was extralobar pulmonary sequestration which was resected by an endostapler. The entire vascular bundle was derived from the thoracic aorta. The patient was discharged from the hospital on the 6th postoperative day. On the routine follow-up, 3 months after surgery, the control chest X-ray was coherent with the performed surgery. There were no signs of new respiratory infections. Histopathological analysis confirmed type II CPAM and pulmonary sequestration **(Figure 2)**.

Figure 1. Computed tomography showing clustered central and peripheral cystic bronchogenic lesions of different sizes and shapes with thin or imperceptible cystic walls
Slika 1. *Kompjuterizovana tomografija: Grupisane centralne i periferne cistične lezije bronha različitih veličina i oblika, tankozidne ili sa neuočljivim zidom*

Case report 2

The second patient, a 41-year-old male with a history of left-sided spontaneous pneumothorax at the age of 16, was referred to a thoracic surgeon due to moderate hemoptysis one month after hospital treatment of left-sided bronchopneumonia. The CT of the chest showed multiple cystic lesions located in the left lower lobe with signs of pericystic inflammation. Some of the parenchymal cysts showed air-fluid levels. With a high suspicion of congenital lung disease, thoracotomy and left lower lobectomy were performed. During the initial VATS procedure, extensive pachypleuritis was found, with signs of recurrent inflammation of both left lung lobes.

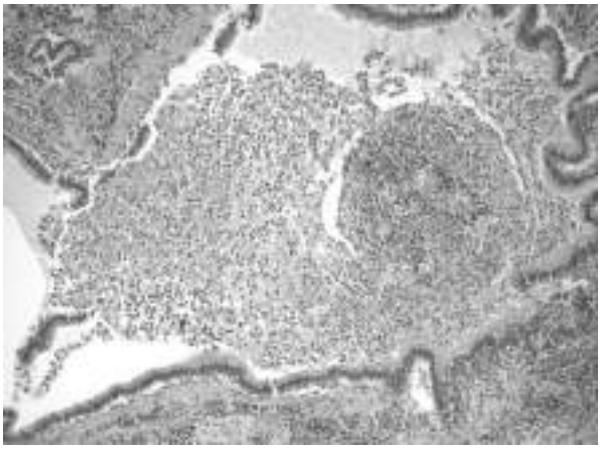

Figure 2. CPAM type 2 - Small cysts resemble dilated bronchioles, without cartilage and filled with mucus mixed with inflammatory cells and macrophages, H&E x 100
Slika 2. *CPAM tip 2 - Male ciste koje svojim izgledom podsećaju na dilatirane bronhiole, bez hrskavice ili ispunjene mukoznim sadržajem pomešanim sa inflamatornim ćelijama i makrofagima, H & E x 100*

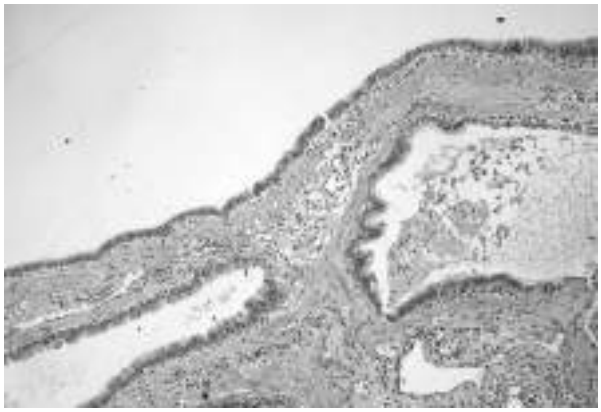

Figure 3. CPAM type 1 - Large cyst wall lined by pseudostratified ciliated cells without cartilage, H&E x 50
Slika 3. *CPAM tip 2 – velike ciste obložene pseudostratifikovanim cilijarnim ćelijama, bez prisustva hrskavice, H & E x 50*

Due to plural deficit after lobectomy, artificial pneumoperitoneum was created, but a prolonged air leak was present on the chest drain. The patient was discharged one month after surgery. On the routine follow-up, 3 mounts after surgery, complete obliteration of the pleural deficit was achieved. Histopathological analysis confirmed type I CPAM **(Figure 3)**.

Case report 3

The third patient, a 16-year-old male with a history of asthma and recurrent right-sided bronchopneumonia, was referred to a thoracic surgeon with high radiological suspicion of congenital lung disease. Chest CT showed extensive alveolar-interstitial lung lesions in the right lower lobe, manifesting as cystic lesions measuring up to 16 mm with bronchiectasis. Signs of necrotizing pneumonia, lung abscess, and mediastinal lymphadenomegaly were found in the affected lobe. During the VAST procedure, extensive mediastinal and hilar inflammation was observed, so thoracotomy, right lower lobectomy, and mediastinal lymphadenectomy were performed. The patient was discharged on the 8th postoperative day. On the routine follow-up, 3 months after surgery, control chest X-ray was coherent with the performed operation. Histopathological analysis confirmed type II CPAM.

Discussion

More than a half of the cases of CPAM are congenital airway malformations with a prevalence of 1 - 4/100,000 [1]. Other congenital lung malformations include pulmonary sequestration, bronchial atresia, lobar agenesis, bronchogenic cysts, congenital lobar emphysema, and polyalveolar lobe. By definition, CPAM is a developmental disorder of small airways of unknown etiology that occurs between 5th and 6th week of gestation, when instead of alveolar tissue there is an expansive growth of terminal respiratory bronchioles and formation of a multicystic mass [3]. So far, no association of this disease with race, sex, birth weight, or with exposure to certain substances in pregnancy has been observed [4]. Our patients are Caucasian, the sex distribution is 2 : 1 in favor of the male sex and the medical histories showed that the pregnancies went smoothly, Apgar score was 10/10.

Back in 1962, CPAM was classified by Stocker into 5 subtypes according to the number and size of cysts and histology:

0 - all lobes are cystically altered, incompatible with life;

I - the most common type (60 - 65%), consists of a single or multiple large cysts with ciliated pseudostratified and columnar epithelium;

II - (20%) consists of multiple smaller cysts and may be associated with other congenital anomalies;

III - consists of large, pseudo-glandular lesions that usually involve the entire lobe;

IV - is composed of large thin-walled cysts that have a malignant potential [1].

Anomalies that may be associated with CPAM are extralobar sequestration, congenital diaphragmatic hernia, pulmonary hypoplasia, hydrocephalus, cardiovascular malformations, esophageal or gastric atresia, and bilateral renal agenesis/dysgenesis [2].

Our two patients had type II and one had type I CPAM. In a patient with type II CPAM, another anomaly was observed - extralobar pulmonary sequestration, which was also operated on.

In developed countries, this anomaly is diagnosed prenatally, during the 18 - 20th week of gestation, after which more frequent ultrasound examinations are required, and in the absence of symptoms after birth, elective surgery is considered. Mon et al. recommend fetal magnetic resonance imaging as well as early postnatal CT of the chest for clearer visualization of blood vessels [5]. On the other hand, Yousef et al. first mentioned the use of postnatal lung ultrasound, which is a faster and cheaper method, without radiation, for monitoring children with suspected CPAM [6]. The question of when it is the right time to operate on asymptomatic children is still debatable and recommendations range from 6 - 7 months [7] to 2 years of age [8]. Spontaneous resolution in some patients, both prenatal and postnatal [9], has been known for some time, so elective surgery is not recommended in the first months of life.

Considering that Serbia is a developing country, there are several possible reasons why our patients have not been prenatally diagnosed. One of the reasons is their age (patient No. 1 is 24 years old, while patient No. 2 is 41 years old), because although ultrasound has been used in gynecology since the 1980s, modern ultrasonography that gives more detailed views of the fetus has developed in the last two decades. Another possible reason is the unavailability of a modern ultrasound machine in all areas, since the youngest patient (aged 16) comes from a smaller town. Training and experience of health

personnel should always be taken into account, because ultrasound is a subjective method.

At birth, people with CPAM are symptomatic or asymptomatic. No predictive factor has been established to indicate when a person will become symptomatic. The severity of symptoms certainly depends on the location of lesions, type of CPAM, association with other congenital anomalies, so the clinical features are diverse - from neonatal hydrops, respiratory distress syndrome, recurrent pneumonia, shortness of breath to pneumothorax [10]. Other congenital anomalies (pulmonary sequestration, lobar emphysema, and bronchogenic cysts), acquired respiratory infections, as well as iatrogenic or traumatic emphysema and atelectasis [2] are considered in the differential diagnosis. Our two patients experienced first symptoms at the age of 16 (spontaneous pneumothorax and pneumonia), they were previously treated for asthma, while the third patient reported "frequent bronchitis" or recurrence of small airway inflammation since childhood.

Surgery is the definitive diagnostic and therapeutic procedure in patients with CPAM. Depending on the size of the lesion, lobectomy, bilobectomy or pneumonectomy is performed. Segmental resection is not recommended, because it is difficult to isolate cysts intraoperatively and identify the final border of the lesion. All three of our patients underwent VATS lobectomy, and the postoperative course was without complications.

Conclusion

In children and adolescents with recurrent small airway inflammation, congenital pulmonary airway malformation should be considered in the differential diagnosis. All three of our patients had a good prognosis since the lesions were confined to one lobe, they were not associated with more serious congenital anomalies, and the patients had no other associated diseases.

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DELIRIUM IN CARDIAC SURGERY – RISK FACTORS AND PREVENTION

DELIRIJUM U KARDIOHIRURGIJI – FAKTORI RIZIKA I PREVENCIJA

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Summary

Introduction. Delirium is defined as an acute change in mental status that leads to disturbance in perception, thinking, memory, attention, emotional status, as well as sleep rhythm disorders and is most often reversible. Postoperative delirium is an acute mental disorder that develops after cardiovascular surgery with an incidence of 20 - 50% of operated patients. This complication is associated with a longer hospitalization, longer stay in the intensive care unit, as well as increased morbidity and mortality. **Risk Factors.** The risk factors are divided into preoperative, intraoperative and postoperative. The most common preoperative risk factors are older age, stenosis of the carotid arteries, previous cerebral diseases, depression, diabetes, hypertension, low ejection fraction of the left ventricle, as well as heart rhythm disorders. Intraoperative risk factors include the type of surgery, type of anesthesia, duration of extracorporeal circulation, and duration of aortic clamp. The most important postoperative risk factors include the use of psychoactive drugs, prolonged pain, the use of opioid drugs, duration of mechanical ventilation, and the length of stay in the intensive care unit. **Prevention.** Prevention is a very important aspect that is most often focused on intraoperative and postoperative precipitating factors. Preventive treatment includes pharmacological and non-pharmacological methods. The main recommendation refers to avoiding routine use of antipsychotics. **Conclusion.** Continuous infusion of dexmedetomidine compared to propofol reduces the incidence of postoperative delirium. Non-pharmacological approach consists of a series of procedures that are carried out postoperatively, such as the protocol that includes monitoring of Awakening, Breathing, Coordination, Delirium, Early mobility, and Family engagement.

Key words: Delirium; Thoracic Surgery; Risk Factors; Dexmedetomidine; Postoperative Complications

Sažetak

Uvod. Delirijum se definiše kao akutni poremećaj mentalnog statusa koji dovodi do narušavanja percepcije, razmišljanja, pamćenja, pažnje, emocionalnog statusa, kao i poremećaja ritma spavanja i najčešće je reverzibilnog karaktera. Postoperativni delirijum podrazumeva akutni poremećaj mentalnog statusa koji se javlja u kardiovaskularnoj hirurgiji sa incidencijom od čak 20−50% operisanih pacijenata. Ova komplikacija sa sobom nosi dužu hospitalizaciju, duži boravak u jedinici intenzivnog lečenja, kao i povećan morbiditet i mortalitet. **Faktori rizika.** Faktori rizika se dele na preoperativne, intraoperativne i postoperativne. Najčešći preoperativni faktori rizika su starije životno doba, stenoza karotidnih arterija, ranija cerebralna oboljenja, depresija, dijabetes, hipertenzija, niska ejekciona frakcija leve komore, kao i poremećaji srčanog ritma. U intraoperativne faktore rizika spadaju vrsta operativnog zahvata, vrsta anestezije, dužina trajanja ekstrakorporalne cirkulacije, dužina trajanja aortne kleme. U najznačajnije postoperativne faktore rizika spadaju upotreba psihoaktivnih lekova, prolongirana bol i upotreba opioidnih lekova, vreme trajanja mehaničke ventilacije i dužina boravka u jedinici intenzivnog lečenja. **Prevencija**. Prevencija predstavlja veoma značajan aspekt koji je najčešće fokusiran na intraoperativne i postoperativne precipitirajuće faktore. Preventivni tretman se može podeliti na farmakološke i nefarmakološke metode. Osnovna preporuka odnosi se na izbegavanje rutinskog davanja antipsihotika. **Zaključak**. Kontinuirana infuzija deksmedetomidina u poređenju sa propofolom smanjuje incidenciju postoperativnog delirijuma. Nefarmakološki pristup se sastoji od niza postupaka koji se sprovode postoperativno, kao što je ABCDEF protokol (Buđenje, Disanje, Koordinacija, Praćenje delirijuma, Rana mobilnost i Porodično angažovanje).

Ključne reči: delirijum; grudna hirurgija; faktori rizika; deksmedetomidin; postoperativne komplikacije

Introduction

Delirium is defined as an acute change in mental status that leads to disturbance of perception, thinking, memory, attention, emotional status, as well as sleep rhythm disorders and is most often reversible [1]. According to the American Psychiatric Association, the diagnosis of delirium can be made if the patient has a disorder of attention, a disorganized flow of thoughts, or an altered level of consciousness that develops over

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Abbreviations

POD – postoperative delirium
ECC – extracorporeal circulation
ICU – intensive care unit
LV – left ventricle
ABCDEF – Awakening, Breathing, Coordination, Delirium monitoring, Early mobility and Family engagement

a short period of time and has a fluctuating course during the day [2].

Postoperative delirium (POD) is an acute mental disorder that occurs after major surgical procedures. The POD is a complication that most often develops in cardiovascular surgery with an incidence of as much as 20 - 50% of operated patients. After an emergency surgery, POD occurs 1.5 to 3 times more often than after an elective surgery. It can develop in all age groups, but more often after a surgery performed in older patients, with an incidence rate of 5 - 52%, depending on the general condition of the patient and the extent of the surgery. It usually occurs in the first five postoperative days [1, 3].

This complication is associated with a longer hospitalization, a longer stay in the intensive care unit (ICU), as well as increased morbidity and mortality. Although POD is reversible, it often leads to permanent consequences, since it may trigger the development of numerous complications that lead to permanent damage, loss of independence and disability. All this affects the health condition and quality of life of both the patients and their families, and from the economic aspect, leads to higher costs of treatment [4, 5]. Due to these facts, it is very important to prevent the development of delirium, especially in patients who, due to their age, health condition or type of surgical intervention, are at increased risk for developing POD [1, 4–6].

Risk Factors

Although the prevalence of delirium after cardiac surgery varies, there are predictors that may indicate patients at increased risk for developing POD. Risk factors are divided into preoperative, intraoperative and postoperative factors **(Table 1)** [7–13].

Among the most common preoperative risk factors for the development of POD is older age, especially in patients older than 65 years. These patients have more comorbidities, and therefore are at a greater risk for developing postoperative complications. Stenosis of the carotid arteries, previous cerebral diseases, depression, diabetes, hypertension, low ejection fraction of the left ventricle (LV), as well as heart rhythm disorders are conditions that lead to disorders of autoregulation of cerebral circulation and thus cause hypotensive periods and non-pulsatile blood flow when using a pump for extracorporeal circulation (ECC) during cardiac surgery [8–10]. The use of alcohol and cigarettes is also a significant predictor [8, 9]. Several studies have proven that these preoperative predisposing factors increase the possibility of POD up to seven times [10]. Unfortunately, these predisposing factors can hardly be influenced, therefore prevention should be focused on perioperative risk factors which, together with all the above-mentioned preoperative factors, will affect a higher incidence of POD and other complications that occur after cardiac surgery [14–16].

Intraoperative risk factors include type of surgery, with a higher incidence of POD after heart valve surgery due to the greater possibility of microembolization and the development of ischemic brain lesions, as well as emergency cardiac surgeries. In addition to the type of surgery, the type of anesthesia is also a risk factor. It has been proven that POD in non-cardiac surgery patients occurs in 21% of cases after general anesthesia, while after regional anesthesia it

Table 1. Risk factors for the development of postoperative delirium
Tabela 1. *Faktori rizika za razvoj postoperativnog delirijuma*

Preoperative/*Preoperativni*	Intraoperative/*Intraoperativni*	Postoperative/*Postoperativni*
Older age/*Starije životno doba*	Type of surgery/*Vrsta operacije*	Psychoactive drugs/*Psihoaktivni lekovi*
Carotid artery stenosis *Stenoza karotidnih arterija*	Type of anesthesia *Vrsta anestezije*	Pain *Bol*
History of cerebral diseases *Ranija cerebralna oboljenja*	Pump duration for ECC *Trajanje pumpe za EKC*	Mechanical ventilation *Mehanička ventilacija*
Depression *Depresija*	Aortic clamp duration *Trajanje aortne kleme*	Anemia *Anemija*
Diabetes mellitus/*Dijabetes melitus*		Septic state/*Septično stanje*
Hypotension/*Hipotenzija*		Length of stay in ICU/*Dužina boravka u JIT*
Low LV ejection fraction *Niska ejekciona frakcija LK*		Length of hospitalization *Dužina hospitalizacije*
Arrhythmia/*Aritmije*		Electrolyte imbalance/*Elektrolitski disbalans*
Alcoholism/*Alkoholizam*		
Nicotinism/*Nikotinizam*		

Legend: ECC – extracorporeal circulation; ICU – intensive care unit; LV – left ventricle
Legenda: EKC – ekstrakorporalna cirkulacija; JIT – jedinica intenzivne terapije; LK – leva komora

occurs in 13% of cases. The ECC duration and aortic clamp duration are also significant factors for the development of POD [9, 10, 14, 15]. There are different theories as to how a longer duration of ECC is associated with a higher incidence of POD. Hypotensive periods, non-pulsatile blood flow and the release of pro-inflammatory mediators in blood contact with parts of the ECC machine are considered to play the most important role, which lead to increased permeability and damage to the blood-brain barrier [10, 14, 15]. However, randomized studies comparing on-pump and off-pump operations showed no difference in the incidence of postoperative cognitive impairment [12]. A logical explanation may be the increased possibility of microembolization by fragments of atherosclerotic plaques that are released into the bloodstream during these surgeries, regardless of whether an ECC pump is used or not. Placement of an aortic cannula and aortic clamp also increases the risk of embolization of cerebral blood vessels and thereby increases the possibility of POD [10, 15]. In addition to possible embolization with parts of atherosclerotic plaques, there is also a possibility of air embolism if at the end of the operation, the air that gets into the arterial circulation is inadequately removed and compromises the cerebral circulation [10, 14–16].

The most important postoperative risk factors include the use of psychoactive drugs, such as benzodiazepines, prolonged pain, use of opioid drugs, duration of mechanical ventilation, septic condition, anemia, hyponatremia, length of stay in ICU and length of hospitalization [8–10, 14–16].

Prevention

Delirium is considered to be a postoperative complication that can usually be prevented, thus prevention is a very important aspect which should receive more attention. Given that the preoperative condition of the patient, his comorbidities and habits can hardly be influenced, most often prevention is focused on intraoperative and postoperative precipitating factors for the occurrence of POD [13]. Preventive treatment can be divided into pharmacological and non-pharmacological methods [10, 13, 14].

So far, preventive pharmacological therapy has shown mixed results. The main recommendation is to avoid routine administration of antipsychotics. Numerous studies have shown that sedation with benzodiazepines causes the development of POD both in cardiac and noncardiac surgeries [13, 17, 18]. Anticholinergics, corticosteroids, certain opioids such as meperidine, and polypharmacy, which implies simultaneous use of more than five drugs at the same time, should be avoided. In recent years, more importance has been given to dexmedetomidine in the prevention of POD. Dexmedetomidine is a potent α2 agonist that has anxiolytic, sedative, analgesic, and sympatholytic effects. Continuous infusion of dexmedetomidine results in hypnosis and sedation, without respiratory depression, and it may provide earlier postoperative extubation of patients and prevent variations in blood oxygen levels. Also, compared to propofol, dexmedetomidine reduces the incidence of postoperative delirium, reduces the duration of mechanical ventilation and enables earlier extubation of the patient. This reduces the complications of mechanical ventilation, the mortality and morbidity of these patients, as well as the length of stay in the ICU and the length of hospitalization [18–24].

Non-pharmacological methods are necessary in the prevention of POD and have shown very good results [13]. In addition to the effort to minimize intraoperative precipitating factors, such as giving an adequate indication for surgery, choosing the best operative technique, reducing the usage of the ECC, aortic clamps, avoiding periods of hemodynamic instability, electrolyte imbalance, adequate pain management and adequate hydration, the non-pharmacological approach is very important, and it includes a series of procedures that are carried out postoperatively. In the ICU, the protocol consisting of Awakening, Breathing, Coordination, Delirium monitoring, Early mobility and Family engagement (ABCDEF) is used daily. This protocol involves the implementation of tests of awakening and spontaneous breathing with the aim of reducing the length of sedation and mechanical ventilation and all the complications they involve. Also, it implies frequent daily reorientation of patients, which refers to the return of wearing glasses, hearing aids, access to calendars, watches, newspapers. Facilitating contact with relatives is one of the most important preventive measures in the occurrence of POD [25–27].

It is very important to provide patients with a day-night rhythm. If possible, patients should be provided with daylight during the day, and lights should be turned off at night. Melatonin is a hormone that plays a significant role in the cycle of sleep and wakefulness, and if its secretion is impaired, it leads to sleep disorders and a higher incidence of POD. Randomized studies have shown that exogenous melatonin supplementation can reduce the development of delirium in ICU in cardiac surgery patients [28, 29].

Another non-pharmacological prevention measure is noise reduction, which means reducing the volume of devices, alarms, telephones, and loud conversation both among the staff and the patients. The World Health Organization has prescribed the upper limit of noise in hospitals, which is 35 dB during the day and 30 dB at night [7, 26, 27]. Early mobilization of patients plays an important role in postoperative recovery, therefore special attention should be paid to it. Patients should start feeding themselves and taking care of personal hygiene as early as possible [27–31]. Family engagement in patient's recovery and early contact with relatives represents an addition to the aforementioned ABCDE protocol. The latest research demonstrated that the ABCDEF protocol is more complete and has showed positive short term clinical outcomes including lower mortality, shorter stay in ICU and shorter hospitalization, as well as lower incidence of POD [32, 33]. Alternative methods include music

therapy and massage. Studies in which relaxing music was played during mechanical ventilation and sedation showed that these patients experienced less anxiety and reduced physiological response to stress [7, 10, 13].

It should also be noted that Emoto et al. proved that the new DELTA - Delirium Team Approach program, reduces the incidence of POD in cardiovascular surgery from 53% to 37%. This program consists of three components: education of medical staff, rational use of drugs that induce POD, as well as screening and assessment of risk factors for the development of POD. What is most remarkable about this program is its simplicity. The use of these very simple principles is associated with a significant reduction in cognitive impairment after cardiovascular surgery [31].

Conclusion

It has already been proven that the identification of high-risk patients, prevention and routine evaluation of the development of delirium in intensive care units are the most important points in reducing the incidence of postoperative delirium. Although protocols for the prevention of delirium have been established, studies examining their application in everyday practice are lacking. Future research should be based on a more detailed examination of the effectiveness and safety of pharmacological prevention, as well as non-pharmacological measures such as the policy of open visits in intensive care units, digital contact with family and friends, as well as alternative methods. Certainly, a multidisciplinary approach to the recovery of patients with proven postoperative delirium is very important, in order to reduce disability and permanent consequences.

Prevention and recognition of postoperative delirium should be of much greater importance for the health system and one of the key points in improving perioperative care of patients, reducing disability, and thus economic prosperity of both individuals and institutions.

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UPUTSTVO ZA AUTORE

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

Od 1. januara 2013. godine *Medicinski pregled* je počeo da koristi usluge *e-Ur* − Elektronskog uređivanja časopisa. Svi korisnici sistema − autori, recenzenti i urednici, moraju biti registrovani korisnici sa jednom elektronskom adresom.

Korisnici časopisa treba da se registruju na adresi:
http://aseestant.ceon.rs/index.php/medpreg/user/register

Prijava rada treba da se učini na adresi:
http://aseestant.ceon.rs/index.php/medpreg/

U postupku prijave neophodno je da se pošalje saglasnost i izjava autora i svih koautora da rad nije delimično ili u celini objavljen ili prihvaćen za štampu u drugom časopisu.

Elektronsko uređivanje časopisa obezbeđuje korišćenje sistema *CrossCheck*, koji prijavljene radove automatski proverava na plagijarizam i autoplagijarizam. Autori ne bi smeli da pošalju isti rad u više časopisa istovremeno. Ukoliko se to desi, glavni urednik časopisa *Medicinski pregled* ima pravo da rad vrati autorima bez prethodnog slanja rada na recenziju; da odbije štampanje rada; da se obrati urednicima drugih časopisa u koje je rad poslat ili da se obrati direktoru ustanove u kojoj su autori rada zaposleni.

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

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

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

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

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

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

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

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

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

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

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

Priprema rukopisa

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

Propratno pismo:

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

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

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

Rukopis

Opšta uputstva

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

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

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

2. Sažetak

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

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

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

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

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

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

3. Tekst članka

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

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

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

Uvod

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

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

∗ Organizacija kao autor

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

∗ Bez autora

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

∗ Volumen sa suplementom

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

∗ Sveska sa suplementom

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

∗ Sažetak u časopisu

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

Knjige i druge monografije

∗ Jedan ili više autora

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

∗ Urednik (urednici) kao autor (autori)

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

∗ Poglavlje u knjizi

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

∗ Zbornik radova sa kongresa

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

∗ Disertacija

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

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

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

∗ Monografija u elektronskom formatu

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

∗ Kompjuterska datoteka

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

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

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

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

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

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

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

∗ *An organization as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

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

∗ *An issue with supplement*

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

∗ *A summary in a journal*

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

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

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

∗ *A chapter in a book*

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

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

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

∗ *Monographs in electronic format*

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

∗ *A computer file*

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

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.