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ELECTIVE CAESAREAN SECTION AND MODALITIES OF ANTIBIOPROPHYLAXIS

Predrag Vukomanović[1,2], Jelena Milošević-Stevanović[1,2], Milan Stefanović[1,2], Aleksandra Petrić[1,2], Ranko Kutlešić[1,2], Milan Trenkić[1,2], Sonja Pop-Trajković[1,2], Dejan Mitić[1,2], Aleksandar Živadinović[2], Vladimir Cvetanović[2], Ivana Conić[3]

Caesarean section (CS) is an often necessary operation widely used in obstetrics. After CS, infectious morbidity is the most common complication. The study aimed to compare the effectiveness of a single dose of ceftriaxone intraoperatively (2.0 g) with a three-day regimen of ceftriaxone postoperatively (2.0 g/24 h) in the prevention of postoperative complications in patients undergoing elective CS. This research included 68 patients for an elective CS. Patients were divided into two groups of 34 subjects randomly assigned to receive ceftriaxone in the form of a single dose (2.0 g) intraoperatively, or three-day ceftriaxone (2.0 g/24 h) postoperatively. A CS was performed using standard technique. Postpartum complications were recorded. An examination, microbiological diagnosis, and adequate dressing of the wounds were performed. At discharge, patients were instructed to report any irregularities. The results were statistically processed. Postpartum complications occurred in 7 patients in the first group, 5 patients had fever and 2 did not have fever. Of the 5 febrile patients, 3 had wound infection, 1 endometritis, and 1 transient postpartum febrility. In the second group, 9 patients had complications, 6 patients had fever, and 3 had no fever. Of the 6 patients with fever, 3 had wound infection, 1 had endometritis, 1 had urinary infection, and 1 transient postpartum febrility. There was no reduction in the incidence of postoperative morbidity in patients who received ceftriaxone in a three-day regimen. Results showed that the three-day use of antibiotics was unjustified because it did not reduce the risk of postoperative morbidity. The prophylactic administration of antibiotics in elective CS is the most adequate modality of antibiotic administration. Research indicates the benefit of intraoperative monodose administration after umbilical cord clamping.

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Key words: *antibiotic prophylaxis, caesarean section, endometritis, infective morbidity*

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Introduction

Caesarean section is the most common, largest and often necessary operation widely practiced in obstetrics. Over the past three decades, the cesarean rate has been steadily increasing and could have reached up to 50% in some centers (1). Infectious morbidity is the most common complication after the caesarean section with reported rates ranging from 18% to 83%, while being less than 10% for vaginal delivery (2).

Antibioprophylaxis in surgery is an effective method for preventing and reducing the risk of surgical site infections (2).

Prophylactic use of antibiotics has reduced the incidence of endometritis by two-thirds to three-quarters, and therefore their routine use in all patients undergoing cesarean section is justified. While the risk of postoperative infection after caesarean section is higher for emergency than for elective cesarean sections, prophylactic antibiotic use was shown to reduce both postoperative endometritis and wound infection after an elective cesarean delivery (3).

Penicillins, cephalosporins, metronidazole, and combinations of clindamycin and gentamicin were used for prophylaxis. There does not appear to be a clear advantage of any of these antibiotics over the others (4–6). There are data that the combination of penicillin and aminoglycosides significantly reduces febrile morbidity in a higher percentage compared to the use of penicillin

alone. The duration of antibiotic prophylaxis and the modality of therapy (one or two antibiotics) are still under discussion. Which antibiotics should be used for prophylaxis and which is the best prophylactic regimen has not yet been defined and determined in detail (7).

Aim

This study aimed to compare the effectiveness of a monodose (2.0 g) of ceftriaxone intraoperatively with a regimen of three-day administration of ceftriaxone postoperatively (2.0 g/24 h) in the prevention of postoperative complications (endometritis, wound infection and other febrile morbidity) in patients undergoing elective caesarean section.

Materials and Methods

This research was conducted at the Department of Perinatology, Clinic for Gynecology and Obstetrics, University Clinical Center Niš. The study included 68 patients who were scheduled for elective caesarean section for various reasons. The patients were divided into two groups of 34 subjects each. The patients were excluded from the study if they had received antibiotics before surgery, had any visible infection or fever before and during surgery, or were allergic to the antimicrobial medicine used.

The patients were divided into two groups, which were assigned to receive either ceftriaxone intravenously in the form of a monodose (2.0 g) intraoperatively, or ceftriaxone in a three-day regimen intravenously postoperatively (2.0 g/24 h). All caesarean sections were performed using standard techniques, and all post-operative care followed standard clinical practice. Also, consent to participate in the study was obtained from all patients. The following postpartum complications were noted:

1. Postoperative febrile morbidity, defined as an axillary temperature of 38 degrees Celsius measured on two occasions, four hours apart

2. Postoperative infection including:

• Endometritis

• Wound infection

3.Other febrile morbidity (urinary tract infection, respiratory infections).

When febrile morbidity was identified, the patients were examined to reveal a potential source of infection (upper respiratory tract, breast, abdominal and pelvic infections). A general urine examination with urine culture, blood count with leukocyte formula and C-reactive protein (CRP) were performed. Wound swabs and lochia were sent for bacteriological examination and sensitivity testing when necessary. Wound infections were treated with local cleaning, hydrogen, saline irrigation and povidone-iodine solution. Upon release from the hospital, the patients were advised to contact their chosen doctor (gynecologist) immediately if they developed a high temperature, noticed a change in the appearance of the wound, pain or discomfort in the lower abdomen or wound area, or felt foul-smelling lochia.

The obtained results were statistically processed using X, Student's T-test and Fisher's test. A p-value < 0.05 was considered statistically significant.

Results

A total of 68 patients included in the study were divided into two groups: the first group of 34 patients received ceftriaxone as a monodose (2.0 g) intraoperatively, and the second group of 34 patients who received the same drug (cefriaxone) for three days (2.0 g/24 h). The groups were similar in terms of age, parity, gestational age, weight, preoperative hemoglobin, and body temperature (Table 1).

Indications for caesarean section were similar in both groups. The patients who had a previous caesarean section made up more than half of the subjects in both groups (Table 2).

The approach to opening the abdomen, duration of surgery, intraoperative complications, intraoperative blood loss, and the abdominal closure technique were practically the same in both examined groups and without statistical significance (Table 3).

Postpartum complications occurred in 7 patients who received a monodose of ceftriaxone intraoperatively (2.0 g): out of these 7, 5 patients had fever and 2 did not. Out of 5 patients with fever, 3 had wound infection, 1 had endometritis and 1 had transient postpartum fever. Two patients without fever had a wound infection.

Considering the second group, that is, the group of patients who received ceftriaxone three days postoperatively (2.0 g/24 h), 9 of them had postoperative complications. There were 6 patients with fever, while 3 of them were without it. Out of 6 patients with fever, 3 had wound infection, 1 had endometritis, 1 had urinary infection, and 1 had transient postpartum febrility (Table 4).

Wound infection was the most common type of postoperative morbidity in both groups, with a prevalence of 14.7% in group I and 17.64% in group II. Microbiologically confirmed wound infection in group I was 8.82%, and in group II was 11.76%. *Staphylococcus aureus* was the most frequently isolated bacterium, while *Enterococcus faecalis*, *Streptococcus B* and *Escherichia* coli were isolated in a smaller number of patients. Although there was no difference in morbidity, patients who received a single dose of ceftriaxone intraoperatively (2.0 g) were hospitalized one day less, which is statistically significant (Table 5).

Table 1. Reproductive and biohumoral characteristics

	Ceftriaxone monodose intraoperatively (2.0 g) n = 34				Ceftriaxone postoperatively for three days (2.0 g / 24h) n = 34			
Age (years)	28.6 ± 1.35				28.1 ± 1.44			
Parity	Primipara		Multipara		Primipara		Multipara	
	12	35.29%	22	64.7%	9	26.47%	25	73.53%
Gestational age (weeks)	38.6 ± 1.12				38.67 ± 1.15			
Body wight (kg)	78.8 ± 5.34				79.1 ± 6.17			
Preoperative HgB (g/L)	95.6 ± 7.49				95.9 ± 7.19			
Body temperature	36.6 ± 0.12				36.7 ± 0.11			

Table 2. Indications for caesarian section

	Ceftriaxone monodose intraoperatively (2.0 g) n = 34		Ceftriaxone postoperatively for three days (2.0 g/24 h) n = 34	
Previous caesarian section	24	70.59%	25	73.52%
Fetal distress	3	8.82%	2	5.88%
Maternal Distress	1	2.94%	2	5.88%
Malpresentation	5	14.7%	3	8.82%
Other	1	2.94%	2	5.88%

Table 3. Surgical data

	Ceftriaxone monodose intraoperatively (2.0 g) n = 34		Ceftriaxone postoperatively for three days (2.0 g/24 h) n = 34	
Pfanennstiel section	31	91.17%	32	94.12%
Median section	3	8.83%	2	5.88%
Duration fo surgery (min)	48.55 ± 8.31		51.12 ± 5.42	
Adhesions	5	14.7%	3	8.82%
Abdominal closure	Single suture	Dermodermal suture	Single suture	Dermodermal suture
	3 8.82%	31 91.18%	2 5.88%	32 94.18%
Atony	0	0%	1	2.94%
Blood loss	1	2.94%	1	2.94%

Table 4. Postpartal morbidity

	Ceftriaxone monodose intraoperatively (2.0 g) n = 34				Ceftriaxone postoperatively for three days (2.0 g/24 h) n = 34			
Postpartum morbidity	n = 7 (20.58%)				n = 9 (26.47%)			
	With t°		Without t°		With t°		Whitout t°	
	5	14.7%	2	5.88%	6	17.65%	3	8.82%
Wound infection	3	8.82%	2	5.88%	3	8.82%	3	8.82%
Endometritis	1	2.94%	0	0%	1	2.94%	0	0%
Urinary infection	0	0%	0	0%	1	2.94%	0	0%
Transient postpartum fever	1	2.94%	0	0%	1	2.94%	0	0%

Table 5. Maternal outcome

	Ceftriaxone monodose intraoperatively (2.0 g) n = 34		Ceftriaxone postoperatively three for days (2.0 g/24 h) n = 34	
Resuture	1	2.94%	1	2.94%
Days of hospitalisation*	4		5	
Microbiologically diagnosed wound infection	3	8.82%	4	11.76%
Change of antibiotics	1	2.94%	1	2.94%

*p-value <0.05- statistically significant

Discussion

According to the Centers for Disease Control and Prevention (CDC) in Atlanta, surgical site infections are considered an important global problem. Surgical site infections are associated with a longer duration of treatment, the need for additional surgical procedures, and a higher rate of postoperative mortality and morbidity. International guidelines and National Clinical Practice Guides provide clear guidelines and recommendations for the proper implementation of antibiotic prophylaxis. Irrational and inadequate use of antibiotics is one of the main drivers of the development of bacterial resistance with the appearance of numerous side effects of antibiotics and increased overall treatment costs (6, 8).

Although prophylactic antibiotic administration has been shown to reduce the incidence of postoperative infectious morbidity after cesarean delivery, the most effective administration regimens have not been determined (7). This study on the prophylactic use of antibiotics in elective caesarean section included 68 patients to compare the risk of postoperative morbidity in two different modalities of antibiotic use. Our research compared two regimens of prophylactic antibiotic administration: intraoperative administration of ceftriaxone monodose (2.0 g) versus three-day administration of the same drug in a dose of 2.0 g/24 h.

The prevalence of febrile morbidity in 35.29% of patients after elective caesarean section was comparable to the data from the literature (8, 9). Febrility can occur after any surgical procedure, and a subfebrile temperature after elective caesarean section is not necessarily an indicator of infection. Febrility with the presence of infection would require initiation of an empiric regimen of antibiotic therapy before the results of wound swabs or lochia are available (10).

Endometritis is another indicator of postoperative cesarean infection. In most studies, as in this one, it is clinically diagnosed based on elevated temperature, uterine tenderness, compromised uterine involution, and abnormal lochia. The low rate of endometritis in this study can be explained by the fact that patients who delivered by elective caesarean section had intact fetal membranes and did not have cervicovaginal infection or, if they did, there was not a sufficient number of pathogenic microorganisms in the vagina to colonize the endometrium (11–13).

Wound infection was the most common postpartum complication in both groups. Although the prophylactic application of antibiotics did not reduce the rate of wound infection, the patients from the first group stayed in the hospital one day shorter. Wound infection and endometritis contributed to prolonging the hospital stay by more than one week in all cases (14). Surgical preparation of the surgical field and failure in surgical technique and hemostasis can affect wound infection. The majority of infected wounds did not require the application of additional antibiotics but were treated with a local cleaning with hydrogen, irrigation with saline and povidone-iodine solution (15).

Conclusion

The study showed that there was no reduction in the incidence of postoperative morbidity of any etiology in patients who received ceftriaxone in a three-day regimen. Adequate surgical technique and adequate surgical hemostasis are probably of greater importance in reducing postoperative morbidity than the therapeutic use of antibiotics. Accordingly, it is

important to emphasize that the three-day use of antibiotics is unjustified because it does not reduce the risk of wound infections, postoperative endometritis, urinary infections and other causes of febrility. Prophylactic administration of antibiotics in the form of a single dose intraoperatively in elective caesarean section is the most adequate modality of antibiotic administration and is therefore recommended as a routine practice. This study indicates the benefit of intraoperative monodose administration after umbilical cord clamping.

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ELEKTIVNI CARSKI REZ I MODALITETI ANTIBIOTIČKE PROFILAKSE

Predrag Vukomanović[1,2], Jelena Milošević Stevanović[1,2], Milan Stefanović[1,2], Aleksandra Petrić[1,2], Ranko Kutlešić[1,2], Milan Trenkić[1,2], Sonja Pop Trajković[1,2], Dejan Mitić[1,2], Aleksandar Živadinović[2], Vladimir Cvetanović[2], Ivana Conić[3]

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Carski rez (CR) predstavlja neophodnu operaciju koja se široko primenjuje. Najčešća komplikacija nakon CR-a jeste infektivni morbiditet. Cilj ovog istraživanja bio je da se uporedi efikasnost primene monodoze ceftriaksona aplikovanog intraoperativno (2,0 g) sa režimom trodnevnog ceftriaksona aplikovanog postoperativno (2,0 g / 24 č) sa ciljem prevencije postoperativnih infektivnih komplikacija pri elektivnom CR-u. Studija je obuhvatila 68 pacijentkinja kod kojih je planiran elektivni CR. Pacijentkinje su podeljene u dve grupe u kojima su bile po 34 ispitanice. Ispitanice iz jedne grupe primale su ceftriakson u vidu monodoze (2,0 g) intraoperativno, dok su ispitanice iz druge grupe primale ceftriakson postoperativno u trodnevnom režimu (2,0 g / 24 č). CR je urađen standardnom tehnikom. Zabeležene su postpartalne komplikacije. Urađeni su pregled i mikrobiološka dijagnostika, a rane su tretirane na odgovarajući način. Pacijentkinje su prilikom otpusta bile upućene da prijave febrilnost, promenu izgleda rane i ostale nepravilnosti. Rezultati su statistički obrađeni. Postpartalne komplikacije javile su se kod sedam pacijentkinja u prvoj grupi: pet pacijentkinja je imalo povišenu telesnu temperaturu, dok je kod dve pacijentkinje, čija telesna temperatura nije bila povišena, došlo do infekcije rane. Od pet pacijentkinja sa povišenom telesnom temperaturom, kod tri pacijentkinje zabeležena je infekcija rane, kod jedne endometritis, a kod jedne tranzitorna postpartalna febrilnost. Do komplikacija je u drugoj grupi došlo kod devet pacijentkinja; šest pacijentkinja imalo je povišenu telesnu temperaturu, dok su tri pacijentkinje bile bez povišene telesne temperature. Od šest pacijentkinja sa povišenom telesnom temperaturom, kod tri pacijentkinje došlo je do infekcije rane, jedna pacijentkinja je imala endometritis, jedna urinarnu infekciju, a jedna tranzitornu postpartalnu febrilnost. Studija je pokazala da ne postoji smanjenje incidencije postoperativnog morbiditeta bilo koje etiologije kod pacijentkinja koje su primale ceftriakson u trodnevnom režimu. Trodnevna upotreba antibiotika nije opravdana budući da ne smanjuje rizik od postoperativnog morbiditeta. Profilaktička primena antibiotika u elektivnom CR-u predstavlja najadekvatniji modalitet primene antibiotika. Ovo istraživanje ukazuje na korist primene monodoze antibiotika intraoperativno nakon klemovanja pupčane vrpce.

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***Ključne reči**: antibiotička profilaksa, carski rez, endometritis, infektivni morbiditet*

Original article

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IMPLANTATION OF THE MICRA ELECTRODELESS MINIATURE ARTIFICIAL HEART GUIDE: EXPERIENCE AND CASE SERIES

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Advances in technology and medicine have brought new solutions to challenges encountered in everyday practice. Since the implantation of the first epicardial pacemaker about half a century ago, the refinement and miniaturization process of the device has resulted in the latest generation of artificial heart guides (VVS), which, with the help of sophisticated technology, overcomes the obstacles of conventional devices. The Micra pacemaker is a single-chamber device that weighs 2 g, has a volume of 0.8 cm², and is capsule-shaped, measuring 25.9 mm in length and 6.7 mm in outer diameter. The size of the device not only does not limit the functions of the device but also represents a significant advantage and novelty in the world of implantable devices.

This paper presents a series of the first 6 cases of transcatheter transvenous implantation of a miniature artificial heart guide Medtronic Micra (Medtronic, Minnesota, USA) device for permanent cardiac stimulation at the University Clinical Center Niš.

The Micra system without electrodes has proven in practice to be a safe and effective option for permanent cardiac pacing in adult patients. In certain patients in whom the usual venous access is impossible (multiple sternotomies, thoractomies, congenital or acquired anomalies), it has become the most useful alternative in the case of indication for permanent pacing.

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Key words: *Micra pacemaker, pacemaker implantation, complications*

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Introduction

Advances in technology and medicine have brought new solutions to challenges encountered in everyday practice. Since the implantation of the first epicardial pacemaker about half a century ago, the refinement and miniaturization process of the device has resulted in the latest generation of artificial heart guides (VVS), which, with the help of sophisticated technology, overcomes the obstacles of conventional devices. The Micra pacemaker is a single-chamber device that weighs 2 g, has a volume of 0.8 cm², and is capsule-shaped, measuring 25.9 mm in length and 6.7 mm in outer diameter. The size of the device not only does not limit the functions of the device, but also represents a significant advantage and novelty in the world of implantable devices. This system retains all the features of existing electrode systems (adaptive guidance concerning frequency and automatic threshold adjustment to extend battery life) (1). Micra (Medtronic, USA) is a single-chamber pacemaker system without electrodes; it is directly implanted transvenously into the right ventricle and passively fixed (2). The technology of VVS implanted transvenously directly into the ventricle was developed to compensate for the shortcomings of traditional VVS with electrodes. Although widely applicable, VVS with electrodes is not always implantable due to difficulties related to anatomical differences between patients, chronic infections of the device bed, and mediastinal tumors that complicate lead placement (3). Also, the presence of a traditional device is visible to the naked eye and the installation results in a scar, which is an aesthetic problem predominantly in younger patients. A less invasive approach favors older patients and facilitates recovery, does not limit movements and disrupts the quality of life less, while not detracting from efficiency (2, 3).

Aim

This paper presents a series of the first 6 cases of transcatheter transvenous implantation of

a miniature artificial heart guide Medtronic Micra (Medtronic, Minnesota, USA) device for permanent cardiac stimulation at the University Clinical Center Niš.

Materials and Methods

At the beginning of 2023, the first 6 Micra pacemakers were implanted at the Cardiology Clinic of the University Clinical Center in Niš. In this series, all patients were male with a mean age of 77 (SD 3.56) years. All patients had indications for implantation of a permanent artificial heart guide due to proven bradycardia and pauses in cardiac work. In 5 out of 6 patients, the basic rhythm was atrial fibrillation (AF), while in 1 patient, a tachycardia-bradycardia disorder was proven. All patients were elderly, of medium osteomuscular build. In the preparatory phase, anamnestic data were collected, complete basic and supplementary diagnostics were performed (electrocardiogram, echocardiographic examination, biohumoral status, antibodies to hepatitis B and C, HIV, treponema pallidum, INR, aPPT and coagulation factor screening). In order to plan the intervention and prevent vascular complications, all patients underwent a color-doppler ultrasound examination of the blood vessels of the femoral region with reference to the patency, diameter and length of the right femoral vein. Patients did not consume food or liquids for 12 hours before the intervention. Interventions were performed under local infiltration anesthesia (with a combination of Lidocaine and Marcaine). In addition, each patient received 0.2 mg Fentanyl IV (4).

After scarification of the access site, a puncture of the femoral vein was performed, and the intravascular position of the puncture needle was verified by aspiration of venous blood and a good return jet. A J guide wire was placed through the puncture needle and advanced into vena cava inferior. After securing the access road, dilation of the access site was performed by successive changes of dilators of increasing dimensions 10-12-14-16-18-F, and the advancement of larger dilators was supported by super stiff wires for better support. A 27-F outer diameter (23-F internal diameter) Micra system implantation catheter was advanced to the right ventricle by manual advancement, and then the tip of the catheter was directed toward the mid-septal area using a fluoroscopy-guided curve-making mechanism on the system's handle. After achieving an adequate position (verified by giving contrast through the system in at least two positions (RAO and LAO 30), the device was positioned by the release mechanism towards the central part of the septum of the right ventricle and fixed to the trabeculae by fixing at least 2 of the 3 apical hooks. An adequate position was achieved on the first attempt in 5 out of 6 cases. The parameters were measured using the telemetry reading of the device. The recommended threshold of < 1 mV, at 0.25 ms was achieved in all patients. After adequate apposition, fixation and obtaining stable impedance and satisfactory parameters, the device was released. The system was constructed so that until the final release, repositioning of the device could be carried out unhindered until adequate parameters were achieved. After the device was implanted, the implantation catheter was inserted, and hemostasis was achieved with a figure-of-eight suture, manual compression for about 20 minutes and compression with a gauze roll for about 4 hours post-intervention. Out of 6 patients, 1 patient developed a minor inguinal hematoma that healed spontaneously in the following weeks.

Patient characteristics, indications, implantation details, and implantation parameters at 1-month follow-up are given in Table 1.

Table 1. Patient characteristics, measured and monitored parameters

Patient	1.	2.	3.	4.	5.	6.
Age (years)	74	74	75	76	84	79
Indication for pacemaker implantation	Permanent AF with 8 defined pauses over 2 sec (longest 3.88 sec)	Permanent AF with 3 defined pauses over 2 sec and average night frequency 34 (longest 2.3 sec)	Sinus node disease with 10 defined pauses longer than 2 sec and episodes of AF	Permanent AF, average frequency during the day 47/min, frequent syncope	Syncope, sinus node disease (minimum frequency 30), transient AV block II degree, episodes of AF	Permanent AF, a large number of pauses in the heart's work longer than 2 seconds
Comorbidities	Hypertension for the past 10 years, benign prostatic hyperplasia, type II diabetes	Type II diabetes	Type II diabetes, arterial hypertension, benign prostatic hyperplasia	Hypertension, benign prostatic hyperplasia	Arterial hypertension	

	chronic obstructive pulmonary disease, asthma					
Implantation-site	The central part of the right ventricular septum	1. Apex of the right ventricle 2. Apical part of the septum of the right ventricle	The apical part of the septum of the right ventricle	The apical part of the septum of the right ventricle	The central part of the right ventricular septum	Apex of the right ventricle
Threshold at implantation (on 0.24 ms)	0.4 V	0.5 V	0.4 V	1.1 V	1.3 V	0.8 V
Impedance at implantation	650 Om	1.>3000 Om 2. 580 Om	485 Om	920 Om	990 Om	399 Om
The height of R wave at implantation	6.8 mV	11.9 mV	10.2 mV	7.8 mV	14.5 mV	8.7 mV
Threshold at 1-month follow-up	0.6 mV	0.8 mV	0.5 mV	0.8 mV	1.0 mV	0.8 mV
Impedance at 1-month follow-up		600 Om	550 Om	800 Om	600 Om	500 Om
The height of R wave at 1-month follow-up	7 mV	11 mV	11.2 mV	8.9 mV	12.2 mV	8.5 mV
Complications	without	without	without	Hematoma at the puncture site	without	without
Duration of the procedure	70 min	45 min	90 min	60 min	50 min	40 min
Duration of the fluoroscopy	26 min	17 min	38 min	22 min	20 min	15 min
Number of implantation attempts	2 (inadequate fixation)	2 (impedance > 2000 Om)	1	1	1	1

Discussion

The elimination of leads and pockets by the introduction of leadless pacemakers provides potential advantages over conventional transvenous systems. Lead and pocket-related complications are the major complications after implantation of standard lead pacemaker systems.

Pacing electrodes and a pacemaker as a foreign body of large volume are an ideal ground for the emergence of infections that usually persist for a long time, representing a therapeutic problem and often requiring a complete extraction of the system. After the extraction of the system, the venous access path is often changed by fibrosis, narrowed, and even during the eradication of the infection, the next system with an electrode cannot be adequately placed. Common causative agents of lodge infections such as *S. Aureus, S. Epidermidis* can create biofilms on implanted materials that are a source of reinfections, so even after the reimplantation of new systems, infections recur and potentially progress to endocarditis as well as systemic infections. In such cases, the Micra pacemaker is a necessity and the only possible solution for permanent heart stimulation (2, 4).

Conventional cardiac pacing devices are associated with significant complications that are not uncommon. It is estimated that 9.5−12.6% of interventions are related to complications. Complications are divided into local lodge complications, lead-related complications, and systemic complications. The most common local complications are hematomas, bed infections, skin erosions and decubitus changes and difficult healing. In the FOLLOW-PACE study, the highest percentage of early (9.2%) and late complications (12.6%) was recorded. The frequency of infections after the implantation of conventional devices, which reaches 16.4% in some centers, is particularly noteworthy. However, large centers record about 1% of lodge infections in the first 3 months after implantation (5, 6).

During the implantation of conventional pacemaker systems with an electrode, there is a

constant risk of effusion caused by perforation of the myocardium with the electrode, which is about 1.2% (7).

Micra's small size, reduced surface area and lack of an electrode significantly reduce the risk of early infection after implantation (8). During long-term follow-up, these characteristics of the device condition early encapsulation and stabilization, which additionally ensures the effectiveness of pacing (8, 9).

An early report on Micra implantation showed a very high procedural success rate of 100% (10). This success rate was reduced to 99.2% in a study involving 725 patients, where 719 patients had the device successfully implanted. Also, this study showed a high rate of device efficiency of 98.3% and safety of 96.0%, which far exceeds the expected values of the mentioned parameters. The septal position of the device has also been shown to bring advantages in terms of reducing mechanical complications (1).

In a study by El-Chami et al. (11), the effectiveness of the Micra pacemaker after implantation was investigated in 1801 patients. Data obtained from the IDE study (Investigational Device Exemption) (12) and the PAR registry (Post-Approval Registry) (13) showed exceptional safety and efficacy. Therefore, the study by El-Chami et al. aimed to substantiate the evidence and confirm on a live model the efficacy and safety of the device. Device implantation was successful in 99.1% of cases. Within 12 months, the complication rate was 2.7%, and the overall risk of major complications was 63% lower than in patients with conventional transvenous systems. Only 3 patients had a reported infection that did not result in device complications or lead to system extraction.

Due to the mentioned advantages, this system is also applied in the pediatric population to patients with multiple open heart interventions in whom it is not possible to place a pacemaker system with electrodes (14).

Conclusion

The Micra system without electrodes has proven in practice to be a safe and effective option for permanent cardiac pacing in adult patients, and in certain patients in whom the usual venous access is impossible (multiple sternotomies, thoractomies, congenital or acquired anomalies) it has become the most useful alternative in the case of indication for permanent pacing.

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IMPLANTACIJA *MICRA* MINIJATURNOG PEJSMEJKERA BEZ ELEKTRODA: ISKUSTVO I SERIJA SLUČAJEVA

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Napredak tehnologije i medicine doneo je nova rešenja za izazove sa kojima se medicinski radnici susreću u svakodnevnoj praksi. Nakon ugradnje prvog epikardijalnog pejsmejkera pre oko pola veka, proces tehničkog napretka i minijaturizacije uređaja rezultirao je najnovijom generacijom veštačkih vodiča srca (VVS), koji uz pomoć sofisticirane tehnologije prevazilazi prepreke konvencionalnih uređaja. *Micra* pejsmejker je jednokomorni uređaj težak dva grama, čija zapremina iznosi 0,8 cm^2. U obliku je kapsule, ima dužinu od 25,9 mm i spoljašnji prečnik od 6,7 mm. Ne samo da veličina uređaja ne ograničava funkcije uređaja već i predstavlja značajnu prednost i novinu u svetu implantabilnih uređaja.

U ovom radu je prikazana serija prvih šest slučajeva transkateterske transvenske implantacije minijaturnog aparata, odnosno pejsmejkera *Medtronic Micra* (Medtronic, Minesota, SAD) za trajnu srčanu stimulaciju u Univerzitetskom kliničkom centru u Nišu.

Micra sistem bez elektroda pokazao se u praksi kao bezbedna i efikasna opcija za trajni pejsing kod odraslih bolesnika. Kod pojedinih bolesnika kod kojih uobičajeni venski pristup nije moguć (zbog višestruke sternotomije, toraktomije, urođene ili stečene anomalije) postao je najkorisnija alternativa u slučaju indikacije za trajni pejsing.

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***Ključne reči**: Micra pejsmejker, ugradnja pejsmejkera, komplikacije*

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COAGULOPATHY AND CORONAVIRUS DISEASE 2019

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Interest in coronavirus disease 2019 (COVID-19) in the world of science is constant. Pathogenesis is the subject of many studies, and coagulopathy occupies an important place in research. In our study, blood samples were collected from 131 patients treated for SARS-CoV-2 infection in University Clinical Center Kragujevac. Blood was sampled on the day of admission, and the disease course was monitored. We concluded that our participants do not meet the criteria for disseminated intravascular coagulation (DIC). We showed the statistical significance of platelet count, prothrombin time value and DIC score concerning the form and outcome of the disease. Patients with a critical form of the disease, as well as those who died, had significantly lower values of the number of platelets and significantly higher values of the DIC score.

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Key words: *coronavirus disease, disseminated intravascular coagulation, disease form, disease outcome*

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Introduction

COVID-19 is a pandemic disease caused by the SARS-Cov-2 virus (1). According to the criteria of the World Health Organization from September 2022, the disease is classified into three forms: critical (critical COVID-19), severe (severe COVID-19) and mild (non-severe COVID-19) (2). It was found that the main prognostic factors for a poor outcome were obesity, hypertension, diabetes and older age (3). Further, data from the literature emphasizes the importance of this virus in contributing to hypercoagulability and thrombosis (4). The most common cause of death in COVID-19 is respiratory failure, but also a hemostasis disorder followed by immune and inflammatory reactions (cytokine storm) (5, 6). Thrombosis and coagulopathy significantly contribute to disease progression and mortality (6). This infection is associated with multiple laboratory abnormalities from the onset of the disease (7). In addition to changes in hemostasis, changes in the leukocyte formula (lymphopenia, neutrophilia, changes in the number of monocytes), and other dysregulations in hematopoietic system may occur (8). COVID-19 is associated with a high rate of micro and macrothrombosis. The differences between coagulopathy caused by the SARS-CoV-2 virus and coagulopathy caused by sepsis remain a matter of debate (9). Unlike classic thrombosis, which is based on uncontrolled activation of the hemostasis system, COVID-19 thrombosis is a combination of endothelial dysfunction, increased circulating procoagulant proteins, platelet hyperreactivity, and altered inflammatory cell function, indicating immune-mediated thrombosis in patients with COVID-19 (10). In coagulopathy associated with this virus, initial laboratory tests show high fibrinogen and D-dimer values, decreased platelet count, and non-significantly prolonged prothrombin/activated partial thromboplastin time (PT/aPTT). In conventional DIC, fibrinogen values are reduced, and bleeding times are prolonged (9, 10). Autopsies showed that multiple thrombi, rich in platelets and fibrin, were present in the small blood vessels of the lungs in addition to the large blood vessels, which indicates that the coagulopathy is present at the local level, but there is also diffuse alveolar damage (11, 12). In COVID-19 ARDS, severe damage of vascular endothelium and presence of large thrombi have been demonstrated. The degree of microthrombosis was 9 times higher in COVID-19 than in influenza, and the degree of angiogenesis was 2.7 times higher (6, 13). DIC and increased D-dimer values are prognostic parameter of poor outcome and a frequent finding in non-survivors (14, 15), also changes in platelet-

to-lymphocyte ratio (PLR) during hospitalization, showed a possible correlation with cytokine storm (16). Changes in hemostasis are certainly a bad indicator of coronavirus disease. Most often, an increased value of D-dimer, a decreased level of fibrinogen, a slight decrease in the number of platelets and a prolonged prothrombin time are registered (14). Many retrospective studies highlight the importance of D-dimer and connection of its levels to disease severity in patients with COVID-19 (mild COVID-19 patients exhibited significantly lower levels of D-dimer compared to moderate COVID-19 patients) (17).

Aim

Our study aimed to analyze coagulopathy in patients treated for COVID-19 through the diagnostic algorithm for DIC proposed by the International Society on Thrombosis and Hemostasis (ISTH) (18). We also want to examine whether any of the hemostasis parameters included in this score affect, and to what extent, the clinical outcome of the disease.

Materials and Methods

In this prospective observational study blood samples were collected from 131 patients who, infected with SARS-CoV-2 virus for the first time, were treated in the University Clinical Center Kragujevac from March to August 2021. Inclusion criteria: patients of both sexes older than 18 years, signed informed consent to participate in the study, positive findings for SARS-CoV-2 (rapid Ag test or PCR test) and presence of any of the three forms of the disease defined by WHO criteria. Exclusion criteria: patients previously treated for COVID-19, pregnant women or patients with conditions or diseases that affect the values of the examined parameters of hemostasis (taking anticoagulant therapy, suffering from chronic inflammatory diseases, hematological diseases or other malignant diseases). Blood was sampled on the day of admission and the course of the disease was monitored. Two tubes of blood (of 3 ml each) were sampled. One tube with EDTA (ethylenediaminetetraacetic acid), the other with citrate, the blood was not frozen. The analyses were performed immediately in the hematology laboratory of the Hematology Clinic of the University Clinical Center Kragujevac on a standardized machine using ALCTOPCTS300 (Instrumentation Laboratory) and UniCel DxH 600 Coulter Cellular Analysis System (Beckman Coulter). To calculate the DIC score, the diagnostic algorithm of the ISTH was used, where scoring was performed as follows: number of platelets (> 100—0 point, < 100—1 point and < 50—2 points), D-dimer value (normal: ≤ 0.5 ng/ml—0 point, moderate increase: 0.5–3 ng/ml—2 points, severe increase: > 3 ng/ml—3 points), PT (extended for < 3 seconds—0 point, prolonged for > 3 seconds < 6 seconds—1 point, > 6 seconds—2 points) and fibrinogen value (> 1 g/l—0 point, < 1 g/l—1 point). A score of 5 or more indicates DIC (18).

Statistical data processing was done using the IBM SPSS Statistics v.21 program. The Kolmogorov–Smirnov normality test was used to check the normality of the data distribution. One-factor analysis of variance (ANOVA) was used for the analysis of the tested values concerning the clinical course for different groups, and the statistically significant results were graphically displayed using a line graph. The Student's t-test for independent samples was used to analyze the tested values concerning the treatment outcome, and the statistically significant results were shown using a bar chart. The chi-square test was used to analyze the clinical course and the outcome of treatment concerning the sex of the patient. One-factor ANOVA for different groups and Student's t-test for independent samples were used to analyze the patient's age concerning the clinical course and treatment outcome, and statistically significant results were shown using line and bar graphs. The results were considered statistically significant if the significance (p-value) was less than or equal to 0.05.

Results

Out of 131 patients, there were 53 women (40.5%) and 78 men (59.5%). The participants were between 19 and 90 years old, with the average age of 62.3 ± 16.3 years. Regarding clinical condition, there were 22.1% of patients with a mild disease, 58.8% of patients with a severe disease and 19.1% of patients with critical disease. Concerning treatment outcome, 111 (84.7%) patients recovered and 20 (15.3%) died. Descriptive statistical analysis of continuous variables is shown in Table 1. Prothrombin time (PT), DIC score, and platelet count (PLT) were the parameters that showed statistical significance when observed concerning clinical forms of the disease (Table 2). A total of 48 patients (36.6%) had an ISTH DIC score of 0, score 1 was given to 4 patients (3.1%), the most significant number of patients had a score of 2 (66 patients, 50.4%), 10 patients (7.6%) had a score of 3, and 2 patients (1.5%) had a score of 4. Finally, 1 patient (0.8%) had a score of 5, which fulfilled the criteria for DIC. From Table 3 it is clearly seen that the patients with critical COVID-19 have significantly higher PT and DIC score values and significantly lower PLT values. Also our research showed that there was a statistically significant difference in the values of the DIC score and PLT concerning the treatment outcome (Table 4). Figure 1 and 2 show that the DIC score values were significantly higher in the patients who died, and PLT values were significantly lower. Using the chi-square test for independence, it was determined that the clinical course and the outcome of the treatment did not depend on the sex of the patients. By applying one-factor ANOVA for different groups

and Student's t-test for independent samples, it was determined that there was a statistically significant difference in the age of the patients concerning the clinical course and treatment outcome. Patients with critical disease and with fatal outcomes were significantly older (Results not shown).

Table 1. Descriptive analysis of the examined parameters of hemostasis

	Lowest value	Highest value	Mean value	Standard deviation	Reference values
aPTT (s) I day	21.4	62.1	35.19	7.43	24.0–35.0
PT (s) I day	11.1	55.3	14.85	4.75	11.8–15.3
INR I day	0.89	4.67	1.18	0.41	0.9–1.1
D-dimer (ng/ml) I day	24	11900	872.59	1380.67	0–230
Fibrinogen (g/l) I day	2.52	9.35	4.88	1.22	2.0–4.5
DIC score	0	5	1.37	1.14	< 5
PLT (x 10*9/L) I day	27	559	208.98	102.13	150–450

Table 2. Analysis of hemostasis parameters concerning the form of the disease

	F statistic	Degrees of freedom	Significance
aPTT (s)	2.063	2;128	0.131
PT (s)	**3.178**	**2;128**	**0.045**
INR	2.183	2;128	0.117
D-dimer (ng/ml)	0.118	2;128	0.889
Fibrinogen (g/l)	1.777	2;128	0.173
DIC score	**4.374**	**2;128**	**0.015**
PLT (x 10*9/L)	**3.703**	**2;128**	**0.027**

Table 3. Analysis of the values of PT, DIC score and platelet count concerning the form of the disease

		Mild	Severe	Critical	Standard deviation
PT (s)		15.483	14.042	16.600	4.7454
DIC score		1.21	1.23	1.96	1.145
PLT (x 10*9/L)		219.931	220.766	159.992	102.1331

Table 4. Analysis of hemostasis parameters concerning disease outcome

	F statistic	Degrees of freedom	Significance
aPTT (s)	0.776	129	0.439
PT (s)	1.186	129	0.238
INR	0.820	129	0.414
D-dimer (ng/ml)	0.159	129	0.874
Fibrinogen (g/l)	0.375	129	0.708
DIC score	**2.570**	**129**	**0.016**
PLT (x 10*9/L)	**2.895**	**129**	**0.004**

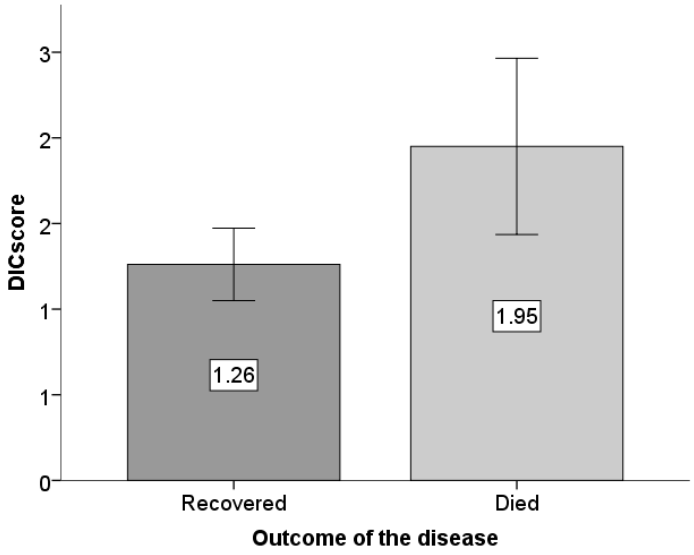

Figure 1. Analysis of the value of DIC score concerning the treatment outcome

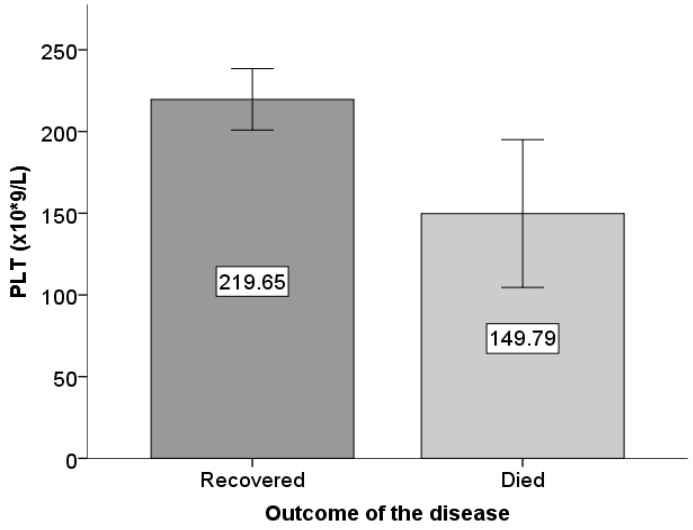

Figure 2. Analysis of the number of platelets concerning the outcome of the disease

Discussion

Due to the large amount of research on coagulopathy and COVID-19, this study aimed to examine the frequency of coagulopathy by analyzing it through the DIC score. In addition, the association of other coagulopathy parameters with the clinical course and the outcome of the disease was examined. In their work, Gerber GF et al. also concluded that average PT/aPTT values were normal or minimally prolonged in COVID-19 (19). In a study that included 183 COVID-19 patients, Arachchillage DR et al. showed that these values were significantly prolonged (20). The increased values of D-dimer and fibrinogen have been described in many studies as indicators of poor outcome (14, 15, 21), but in present study, these parameters were not correlated with severe disease or fatal outcome. Some studies emphasize the significant role of platelets in the pathogenesis of the disease itself, suggesting that platelets abnormalities can be qualitative as well as quantitative ones (22, 23). On the other hand, there are not many studies in the literature investigating the DIC score as a marker of disease severity and prognosis. The question arises whether the existing DIC score can be used in COVID-19 given that the pathogenesis is different compared to sepsis induced DIC (24). In this study, it was found that there was a statistically significant difference in the values of PT, DIC score and platelet count concerning the clinical course. Further, it was shown that there was a statistically significant difference in the value of the DIC score and the number of platelets concerning the outcome of the disease. Other examined parameters had no significant influence on the outcome of the disease. It was found that the outcome and form of the disease did not depend on the sex of the patients, but that there was statistical significance concerning age.

Conclusion

Based on our research, it can be concluded that the patients did not meet the criteria for conventional DIC, but that coagulopathy was registered. Patients with a critical form of the disease, as well as patients who did not survive, had statistically significantly higher values of the DIC score. Patients with a critical form of the disease had significantly higher values of prothrombin time and significantly lower values of the number of platelets than patients with a mild and severe form of the disease. Patients in whom the disease ended fatally had a statistically significantly lower number of platelets compared to patients who recovered.

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KOAGULOPATIJA I KOVID 19

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Interesovanje za kovid 19 u svetu nauke ne prestaje. Patogeneza kovida 19 i dalje je predmet velikog broja studija, a koagulopatija zauzima važno mesto u istraživanjima. Glavni cilj ovog rada bilo je ispitivanje karakteristika koagulopatije izazvane kovidom 19. Za potrebe ove studije prikupljeni su uzorci krvi 131 bolesnika koji se zbog infekcije SARS-CoV-2 prvi put bolnički lečio u Univerzitetskom kliničkom centru u Kragujevcu. Uzorak krvi uzet je na dan prijema, a potom je praćen tok bolesti. Došlo se do zaključka da ovi ispitanici ne ispunjavaju kriterijume za diseminovanu intravaskularnu koagulaciju (DIK). Polazeći od forme i ishoda bolesti, predstavili smo statistički značaj broja trombocita, vrednosti protrombinskog vremena i DIK skora. Pacijenti sa kritičnom formom bolesti, kao i oni kod kojih je ova bolest dovela do smrtnog ishoda, imali su značajno niže vrednosti broja trombocita, a značajno veće vrednosti DIK skora.

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***Ključne reči**: kovid 19, diseminovana intravaskularna koagulacija, forma bolesti, ishod bolesti*

Original article

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SIDE EFFECTS OF HYGIENE PRODUCTS IN HEALTHCARE WORKERS AND TEMPORARY WORK INCAPACITY DUE TO THE USE OF HYGIENE PRODUCTS

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When performing their duties, healthcare professionals encounter a large number of diseased people on a daily basis at their workplaces in healthcare clinics and hospitals. This requires a special code of conduct. Prevention of infections and cleanliness are imperative. This process may cause side effects from the use of hygiene products, which is evident in every analysis of skin diseases, allergic and occupational conditions in particular. There is always a number of healthcare workers with contact dermatitis and the most common etiological factors are soaps, detergents, cleaning agents, infectious agents, medicines and disinfectants. Diagnostics, prevention, treatment and occupational rehabilitation, and assessment of work capacity are implemented in all cases of those affected by occupational allergic contact dermatitis.

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Key words: *healthcare workers, allergic contact dermatitis, hygiene products, work capacity*

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Introduction

Changes in the skin may occur in any profession depending on the individual features of the skin, work conditions and occupational hazards.

These are more occupational dermatoses caused by chemical hazards (1):

1. Occupational Contact Dermatitis

a. Occupational Irritant Contact Dermatitis (most common type (2))

b. Occupational Allergic Contact Dermatitis (type IV (3, 4))

2. Occupational Contact Erythema Multiforme

3. Occupational Contact Urticaria Syndrome

a. Occupational Contact Urticaria

b. Occupational Protein Contact Dermatitis.

Occupational allergic dermatosis, i.e., Occupational Allergic Contact Dermatitis (OACD) is of particular medical, social and economic significance.

In their workplace, healthcare workers encounter a large number of people, both ill and healthy on a daily basis. This requires a special code of conduct. Naturally, all healthcare institutions have hygiene rules and use appropriate means. The employees may be exposed to those hygiene products, which in turn may be the cause of undesired changes in the skin as a consequence of the effects of those hygiene products.

If changes in the skin occur, it is necessary to perform an exposure and elimination test, as well as a patch test. Then the appropriate course of therapy should be decided. As for the diseased healthcare worker, further actions will be determined following the appropriate and regulated measures. Regarding the working environment, in which the allergic reaction to the product occurred, there must be insistence on implementing and strictly following protective measures, which will be dealt with in the text to follow.

Aim

This study aimed to recognize and diagnose the occurrence of side effects in healthcare workers following the use of hygiene products, the administration of appropriate treatment and protection. This was intended to be done by following suitable measures of protection and enforcing rules for the strict administration of

protective measures in an adequate and approved manner for the use of the necessary hygiene products.

Materials and Methods

The first step was to gather first-hand information about the possibility of allergic reactions in healthcare workers and study literature on the topic. This was followed by getting acquainted with all measures intended for treating and preventing side effects to the hygiene products when strictly following the prescribed measures.

Results, Reference Data and Discussion

In 15 years, the results of epicutaneous testing in 962 diseased persons were analyzed at the Dermatological Clinic in Niš (5). Six hundred and sixty people (68.60%) tested were men and 302 (31.39%) were women; they belonged to different occupations (construction workers, housewives, farmers, miners, workers in the rubber and electronics industry, mechanics, hairdressers), as well as healthcare professionals (a total of 14 people).

Other occupations that were subject to the examination were workers in the wool and leather industry, textile and wood processing, wall and ironworks painters, custodians, healthcare professionals, etc.

In the patch tests, healthcare workers tested positive for procaine, aniline, aneurine, dental, peril, asepsol, lizol, kavit, and Teptih.

Custodians tested positive for Teptih, Ursol, lizol, and bis.

It was proved that healthcare professionals exhibit sensitivity to medicines, disinfectants and cleaning agents. According to reference materials (6, 7) this is a matter of allergies to penicillin, streptomycin, novocain, sulfonamide, iodine compounds, largactil, procaine, gingicaine and peril spray. The role of latent sensibilization in the pathogenesis of occupational allergic dermatosis in healthcare professionals is stressed.

According to a report from 2002 (8), out of 5,839 tested patients with contact dermatitis, in 1,097 (19%), it was linked to their profession, and 60% of those patients suffered from allergic contact dermatitis. The most common allergens were carba mix, thiuram mix, epoxy resin, formaldehyde, and nickel.

Laberge et al. (9) assessed the importance of allergies to p-phenylenediamine (PPD) and determined the cross-reaction with other para-amino compounds. Contact allergy to PPD occurred in 13234 patients: 13.4% were hairdressers, 18.7% were people with atopy, 90.3% were sensitive to hair dye, 2.2% were sensitive to henna tattoos, 7.5% reacted to benzocaine, 6.0% to sulfa drugs, 1.5% to isopropyl-para-phenylenediamine, while 1.5% of patients reacted to para-aminobenzoic acid. It was concluded that PPD is a major cause of contact allergies. Dentistry professionals may be at increased risk of occupational allergic diseases, especially to methacrylates (10). A 28-year-old dental technician exhibiting itching and cracks on the fingers in the previous 6 months was presented. Patch testing showed a positive reaction to methyl methacrylate. Methacrylates are a compound of acrylic resins and can penetrate disposable surgical gloves. The use of nitrile rubber gloves when performing work duties is a sufficient protective measure in addition to appropriate preventive measures.

Table 1. Structure of examined patients by sex and place of residence

Sex	Male	Female	Total
Number	660	302	962
%	68.60%	31.39%	99.99%
Place of residence	Town	Village	Total
Number	490	472	962
%	50.92%	49.07%	99.99 %

Table 2. Age of examined patients

Age	No.	Percentage
Up to 20 y	57	5.90%
21–30 y	234	24.30%
31–40 y	255	26.40%
41–50 y	261	27.30%
51–60 y	109	11.31%
Over 60 y	46	4.78%
Total	962	99.99%

Table 3. Structure of examined patients by occupation

Occupation	Number of patients	Percentage
Construction workers	195	20.27
Housewives	85	8.83
Metal workers	67	6.96
Rubber workers	59	6.13
Electronic specialists	44	4.57
Hairdressers	41	4.26
Farmers	41	4.26
Miners	31	3.22

Table 4. Most common allergens (top 10)

Allergen	Number	Percentage
1. Kalium bichromate	91	28.60%
2. PAN	41	12.97%
3. PBN	40	12.65%
4. Formalin	23	7.29%
5. Anilin	21	6.64%
6. DM	18	5.69%
7. 4010	17	5.37%
8. Nickel sulfate	16	5.06%
9. Vikacid D	12	3.79%
10. Ursol	12	3.79%

ACD is most frequently caused by chemicals in rubber gloves (thiuram mix and tetraethylthiuram disulfide), preservatives (formaldehyde, formaldehyde emanators and isothiazolinones), excipients in handwashing liquids (weak allergens that are difficult to avoid) (8). To develop a preventive strategy, the authors suggest that skincare counseling be included in the education on hand hygiene.

The results from testing conducted at a clinical hospital and a private clinic in New Zealand were announced (11). Of 837 patients, 67 were healthcare professionals: 40% of nurses, 20% of allied health and 18% of doctors. Fifty-seven percent of these patients had positive patch tests: 16 reactions to accelerator rubber, 11 to fragrances, 10 to preservatives, and 6 to corticosteroids. The most common relevant antigens were methylisothiazolinone, hydroxyisohexyl 3-cyclohexene carboxaldehyde and methylisothiazolinone.

According to Mathias (12), the most common etiological factors that lead to the development of dermatosis in healthcare are soaps, detergents, cleaning agents, infectious agents, drugs and disinfectants.

Higgins CI et al. (13) performed an analysis of occupational skin diseases among Australian healthcare workers. In 22 years, they diagnosed occupational skin diseases in 555 (81.0%) out of the 685 healthcare workers included in the analysis. The most common occurrence was that of irritant contact dermatitis (79.19%), followed by allergic contact dermatitis (49.7%). Natural rubber latex was registered as the cause of allergy in 13.0% of the examinees. The largest number of substances causing allergic contact dermatitis are runner chemicals found in gloves (thiuram mix and tetraethylthiuram disulfide), preservatives (formaldehyde, formaldehyde releasers and isothiazolinones), excipients in hand cleaners and antiseptics. It is suggested that skin care advice should be incorporated into hand hygiene education. The use of alcohol-based hand rubs should be encouraged, weak allergens in skin cleaners should be substituted, and accelerator-free gloves should be recommended for healthcare workers with occupational skin diseases.

Franca et al. (14) have presented a study about occupational dermatoses in healthcare workers in a medical center in Portugal.

Contact dermatitis (eczema) represents about 90% of occupational dermatoses (15, 16). Healthcare workers are particularly susceptible to this type of skin disorder (17) as a result of their frequent contact with a large number of potential irritants and sensitizing agents, e.g. rubber gloves and disinfectants (13). The study involved 1,338 (76.85%) women and 403 (23.15%) men, whose median age was 41. A total of 1741 healthcare workers of different professions were analyzed. With a prevalence of 3.56%, occupational dermatoses were more frequent in women (82.26%). In the group with occupational dermatoses, 34 workers (54.84%) suffered from irritant contact dermatitis, 17 (27.42%) had latex allergy, 6 (9.68%) had allergic dermatitis, and 5 (8.06%) had two simultaneous conditions—4 people had latex allergy and irritant contact dermatitis and 1 person had latex allergy and allergic dermatitis.

Cases of dermatitis were more common among individuals who had a personal atopic history, but the margin was not statistically significant.

Many other important and interesting findings were presented in the study. The definitive data showed that there was a prevalence of occupational dermatoses in the analyzed group of 1.741 workers of 3.56%. Primary prevention measures and the use of less sensitizing materials can reduce the occurrence of dermatoses in this professional group.

A retrospective study was conducted on 294 patients with OACD in the Allergy Unit of the Dermatology Department in Istanbul between 1996 and 2019 (18). OACD was registered in 10.5%, predominantly men. These were mostly construction workers, followed by hairdressers, metalworkers, healthcare workers, etc. The most common allergens were chromium in cement, thiuram in rubber gloves, hairdressing chemicals, resin/glues/plastic, metals, isothiazolinones, and fragrances.

Schwensen JF et al. (19) examined the occurrence of contact allergies among healthcare workers in Denmark. A retrospective study of patch test results of 1402 healthcare workers who had contact dermatitis was conducted as opposed to a control group of 1402 individuals with contact dermatitis. It was found that, in patients who have contact dermatitis and work in healthcare, there was a significant combination of contact allergy to thiuram mix, hand dermatitis and occupational contact dermatitis. In the future, legislative authorities may focus on the use of thiuram and carbamates in, for example, protective gloves, as it seems that improved production methods of protective gloves have not yet paid dividends to skin health or the workers in the healthcare sector.

After examining the diseased person and recording the specific clinical condition, it is highly relevant to collect a detailed history of the beginning of the disease, its localization and appearance, the person's lifestyle and habits, and movement within the workspace. This is done to establish possible links between the onset of the disease and working in a specific position, changes that may occur when absent from work and upon returning along with a description of the working conditions.

When providing a diagnosis, a test of exposition and elimination may be of great importance, with the patch test serving as the gold standard in diagnosing ACD (20).

Prevention has a great impact on the occurrence and frequency of ACD (21, 22). The first measure would be appropriate occupational treatment. Individuals with dry and sensitive skin should not work with irritants and sensitizers. It would be beneficial to conduct epicutaneous

testing before commencing work. Educating employees from the beginning of their formal education until the end of their service. Persistence on mechanization, automation and closed-circuit systems to eliminate the presence of sensitizers from the process whenever possible, adherence to sanitary regulations, make provisions that individual protective measures do not inhibit the work process , and make provisions that additional hand protective means do not irritate and sensibilize the skin.

Treatment is symptomatic. Locally, one administers corticosteroid creams and if necessary, antibiotics, systemic antihistamines and possibly corticosteroids.

Causal treatment would be to prevent contact with the allergen causing the reaction.

By implementing adequate protective measures, one may attempt treatment while continuing service.

The diseased person may become temporarily incapacitated for work (23). In cases of high intensity and spread of the disease, it is necessary to exclude the person from work obligations for 2–3 weeks due to the possibility of further provocation of the disease by irritants. Then, for at least 2–3 additional months, they should be allowed to work in positions where they would not be in contact with irritants (7). According to some authors (24, 25), attempts should be made for the diseased person to stay in the same work position and accept minor outbreaks of OACD.

In cases when OACD is severe and frequently relapses, steps towards occupational rehabilitation must be taken. This implies a change of the work position or occupation. The worker should be referred to the Disability Board, which should (26):

- Establish the cause of the disability
- Denote loss of or diminished work capacity
- Denote risk of disability
- Assess remaining work capacity
- Denote the persistence of risk of developing a disability
- Give opinion on the possibility of occupational rehabilitation
- Point to the direction in which occupational rehabilitation should progress
- Give an opinion on the possibility of changing the position to a more suitable post without requiring occupational rehabilitation.

A person who still maintains work capacity for another full-time job is placed in the III category disability list. The right to disability retirement benefits is granted to an employee or a self-employed insured person who is placed in the III category disability list, but is not given the right to retraining or additional training due to age—50 years of age (for men) and 46 years of age (for women) (27).

Work capacity is assessed on the basis of the following elements:

- Work history—position where the person works, where the changes occurred and previous years of service
- Job description of the position where the worker is assigned (contact with denoted chemicals, duration of contact—in the course of the full working hours or occasionally and in which time intervals)
- In case of contact constant, exposure at the workplace should persist for at least a year, with 2–3 years if the contact is occasional—this does not apply to chemicals with high allergenic potential
- Worker's personal history—atopic constitution or previous allergic manifestations on the skin or other organs
- Dermatologist's report containing the diagnosis of allergic contact dermatitis with description of the clinical condition and course of the disease—a chronic illness with severe relapses, course of the disease at the workplace and home, duration of relapses after exposure and whether rehabilitation occurs with or without treatment.

If the listed conditions are fulfilled, the disease can be labeled as occupational.

Care should be taken that the new work position does not pose the same threat, i.e., that contact with the same or chemically similar matter does not continue, as well as contact with other irritants or matters with high allergic potential. This could lead to the persistence of the disease or polysensitization. Persons with atopy are especially problematic, as well as so-called ubiquitous matters, contact with which continues in and out of the workplace. If one is dealing with an atopic person with any kind of allergic manifestations, even if contact dermatitis is not present, there should be follow-up check-ups every 6 months. Special attention should be paid to young people who are still being educated or are at the beginning of their careers and already have contact dermatitis. Professional orientation or retraining should be conducted immediately to avoid the development of the disease and the occurrence of disability (28).

Many of the consequences of the effects of the use of hygiene products among professionals in healthcare institutions would not occur should all follow the protocol prescribed by the Public Health Institute "Dr Milan Jovanović Batut" in the article Maintaining Hygiene in Healthcare Institutions (29).

Sections of this article will be cited here to be at hand to whoever is reading this paper.

Basic principles of cleanliness in a healthcare institution include: personal hygiene and hand hygiene; proper use of personal protective equipment; proper use of cleaning agents and/or disinfectants; use of suitable cleaning equipment, its maintenance and proper disposal; and waste management. Precise advice is given on every one of these points.

We arrive at the point of contact—cleaning agents and/or disinfectants.

It is prescribed that all detergents and disinfection agents used in healthcare institutions must be approved by the Ministry of Health. The choice is made by a hospital infection commission within the healthcare institution. Chemical cleaning agents and disinfectants must be properly labeled and stored to eliminate the risk of contamination, inhaling or contact with skin or mucosa. A safety technical list must be available for cases of emergency. Cleaning chemicals include neutral detergent, disinfectants, toilet and bathroom cleaning agents, as well as other chemicals procured at the request of and according to the needs of the healthcare institution.

Detergent is used for regular cleaning and removal of dirt.

Disinfectant is used after cleaning to remove blood, urine, saliva, and other excretion. It quickly kills most microorganisms and reduces their number.

Detergent and disinfectant packaging labels contain warnings and restrictions for their use with pictorial features:

● Corrosive

This symbol indicates products that are corrosive to metal, may cause severe skin burns and are harmful to the eyes. Example include hydrochloric and acetic acid, amoniac and pipe-unclogging agent.

● Health hazard (exclamation mark)

This symbol represents irritants to the respiratory system, and indicates that the product can be harmful if inhaled. Potential effects include drowsiness, fainting, skin irritation and allergic reactions.

● Environmental toxicity (image of branched tree)

This label signifies products that are toxic to the environment and can lead to long term consequences in water systems. Examples include pesticides, biocides (disinfectants) (30), gasoline, and turpentine.

● Flammable (flame over circle)

This symbol warns that the product may cause a fire or an explosion. Examples include bleach, alcohol-based agents, oxygen for medical purposes.

● Serious health hazard (image danger)

Products marked with this symbol pose severe health risks if swallowed or inhaled, potentially causing death, organ damage, cancer, genetic defects, or asthma. Examples include biocidal products, turpentine, gasoline, and lamp oil.

The use of disinfection agents as part of the routine cleaning process is recommended in areas of high and medium risk: operating rooms, intensive and semi-intensive care units, maternity wards, newborn care wards, hemodialysis, transplant units, etc. Precise instructions are given on how to clean different rooms and, finally, wash hands, remove personal protection equipment and repeat hand washing before changing into personal clothes and footwear.

These recommendations for maintaining hygiene in a healthcare institution are so detailed and well-written that it is impossible to get around them quickly. It is very important to behave according to these recommendations.

Conclusion

Healthcare institutions are filled with large numbers of people daily, both healthy and sick, thus making hygiene imperative. It is the reason for the use of hygiene products (soaps, detergents, cleaning agents, medicines, disinfectants, etc.). One must not forget that these agents may have side effects and cause irritant contact and/or allergic dermatitis, which in turn can affect one's health condition and even incapacitate a person. This would require absence from work, possible change of jobs or even cause one to retire on grounds of disability. The topic of present paper reveals an attempt to approach this issue from different points to achieve maximum effect.

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NEŽELJENA DEJSTVA PREPARATA ZA ODRŽAVANJE HIGIJENE I PRIVREMENA RADNA NESPOSOBNOST KAO POSLEDICA NJIHOVE PRIMENE KOD ZDRAVSTVENIH RADNIKA

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S obzirom na to da se prilikom obavljanja posla zdravstveni radnici na radnim mestima u zdravstvenim ustanovama svakodnevno sreću sa velikim brojem osoba, bolesnih ili zdravih, neophodan je poseban režim ponašanja. Mora se, između ostalog, voditi računa o sprečavanju infekcija i redovnom čišćenju. Međutim, pri tome može doći i do ispoljavanja neželjenih dejstava samih preparata za održavanje higijene, što postaje očigledno pri osvrtu na svaku analizu oboljenja kože, posebno alergijskih i profesionalnih. Zdravstveni radnici često obolevaju od kontaktnog dermatitisa, a najčešći etiološki faktori su sapuni, deterdženti, sredstva za čišćenje, infekcijski agensi, lekovi i dezinficijensi. Dijagnostika, prevencija, terapija, kao i profesionalna rehabilitacija i ocena radne sposobnosti, tada se sprovode kao kod svih obolelih od profesionalnog kontaktnog alergijskog dermatitisa.

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***Ključne reči**: zdravstveni radnici, kontaktni alergijski dermatitis, sredstva za održavanje higijene, radna sposobnost*

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PROGNOSTIC DIFFERENCES IN TUBO-OVARIAN HIGH–GRADE SEROUS CARCINOMA STAGE IIIC

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Quantitative variations in peritoneal carcinomatosis and primary pelvic tumor size (TS) may reflect the diversity in high-grade serous carcinoma (HGSC) stage IIIC. The peritoneal cancer index (PCI) provides accurate evidence about the extent and distribution of tumor volume. The study aimed to investigate whether there is a difference among HGSCs in the International Federation of Gynecology and Obstetrics (FIGO) stage IIIC based on the principal disease burden and its impact on overall survival (OS). Medical records of primary tubo-ovarian HGSCs were reviewed from January 2019 to December 2022. Patients were separated into a group with PCI ≤ 10 and large TS (Group 1, n = 39) and a group with PCI > 10 and small TS (Group 2, n = 36). Group 2 was significantly more likely to have a larger volume of ascitic fluid (p = 0.017). Optimal cytoreduction (OC) was achieved in 53.9% of patients in Group 1 and in only 11.1% of those in Group 2 (p < 0.001). *BRCA1/2* mutation was significantly more frequent in Group 1 (p = 0.012). OS was significantly better in Group 1 versus 2 (p < 0.001). Multivariate analysis identified group, ascitic volume, and cytoreduction completeness as independent prognostic survival factors. The FIGO stage IIIC of HGSC should evolve from a "one-size-fits-all" approach toward a more personalized treatment strategy that incorporates surgery, chemotherapy, and targeted therapy. The localization of the main tumor burden is a factor that makes a prognostic difference in stage IIIC HGSCs.

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Key words: *high-grade serous carcinoma, FIGO stage, peritoneal cancer index, difference, prognosis*

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Introduction

Epithelial ovarian cancer (EOC) is a heterogeneous disease comprising several histotypes with different modes of carcinogenesis, epidemiological, clinical, molecular, and microenvironmental features, all of which affect the tumor behavior (1). Among them, the most common histological type is high-grade serous carcinoma (HGSC), which originates from a noninvasive precursor called serous tubal intraepithelial carcinoma (STIC) in the distal end of the fallopian tube (2). Frequently, HGSC is diagnosed at the International Federation of Gynecology and Obstetrics (FIGO) stage III/IV. Therefore, the five-year cancer-specific survival for HGSC is much lower than for other common histological types despite the intense research efforts to improve treatment modalities and survival rates (3). Regardless of the same histotype and disease stage, HGSCs staged as FIGO IIIC represent a diverse group of patients with distinct prognoses (4). Consequently, there is a need to define more precise indicators that influence survival within the same stage.

Contrary to the conventional dissemination route for other carcinomas, HGSC does not require blood or lymph vasculature. HGSC characteristically metastasizes throughout the abdominal peritoneal cavity via cell detachment from the primary tumor. Secondary tumors bind the mesothelial cell layer and continue to grow in a completely altered setting. Some tubo-ovarian HGSCs favor abdominal peritoneal metastatic sites for future development rather than the original site of occurrence (5). This results in shifting the

disease from the pelvis to the abdomen. Quantitative variations in peritoneal carcinomatosis and primary pelvic tumor size (TS) may reflect the diversity in the stage IIIC of HGSCs.

There are many proposed systems for estimating abdominal and pelvic tumor load (6). One widely adopted score is the peritoneal cancer index (PCI) introduced by Jacquet and Sugarbaker initially used for metastatic colorectal and appendiceal cancers (7). In advanced ovarian cancer, PCI can be utilized as an efficient tool for evaluation of the peritoneal spread and provides accurate evidence about the extent and distribution of tumor volume (8).

The study aimed to investigate whether there is a difference among HGSCs currently grouped as FIGO stage IIIC based on the principal disease burden and its impact on overall survival (OS) in order to justify further stage subcategorization and distinctive therapeutic approach.

Materials and Methods

Patient Selection

Medical records of women diagnosed with primary tubo-ovarian HGSC FIGO stage IIIC were reviewed from January 2019 to December 2022. All patients underwent surgery at the Clinic of Gynecology and Obstetrics, University Clinical Center Niš, Niš, Serbia. Each surgery was performed via median laparotomy to remove as much of the visible tumor. Gynecologic pathologists reexamined hematoxylin and eosin-stained slides of operative tumor samples at the Center for Pathology, University Clinical Center Niš, Niš, Serbia. HGSC was classified as tubo-ovarian versus peritoneal primary based on criteria for primary site assignment in non-uterine HGSC proposed by Singh et al. (9).

Patients were excluded if they had prior surgery for tubo-ovarian cancer and if they received neoadjuvant chemotherapy. The following data were included: patients' age at diagnosis, PCI, TS, completeness of cytoreduction, ascitic volume (L), regional lymph node involvement, germline or somatic *BRCA1/2* mutation status, value of preoperative CA125 (U/ml), date of last follow-up, and cancer-specific death at last follow-up.

The PCI was calculated based on computed tomography (CT), magnetic resonance imaging (MRI), and operative and pathology reports, according to Jacquet and Sugarbaker's propositions (7). After calculation, PCI values were dichotomized at value 10 (8). A small TS indicates a primary tubo-ovarian tumor less than or equal to 5 cm and a large TS indicates a tubo-ovarian tumor greater than 5 cm in its largest diameter. Optimal cytoreduction (OC) is defined as complete removal or residual disease less than or equal to 1 cm, while suboptimal cytoreduction (SC) is defined as leaving tumor residues larger than 1 cm. The molecular evaluation of breast cancer genes *BRCA1/2* was performed at the Institute for Oncology and Radiology of Serbia, Belgrade, Serbia, to identify patients for poly-ADP-ribose polymerase (PARP) inhibitors treatment. OS was calculated from the date of surgery to the date of cancer-specific death. Surviving patients were censored at the date of the most recent follow-up.

All participating patients were well-informed and signed the consent form.

Statistical analysis

All statistical analyses were processed using the Statistical Package for Social Sciences (SPSS version 25.0; IBM, Armonk, NY, USA). The normality of the data was tested using the one-sample Kolmogorov–Smirnov test. The χ^2 test was used to compare differences between the categorical variables. The Student's t-test analyzed differences in the means of continuous measurements. The survival curves were obtained using the Kaplan–Meier method and the log-rank test was engaged to compare survival curves. Multivariate analyses were performed using the Cox proportional hazards regression model.

A two-tailed p-value of less than 0.05 was considered statistically significant for all tests.

Results

A total of 75 women with FIGO stage IIIC primary tubo-ovarian HGSC were included in this study after applying the above criteria. They were separated into two groups: patients with PCI ≤ 10 and large TS (Group 1, n = 39) and patients with PCI > 10 and small TS (Group 2, n = 36). Table 1 summarizes a comparison of baseline characteristics between the patients' groups. The mean age at the time of diagnosis was similar in both groups: 61.26 ± 12.23 years old for women in Group 1 and 60.58 ± 9.39 years old for Group 2 (p = 0.791). Patients in Group 2 were significantly more likely to have a larger volume of ascitic fluid than those in Group 1 (p = 0.017). Furthermore, OC was achieved in 23 (53.9%) patients in Group 1 and only 4 (11.1%) of those in Group 2, with a statistically significant difference (p < 0.001). Germline or somatic *BRCA1/2* mutation was observed significantly more frequently in women in Group 1 compared with Group 2 (p = 0.012). Although patients in Group 2 tended to have higher values of preoperative CA125 levels, the difference did not reach statistical significance (p = 0.087). We found no significant intergroup differences concerning lymph node involvement (p = 0.701).

Table 1. Comparison of groups according to baseline characteristics

	Group 1	**Group 2**	**p-value**
No. patients	39	36	
Age (yrs)			
Mean ± SD	61.26 ± 12.23	60.58 ± 9.39	0.791
Ascitic volume (L)			
Mean ± SD	2.47 ± 1.63	3.59 ± 2.27	**0.017**
Cytoreduction, n (%)			
OC	21 (53.9)	4 (11.1)	**< 0.001**
SC	18 (46.1)	32 (88.9)	
BRCA1/2 mutation, n (%)			
Present	14 (39.9)	4 (11.1)	**0.012**
Absent	25 (64.1)	32 (88.9)	
CA125 level (U/ml)			
Mean ± SD	823.00 ± 360.67	980.75 ± 425.68	0.087
Lymph node involvement, n (%)			
Present	9 (23.1)	7 (19.4)	0.701
Absent	30 (76.9)	29 (80.6)	

Bold values indicate that the difference reached statistical significance

Table 2. Results of multivariate analysis

Variable	**B**	**SE**	**HR**	**95% CI HR**		**p-value**
				Lower	Upper	
Group	-1.018	0.499	0.361	0.136	0.962	**0.042**
Age	0.023	0.018	1.023	0.987	1.061	0.211
Ascitic volume	0.220	0.095	1.246	1.033	1.502	**0.021**
Cytoreduction	-1.479	0.578	0.228	0.073	0.708	**0.011**
BRCA1/2 mutation	0.785	0.533	2.193	0.772	6.235	0.141
CA125 level	0.001	0.000	1.001	1.000	1.001	0.113
Lymph node involvement	-0.602	0.438	0.548	0.232	1.293	0.170

Bold values indicate variables with a significant impact on the OS

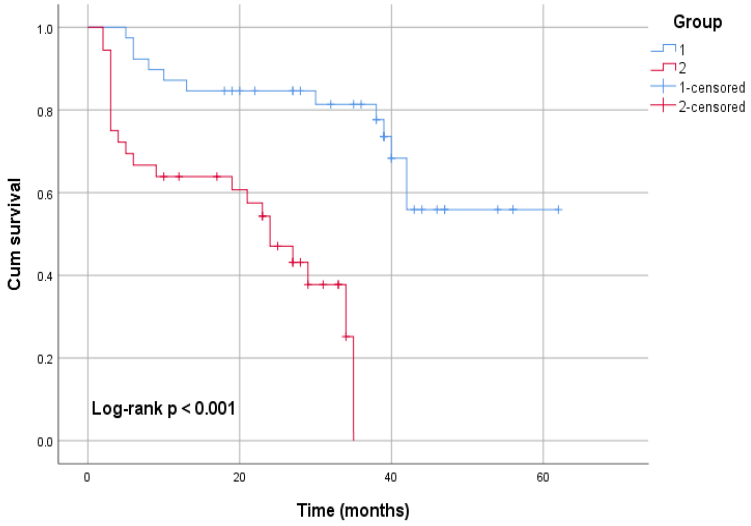

Figure 1. Comparison of OS by groups

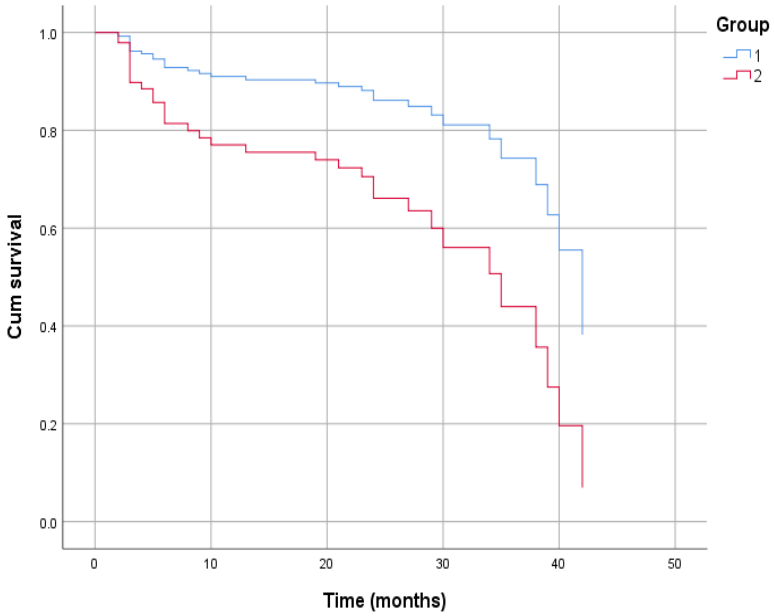

Figure 2. OS adjusted for prognostic variables and separated by groups

Survival analysis

The median OS for the entire population was 27 months (range 2–62). Separately, the median OS for patients in Group 1 was 38 months (range 5–62 months) while for patients in Group 2 was 22 months (range 2–35 months). As expected, Kaplan–Meier survival curves revealed a significantly better OS in Group 1 versus 2, as seen in Figure 1 ($p < 0.001$).

Multivariate analysis of the entire cohort with all data identified group, ascitic volume, and cytoreduction completeness as independent prognostic survival factors (Table 2). Group 1 was an independent predictive parameter for improved OS (HR = 0.361; p = 0.042). Another independent prognostic marker associated with a better outcome was OC (HR = 0.288; p = 0.011). The larger volume of ascitic fluid was significantly linked with worse OS (HR = 1.246; p = 0.021). Age, *BRCA1/2* mutation status, CA125 level, and lymph node involvement were not significant predictors of survival in the multivariate analysis. Figure 2 shows the different survival plots for patients in two groups after adjustment for prognostic variables.

Discussion

Extrapelvic peritoneal carcinomatosis is the most common presentation of HGSC. Peritoneal tumor spread depends on the unique and complex cooperation of the tumor microenvironment within the peritoneal cavity and ovarian cancer cells. Ascitic fluid, rich in cytokines, chemokines, growth factors, and proteinases additionally contributes to the growth and invasion of malignant cells. Although virtually every organ or structure in the peritoneal cavity may be involved, HGSC prefers the omentum (10).

Several reports have suggested a less favorable outcome for HGSC patients stage III/IV with large-volume extrapelvic disease especially for its upper abdominal distribution, even if complete cytoreduction was achieved (11, 12). There is an appreciable number of advanced HGSCs without definite adnexal enlargement and pelvic symptoms. Thus, some HGSCs can cause diffuse metastatic abdominal disease before reaching a detectable pelvic size by diagnostic procedures. After the splitting of advanced-stage HGSCs according to the presence of a normal-sized or enlarged adnexa, Paik et al. demonstrated a statistically significant poorer OS in patients with a normal-sized ovary than with an enlarged ovarian tumor. Moreover, a normal-sized ovary remained a significant factor for OS after multivariate analysis (13).

The patients are staged as FIGO IIIC if the minimal tumor size above the pelvic rim is more than 2 cm and/or if they have retroperitoneal lymph node involvement. This current classification does not give valuable information about disease extent since patients with stage IIIC may have an easily resectable tubo-ovarian tumor with localized, relatively small peritoneal carcinomatosis, but may also have widespread unresectable disease. We investigated whether some HGSCs stage FIGO IIIC are more aggressive than others according to the extensivity of pelvic and abdominal tumor burden. In this regard, we divided the FIGO IIIC HGSC patients based on dominant tumor load (pelvic versus abdominal), calculated using PCI. Comparing the two groups, we found a significant difference in OS. Women without notable tubo-ovarian tumor but with greater peritoneal carcinomatosis had a worse prognosis than women with large primary tumor, but smaller peritoneal disease. In multivariate analysis, the Group remained a significant prognostic marker for OS. These findings support the hypothesis that HGSCs behave differently, with some preferring the abdominal cavity for tumor growth more than their primary localization, causing an adverse end result.

The large volume of ascites has traditionally been accepted as an unfavorable prognostic sign in ovarian cancer patients. Szender et al. concluded that patients with more than 2 l ascites achieve fewer complete surgical resections. When they limited calculations to patients with FIGO stage IIIC/IV of disease, those with large volume ascites had significantly shorter OS when compared with patients with lower volume ascites (14). In the current analysis, Group 2 patients had a notably larger volume of ascites than Group 1. The amount of ascites was associated with cancer-specific death, which is in concordance with the previous study that recognized massive ascites as an independent poor prognostic factor in patients with advanced-stage EOC (15). It was even recommended that the presence of ascites should be included in a nomogram for the prediction of OS in patients with platinum-resistant EOC (16).

Cumulative data have shown that maximal-effort cytoreduction to microscopic residual disease is related to improved OS in HGSC patients. The operative possibilities are often challenged for patients with a high tumor burden, in which, not only the disease itself but also infrastructural resources and expertise may limit optimal treatment. Increasing tumor volume per number of involved abdominal fields negatively affects OS (17). We noticed that Group 1 patients had a significantly higher percentage of OC than Group 2. Multivariate analyses identified OC as an independent prognostic variable for better OS.

Petrillo et al. documented an inverse correlation between *BRCA* mutation status and extrapelvic tumor load in HGSC patients. *BRCA1/2* mutation carriers exhibited a higher rate of peritoneal and diaphragmatic carcinomatosis with greater intraperitoneal tumor size than those without the mutation. They also found a reduced incidence of ovarian masses in *BRCA1/2* mutated women (18). In contrast to previous conclusions, our results suggest that women with larger pelvic tumor, but with lesser abdominal carcinomatosis (Group 1) were significantly more frequently associated with *BRCA1/2* mutation than Group 2. The reason for this conflicting data could be that more BRCA1/2 mutated patients were included in previous investigation. We did not find in a multivariate analysis that *BRCA1/2* mutation status influenced OS. Other studies established that advanced-stage HGSC patients with *BRCA1/2* mutation have better prognosis with longer progression-free survival than those lacking BRCA mutations (19, 20). *BRCA1/2* mutation was more frequent in Group 1, an independent prognostic factor for improved OS.

Although CA125 has its limitations as a prognostic biomarker, it is the most used serum marker in diagnosing, following up, and validating the treatment response of patients with HGSC. In addition, CA125 has received attention in the role of oncogenesis, metastatic potential of EOC, and targeted therapy via interaction with mesothelin, β-catenin, and p120ctn translocation (21). Two CA125 glycoforms, CA125-STn and CA125-MGL, are recognized to have a high specificity to HGSC. Salminen et al. detected a significant difference in the serum levels of these glycoforms in patients with low tumor load and high tumor load while the serum levels of conventional CA125 did not differ

significantly between groups (22). Women with higher abdominal tumor load (Group 2) showed a trend towards increased values of circulating CA125, however, the difference was not statistically significant.

In one large prospective trial, patients with advanced EOC did not benefit from pelvic and paraaortic lymphadenectomy. In contrast, lymphadenectomy resulted in a higher incidence of postoperative complications (23). Significant risk factors for pelvic and paraaortic lymph node involvement in HGSC patients are tumor stage and CA125 level at diagnosis (24, 25). Both of our groups had a similar number of involved lymph nodes. Dominant tumor size did not have a significant influence on lymph node metastasis. Furthermore, lymph node involvement did not affect OS in the present research.

Various analyses speculated that the disease distribution and outcome may be determined by specific cell and molecular subtypes of HGSCs (26, 27). Opponents of extensive surgery advocate that despite the well-established importance of surgical treatment, it is the inherent tumor biology that regulates the resectability of the tumor, not surgical aggressiveness (11). Therefore, other reasons for the survival difference among HGSCs, such as tumor biology and genetic characteristics, need to be analyzed in the future. Heterogeneity within the tumor microenvironment and diverse interactions between tumor, immune, and stromal cells also contribute to the complexity of the HGSC (28).

A few limitations of the study must be taken into consideration. This study is retrospective with a moderate number of patients from a single institution and a relatively short length of follow-up. Detailed information such as dimensions of post-operative tumor residuals, amount of ascites, and a comprehensive description of the tumor spread should be part of every surgical report with translation into a standardized form of the digital bank.

Conclusion

The FIGO stage IIIC of HGSC should evolve from a “one-size-fits-all” approach toward a more personalized treatment strategy that incorporates surgery, chemotherapy, and targeted therapy. The study confirmed the difference in behavior and its impact on survival in the same stage of HGSC. The localization of the main tumor burden (pelvic versus abdominal) is a factor that makes a prognostic difference in FIGO stage IIIC HGSCs.

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PROGNOSTIČKE RAZLIKE TUBO-OVARIJALNOG SEROZNOG KARCINOMA VISOKOG GRADUSA U STADIJUMU IIIC

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Kvantitativne varijacije u peritonealnoj karcinomatozi i veličini primarnog pelvičnog tumora (engl. *tumor size* – TS) mogu odražavati raznolikost u seroznom karcinomu visokog gradusa (engl. *high-grade serous cacinoma* – HGSC) u stadijumu IIIC. Indeks peritonealnog kancera (engl. *the peritoneal cancer index* – PCI) daje precizan dokaz o proširenosti i lokalizaciji volumena tumora. Cilj ove studije bio je da se istraži postojanje razlika između HGSC-a u stadijumu IIIC FIGO klasifikacije (*International Federation of Gynecology and Obstetrics* – FIGO) na osnovu lokalizacije najvećeg volumena tumora i uticaja lokalizacije na ukupno preživljavanje (OS). Pregledana je medicinska dokumentacija primarnih tubo-ovarijalnih HGSC-a od januara 2019. do decembra 2022. godine. Bolesnice su podeljene u dve grupe: grupu sa PCI-jem ≤ 10 i velikim TS-om (Grupa 1, n = 39) i grupu sa PCI-jem > 10 i malim TS-om (Grupa 2, n = 36). Grupa 2 je imala značajno veću zapreminu ascitne tečnosti (p = 0,017). Optimalna citoredukcija (OC) postignuta je kod 53,9% bolesnica u Grupi 1 i samo kod 11,1% bolesnica u Grupi 2 (p < 0,001). *BRCA1/2* mutacija bila je značajno češća u Grupi 1 (p = 0,012). Ukupno preživljavanje bilo je značajno bolje u Grupi 1 nego u Grupi 2 (p < 0,001). Multivarijantna analiza identifikovala je grupu, volumen ascitesa i kompletnost citoredukcije kao nezavisne prognostičke faktore preživljavanja. FIGO stadijum IIIC HGSC-a trebalo bi da evoluira od univerzalnog pristupa do indvidualizovanog pristupa kada je reč o upotrebi hirurgije, hemioterapije i ciljane terapije. Lokalizacija najvećeg volumena tumora predstavlja faktor koji čini prognostičku razliku u stadijumu IIIC HGSC-a.

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***Ključne reči**: serozni karcinom visokog gradusa, FIGO stadijum, indeks peritonealnog kancera, razlika, prognoza*

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1,3-DISUBSTITUTED BENZIMIDAZOL-2-ONE DERIVATIVE AS A DIPEPTIDYL PEPTIDASE-4 INHIBITOR

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The benzimidazole core is a valuable moiety among biologically active compounds, providing a synthetically tractable drug-like scaffold. Some benzimidazole derivatives with inhibitory potential against multifunctional aminopeptidase dipeptidyl peptidase-4 (DPP-4), a promising therapeutic target for type 2 diabetes, have been reported so far. After studying DPP-4 inhibitors with 1,3-disubstituted-benzimidazol-2-imine scaffold, the inhibitory activity of 1,3-disubstituted benzimidazol-2-one derivatives against DPP-4 was evaluated here. 5-Methyl-1,3-bis(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-benzimidazol-2-one (compound **5**) inhibited this protease with IC_{50} value about 200 μM. Although not as potent an inhibitor, compound **5** might contribute to further design and optimizations of benzimidazole based DPP-4 inhibitors.

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Key words: *dipeptidyl peptidase-4, benzimidazole, DPP-4 inhibitors*

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Introduction

Type 2 diabetes is a highly prevalent metabolic disorder, associated with acute and chronic complications, with multifunctional aminopeptidase dipeptidyl peptidase-4 (DPP-4) as a promising therapeutic target (1, 2). The substrates of DPP-4 are incretins, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, participants in the regulation of glucose homeostasis (1). Besides diabetes type 2 as the primary indication for DPP-4 inhibitors, their pleiotropic effects are beneficial in many conditions, encompassing postischemic angiogenesis and myocardial repair following infarction (3), vascular and connective tissue remodeling in pulmonary hypertension (4), with well-established cardiovascular and renal protection (5) etc., which make them a powerful weapon for the treatment (2). The search for new inhibitors continues, and we believe that our previous analysis of the structure-activity relationship (6), so far (7, 8) and these reported results on the assayed DPP-4 inhibitory potential of structurally different candidates, might be a source of ideas for optimizations and contribute to the design of inhibitors with improved activity and more favorable profiles.

Amongst heterocycles, benzimidazole core represents a worthy framework in drug development, due to its valuable diverse pharmacological activities and synthetic tractability in medicinal chemistry, as well as the ease of interactions with biomolecules, enzymes and receptors (9). There are also benzimidazole derivatives among DPP-4 inhibitors (10). Recently, we evaluated a small library of 1,3-disubstituted-benzimidazol-2-imines for inhibitory potential on DPP-4 and xanthine oxidase (XO) and obtained the representative of dual inhibitors (7). After determining DPP-4 inhibitory potential among structures with 1,3-disubstituted-benzimidazol-2-imine scaffold, the inhibitory activity of 1,3-disubstituted benzimidazol-2-one derivatives against DPP-4 was evaluated here.

Materials and Methods

Compounds

The synthesis of the target 1,3-disubstituted benzimidazol-2-one (**1–7**) derivatives was performed as previously described (11).

DPP-4 inhibition assay

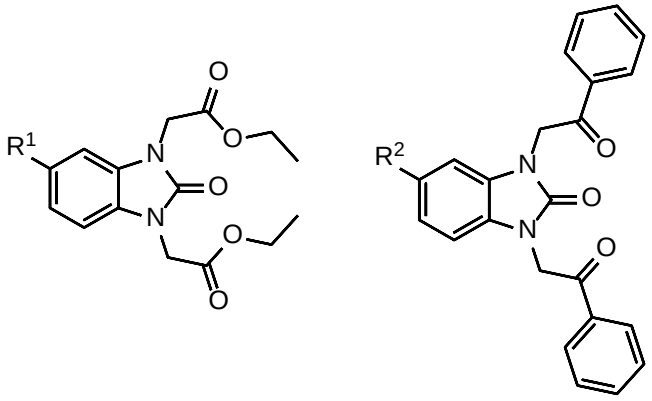
Inhibition of DPP-4 was evaluated on the recombinant human enzyme *in vitro* by the absorbance difference measured at 385 nm, as described in our previous studies (7, 8). Briefly, the enzyme (0.005 units) in 90 mM tris (hydroxymethyl) aminomethane hydrochloride (TRIS-HCl) (pH 7.60) was treated with compounds dissolved in dimethyl sulfoxide. The solvent concentration was 5% v/v. After 15 min of incubation at room temperature, Gly-Pro-*p*-nitroanilide *p*-toluenesulfonate (260 μM) substrate was added, and the reaction was carried out for 60 min at 37 °C. The highest initial concentration of the tested compounds was 200 μM. Diprotin A was used as a reference inhibitor.

Results

The inhibitory activity of the previously synthesized 1,3-disubstituted benzimidazol-2-ones (11) on DPP-4 was evaluated *in vitro*.

Diprotin A (IC_{50} = 17.00 ± 5.15 μM) was used as a reference inhibitor. Only 5-methyl-1,3-bis(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-benzimidazol-2-one (compound **5**) showed inhibitory potential on DPP-4 with IC_{50} value 198.72 ± 4.11 μM (Table 1).

Table 1. *In vitro* DPP-4 inhibitory activity of 1,3-disubstituted benzimidazol-2-ones **1-7**.



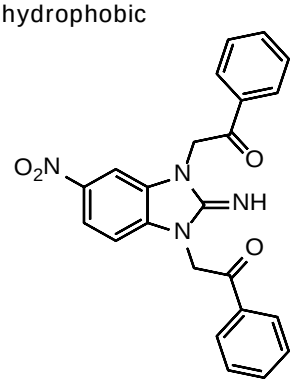
Compound	R^1	R^2	IC_{50} (μM) (mean value ± SD)
1	H		> 200
2	CH_3		> 200
3	NO_2		> 200
4	Cl		> 200
5		CH_3	198.72 ± 4.11
6		NO_2	> 200
7		Cl	> 200

Discussion

In the literature, there are representatives of DPP-4 inhibitors among benzimidazole derivatives, with benzimidazole core involved in the interactions with the protease (10). Recently, we evaluated the inhibitory activity of a small series of 1,3-disubstituted-benzimidazol-2-imines on DPP-4 and XO, and obtained the representative 2-[2-imino-5-nitro-3-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-benzimdazol-1-yl]-1-phenylethanone (Figure 1) as a dual inhibitor, with IC_{50} values below 200 μM on both enzymes, which might contribute to the design of such multitarget candidates (7).

Here, the tested 1,3-disubstituted-benzimidazole (compound **5**) with carbonyl instead of imino group at position 2, with methyl instead of nitro group at position 5, and containing the same substituents at positions 1 and 3, showed lower inhibitory potential compared to the previously examined analogue 2-[2-imino-5-nitro-

3-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-benzimdazol-1-yl]-1-phenylethanone as proved DPP-4 inhibitor. By introducing a methyl instead of a nitro group at position 5, the hydrogen bonding interactions with the enzyme that were achieved with the nitro group in the active structure are presumably absent now. The hydrophobic interactions of the benzimidazole core with the protease will presumably be present. Generally, derivatives with 2-ethoxy-2-oxoethyl instead of 2-oxo-2-phenylethyl substituent at positions 1 and 3 were inactive in tested concentrations.



IC_{50} (DPP-4) = 151.04 ± 3.84 μM
IC_{50} (XO) = 95.94 ± 3.16 μM

Figure 1. Already reported 1,3-disubstituted-benzimidazol-2-imine derivative as dual DPP-4 and XO inhibitor (7)

Conclusion

Benzimidazole is a significant moiety in the libraries of biologically active and therapeutically effective agents. It is a highly privileged drug-like scaffold in medicinal chemistry, synthetically tractable in derivatizations (9). After recently found DPP-4 inhibitor with 1,3-disubstituted-benzimidazol-2-imine scaffold (7), the inhibitory activity of 1,3-disubstituted benzimidazol-2-one derivative 5-methyl-1,3-bis(2-oxo-2-phenylethyl)-1,3-dihydro-2*H*-benzimidazol-2-one (compound **5**) against DPP-4 was proved here. Although it is not a high-potency inhibitor, compound **5** might be useful as a guideline for further optimizations of benzimidazole based DPP-4 inhibitors.

Acknowlegments

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1,3-DISUPSTITUISAN BENZIMIDAZOL-2-ON DERIVAT KAO INHIBITOR DIPEPTIDIL PEPTIDAZE-4

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Benzimidazol je vredan sintetski povoljan *drug-like* skelet. Derivata benzimidazola ima i među inhibitorima multifunkcionalne aminopeptidaze dipeptidil peptidaze-4 (DPP-4), ciljane proteaze u terapiji dijabetesa tipa 2. Nakon proučavanja serije DPP-4 inhibitora sa 1,3-disupstituisanim benzimidazol-2-iminom kao osnovom, u ovom radu je ispitivan inhibitorni potencijal 1,3-disupstituisanih benzimidazol-2-on derivata na ovoj proteazi. 5-Metil-1,3-bis(2-okso-2-feniletil)-1,3-dihidro-2*H*-benzimidazol-2-on (jedinjenje **5**) inhibirao je aktivnost DPP-4 sa IC_{50} vrednošću koja je iznosila oko 200 μM. Iako nije tako potentan inhibitor, jedinjenje 5 može doprineti dizajnu i optimizaciji inhibitora DPP-4 sa benzimidazolom kao osnovom.

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***Ključne reči**: dipeptidil peptidaza-4, benzimidazol, inhibitori dipeptidil peptidaze -4*

Original article

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ASSESSMENT OF SPONTANEOUS MOTOR ACTIVITY IN PREDICTING NORMAL NEUROMOTOR DEVELOPMENT IN PRETERMS

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Conventional methods of neurological assessment of newborns and infants are in daily clinical use. Since preterm newborns often have multiple risk factors for further neuromotor developmental disorders, this study aimed to determine the predictive value of spontaneous motor activity in preterms during the fidgety period for normal neurological and functional outcomes at the age of 24 months.

The study was performed as a prospective clinical study and included 80 preterm children. Observation of spontaneous motor activity was carried out according to the basic principles of Prechtl's method in the period 50–54 weeks of postmenstrual age.

All participants who showed normal fidgety movements during this period had normal neuromotor development after 24 months. Among participants with a final neurological outcome of minimal neurological dysfunction after 24 months, 73% showed abnormal fidgety movements. In the study, there were no subjects who had a normal presentation of fidgety movements and later, at the age of 24 months, were found to have neurological deficits and clinical signs suggesting the subsequent development of cerebral palsy. Preterm infants with (very) low birth weight, those born before the 30th gestational week, and those with a low Apgar score have a higher chance of neurodevelopmental deviations.

Such a high predictive value of normal general movements in period 50–54 weeks of postmenstrual age, confirms the practical importance of assessing general movements and the need for developmental follow-up for all preterm infants.

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Key words: *preterm infants, spontaneous motor activity, Prechtl's method, neurodevelopmental outcome*

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Introduction

The motor development of newborns and infants occurs completely spontaneously and directly depends on the state of the central nervous system. Conventional methods of neurological assessment of newborns and infants include neurological examination, neurokinesiological examination, quantitative assessment using scales and tests, as well as the use of supplementary diagnostic procedures such as magnetic resonance imaging, ultrasound diagnostics, and electroencephalography. All the aforementioned methods are in daily clinical use for the neurological assessment of newborns and infants (1).

These methods can provide very precise data on the damage to the central (and peripheral) nervous system, but they all share a common drawback: the inability to adequately predict neurological deficits. This fact prompted the need for a new technique and a new approach. In the early 1960s, Professor Heinz Prechtl, an Austrian neurophysiologist, attempted to create an adequate method for neurological examinations of newborns. Prechtl believed that birth could not be the starting point, but that spontaneous motor activity (SMA) must have a prenatal history. His research especially advanced with the advent of ultrasound diagnostics. The first breakthrough was discovering that complex whole-body movements occur intrauterine in the ninth and tenth weeks of postmenstrual age (PMA). Prechtl called these movements "general movements" (GMs). Their characteristic is that they are generated endogenously, are complex, and have a specific sequence of body parts involvement. Prechtl proved that GMs are present throughout the entire prenatal period and continue to exist until the 5th–

6th months post-term. Pre-term, Prechtl referred to GMs as fetal or preterm movements. At term, post-term, and up to the 6th (sometimes up to the 9th) week post-term, Prechtl called GMs "writhing" movements. During the period from the 6th to the 9th week post-term, "writhing" movements gradually disappear, and new GMs appear, which Prechtl called fidgety movements. Fidgety movements cease to manifest between the 5th and 6th month post-term. After that, voluntary and anti-gravitational movements appear and dominate (2).

Given the inconsistent and variable responses of the immature nervous system, a one-time assessment of newborns cannot provide a definitive answer regarding the presence of a particular neurological disorder. Therefore, examinations need to be repeated, which in clinical practice is called developmental monitoring. Developmental monitoring should be conducted for preterm infants, children with complications during birth, and generally for children born from high-risk pregnancies, with the aim of early diagnosis and timely treatment.

Risk factors for neuromotor developmental disorders in newborns are divided into prenatal, perinatal, and postnatal. Prenatal risk factors include all adverse morphological, circulatory, chemical, and infectious agents originating from the mother, such as anatomical and functional anomalies of the mother's reproductive system. Perinatal risk factors relate to prematurity, low birth weight of the newborn, Apgar score, multiple pregnancies, birth trauma, inadequate fetal presentation, delivery by cesarean section, etc. Postnatal risk factors are numerous, with the most common being intracranial hemorrhages, afebrile convulsions, exposure to toxic substances, and severe septic conditions (3).

Since there is a reasonable suspicion that a newborn exposed to risk factors could have a developmental deficit as a consequence, the aim of this study was to determine the predictive value of spontaneous motor activity in preterm newborns with certain risk factors, during the fidgety period, for normal neurological and functional outcomes at the age of 24 months.

Materials and Methods

The study was conducted as a prospective clinical trial as part of an investigation for the doctoral thesis (4, 5). All babies born between January 1, 2012, and December 12, 2012, at the maternity ward of the Gynecology and Obstetrics Clinic of the Clinical Centre Niš, with a gestational age ≤ 37 weeks were included in the study.

Exclusion criteria were parental refusal to participate in the study, presence of congenital anomalies, deformities, and genetic syndromes in the newborn, invalid video recordings, and failure to attend follow-up examinations (incomplete study).

During the study period, 3328 babies were born at the Gynaecology Clinic of the Clinical Centre Niš, of which 233 were preterm infants (≤ 37 weeks GA). During the study, a certain number of newborns were excluded due to fatal outcomes, transfer to other healthcare facilities (deterioration of general condition, other diseases), and failure to attend follow-up examinations (incomplete study). A total of 80 newborns completed the study.

For each newborn included in the study, detailed anamnestic data were collected, including gender, gestational age, birth weight and length, head circumference, Apgar score at the 1st and the 5th minute, data on multiple (twin) pregnancies, data on the mode of delivery, and cranial ultrasound findings. Cranial ultrasound findings were categorized as follows: US 1—normal finding; US 2—hyperechogenicity of the brain parenchyma lasting up to 14 days; US 3—hyperechogenicity of the brain parenchyma lasting more than 14 days; US 4—intraventricular hemorrhage; US 5—periventricular leukomalacia.

Assessment of spontaneous motor activity was performed according to the basic principles of Prechtl's method. The assessment of spontaneous motor activity was conducted by a trained individual with a valid license for evaluating spontaneous motor activity, based on video analysis.

A video camera was used to record the video. Necessary conditions for an adequate video recording included the relaxed awake state of the newborn: absence of crying, open eyes, irregular respiration, and the presence of movements. Given that behavioural states are not established before the 36th week of postmenstrual age, preterm infants below 36 gestational weeks were recorded during movement episodes, regardless of whether the newborn was awake or asleep. During the recording, the newborns were in a supine position on a flat surface (bed, mat), in diapers or minimal clothing to ensure unrestricted movement, with the face constantly visible and without a pacifier. During video recording, all distracting items from the environment, such as noise, the presence of parents and other people, toys, colourful blankets, mirrors, and similar objects, were removed. The room temperature was appropriate for the newborn's age and clothing.

For the assessment of spontaneous motor activity in the fidgety period, newborns were recorded between 50 and 54 weeks PMA. For this period, three types of movements were defined:

- F—Fidgety movements, movements of small amplitude, moderate speed, and variable acceleration, occurring in the head, neck, trunk, as well as the extremities, primarily in the distal parts (radio-carpal and talo-crural joints). They manifest continuously in the awake infant, except during crying. They can be observed as early as the 6th week post-term, but usually appear around the 9th

week and are present until the 20th week or even a few weeks longer.

● F—Absence of fidgety movements represents motor activity where the described fidgety movements are not registered.

● AbF—Abnormal fidgety movements look like normal fidgety movements, but their amplitude and speed are moderately or significantly greater.

The definitive neurological outcome was assessed based on a detailed neurological examination at 24 months of age (corrected calendar age). The examination was conducted by a well-trained and experienced neurologist specializing in paediatric neurology. The examination included a detailed assessment of muscle tone, reflexes, posture, and movements. The neurological outcome was classified as follows:

●Normal (completely normal neurological findings);

●MND—minimal neurological dysfunction, according to TINE criteria (Touwen Infant Neurological Examination) or nonspecific signs without clear and definitive signs of cerebral palsy;

●CP—cerebral palsy according to SCPE criteria (6, 7).

For subjects who exhibited motor deficits corresponding to CP at the age of 2 years, the neurological examination was repeated, and the definitive diagnosis was made at the age of four years according to the previously described SCPE criteria (6, 8).

Statistical data analysis was performed using SPSS 16.0 software. Mann–Whitney and Kruskal–Wallis tests were used to compare the values of continuous variables between groups. Proportions of categorical variables between groups were compared using the Pearson Hi2 test. To evaluate the diagnostic value of the assessment of spontaneous motor activity of newborns and infants in predicting the outcome after 24 months, the following were used: sensitivity, specificity, prevalence, positive predictive value, negative predictive value and 95% confidence interval (CI). Statistical significance was defined as p-value < 0.05.

Results

Table 1 presents the clinical characteristics of the participants, as well as their relation to the final neurological outcome at 24 months of the corrected calendar age. The final neurological outcome of the participants is categorized as normal, MND, and CP. Statistically significant outcomes associated with CP were observed more frequently in preterm infants born before 30 weeks of gestation, those with very low birth weight and length, and those with low Apgar scores at the 1st and 5th minute. Other monitored characteristics did not statistically significantly affect the neurological outcome at 24 months corrected calendar age.

The prevalence of general movements (GMs) in the observation period of 50–54 weeks of gestational age significantly differs concerning the neurological outcome after 24 months ($p < 0.001$). One hundred percent of participants who exhibited normal fidgety movements during this period had normal neuromotor development. In the CP group, there were no participants with normal presentation of fidgety movements. During the same observation period, among participants with a final neurological outcome of MND at 24 months, 73% showed abnormal fidgety movements (Table 2).

Table 1. Clinical characteristics of preterms in relation to neuromotor outcome after 24 months

Clinical characteristics	Outcome after 24 months				
	Normal	MND	CP	Summarized	p
Gestational age	35 (35–36) GW	35 (33–35) GW	29 (27–29) GW	35 (34–36) GW	< 0.05
< 30 weeks	2%	–	100%	10%	< 0.001
≥ 30 weeks	98%	100%	–	90%	
Gender					
Female	48%	45%	57%	49%	n.s.
Male	52%	55%	43%	51%	
Twins					
No	74%	82%	100%	77.5%	n.s.
Yes	26%	18%	–	22.5%	
Caesarean section					
No	65%	55%	43%	61%	n.s.
Yes	35%	45%	58%	39%	
Birth weight (g)	2150 (2000–2350)	1750 (1350–2400)	1320 (1250–1350)	2125 (1800–2350)	< 0.01
Birth body length (cm)	45 (42–47)	44 (43–45)	39 (35–40)	44 (42–47)	< 0.05
Head circumference (cm)	30 (29–32)	30 (28–32)	28 (26–29)	30 (28.5–31)	n.s.
Apgar score (1st minute)	8 (8–9)	8 (8–8)	6 (1–7)	8 (8–9)	< 0.001
Apgar score (5th minute)	9 (8–9)	8 (8–8)	7 (5–8)	9 (8–9)	< 0.001

n.s.—non significant

Table 2. General movements of preterms in the fidgety period in relation to neuromotor outcome after 24 months

	Outcome after 24 months				
GMs 50–54 gestational weeks	**Normal (n = 62)**	**MND (n = 11)**	**CP (n = 7)**	**Summarized (n = 80)**	**p**
F	62 (100%)	–	–	62 (72.5%)	< 0.001
AbF	–	8 (73%)	–	8 (10%)	
F-	–	3 (27%)	7 (100%)	10 (12.5%)	

To further determine the significance of normal findings, i.e., fidgety movements in the period of 50–54 weeks of gestational age, the diagnostic value of this finding in predicting CP as a final outcome was evaluated (Table 3). Without any test, the probability of developing CP was 8.8% (95% CI; 3.6–17.2%). If the GMs findings were normal during the 50–54 weeks of gestational age, the probability that the participant would have CP as a final outcome was 0% (95% CI; 0–5.8%). Without any test, the probability that the participant would not develop CP was 91.2% (82.8–96.4%). If the GMs findings were abnormal during the 50–54 weeks of gestational age, the probability of the participant not developing CP as a final outcome was 61.1% (35.8–82.6%).

Figure 1 shows that significant deviations from normal intracranial ultrasound findings were the least in the group of participants who had a normal final neurological outcome. The greatest deviations were observed in the group of participants with CP as the final neurological outcome ($p < 0.001$). Pathological or altered intracranial ultrasound findings statistically significantly differed between groups with final neurological outcomes (normal, MND, CP) ($p < 0.05$). Altered findings were most common in participants with CP and least common in those with a normal neurological outcome.

Table 3. Evaluation of the diagnostic value of normal findings during the observation period in predicting the development of CP in the final neurological outcome

Normal finding GMs 50–54 gestational weeks	**CP**		**Summarized**
	Yes	**No**	
Yes		62	62
No	7	11	27
Summarized	7	73	80
Sn	0% (95% CI; 0–41%)		
Sp	15.1% (95% CI; 7.8–25.4%)		
Prev	8.8% (95% CI; 3.6–17.2%)		
PPV	0% (95% CI; 0–5.8%)		
NPV	61.1% (95% CI; 35.8–82.6%)		

Sn—sensitivity; Sp—Specificity; Prev—prevalence; PPV—positive predictive value; NPV—negative predictive value

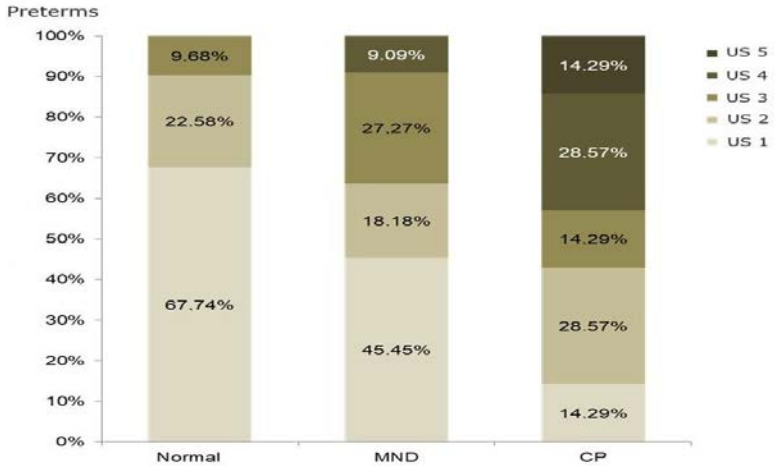

Figure 1. Neurological outcome of preterms in relation to intracranial ultrasound findings (by categories)

Discussion

In this study, the assessment of spontaneous motor activity was performed on newborns belonging to the preterm infant group. The reason for selecting this group is the fact that preterm infants have a higher chance of neuromotor developmental deviations, making their identification a significant challenge (9–14). According to this study, preterm infants with very low birth weight and length, those born before the 30th gestational week, and those with a low Apgar score at the 1st and 5th minute have a higher chance of these deviations. Similar results were published previously (15–17).

This study was performed during the period of fidgety movement manifestation, specifically at the time when the most intense presentation of these movements is expected, between 50–54 weeks postmenstrual age (PMA). The final neurological outcome was assessed at the age of 2 years (corrected calendar age—CCA). For subjects who exhibited motor deficits corresponding to CP at the age of 2 years CCA, a repeated neurological examination was performed, and the definitive diagnosis was established at the age of four years according to the SCPE criteria (8).

The earlier manifestation of fidgety GMs is characteristic of preterm infants. Numerous experiments have been conducted to investigate the effects of visual, acoustic, social, and proprioceptive stimuli on the quality and timing of fidgety movements. No stimulus changes the quality of fidgety movements. Prechtl et al. studied the fidgety movements of completely blind infants with no evidence of brain injury. The research showed an increased frequency of fidgety movements, and Prechtl et al. concluded that this was a form of compensation due to the lack of visual integration. Prechtl considered that fidgety movements represent a precise adjustment of the proprioceptive system (18).

We can wonder if newborns and infants with normal presentation of spontaneous movements can have a pathological neurodevelopmental outcome. Recent studies have shown that such cases are rare but do exist (19, 20). The pathological outcomes range from mild forms of CP to ADHD syndrome, particularly in high-risk infants who have shown normal fidgety movements. In the present study, this was not the case. The evaluation of diagnostic value in this study concluded that if the finding was normal, i.e., if there was a presentation of F GMs, the probability of CP as the final neurological outcome was 0%. This data confirms the high predictive value of F GMs, which is also supported by eminent experts in the field of GMs (21).

Fidgety movements also have their pathological forms. One of them is AbF GMs. In this study, AbF GMs were registered in 8 preterm infants. The results of this study indicate that AbF GMs have low predictive value for the development of CP. They also indicate that the probability of an infant with AbF GMs developing CP as the final outcome is 0%. All subjects in this study who had AbF GMs developed MND as the final neurological outcome. Similar studies have been conducted by other researchers. Einspieler et al. investigated AbF GMs as an early marker for MND (22). They concluded that AbF GMs have low predictive value for the development of CP and complex forms of MND. This movement manifestation has good predictive value for the simple form of MND, which involves a lack of fine motor skills.

In this study, all 10 subjects who had registered F- GMs during the observation period had a neurological deficit as the final neurological outcome, with 7 subjects having CP and 3 subjects having MND. This result is consistent with previous research (23–25). All previous studies that have examined GMs have confirmed the high predictive value of F- GMs. They have shown that infants who do not exhibit F GMs during the expected manifestation period have a high risk of developing neurological deficits later in life. Morgan et al., in their study conducted in Australia on 259 subjects, registered F- GMs in 48 of them. Of these 48 subjects, 39 developed CP as the final neurological outcome, while the remaining 9 also did not have a normal neurological outcome, instead showing neurological deficits of the MND type (26). Burger et al. systematically analyzed 17 studies on the predictive value of fidgety movements, particularly the absence of fidgety movements. A total of 1926 subjects were observed, of which 90% belonged to the preterm group. The subjects were followed up to the age of 12–24 months corrected calendar age. The conclusion of their study is the high sensitivity and specificity for fidgety movements (sensitivity 98%, specificity 94%) (27). In a similar study on the predictive value of fidgety movements, Romeo et al. published identical results in their study on 900 newborns (28).

Comparing the ultrasound (US) findings of the brain with the final neurological outcome in this study, it can be concluded that a normal US finding does not have a high predictive value for later neurological deficits and the development of MND and CP. The results of this study indicate that subjects with normal US brain findings can have a pathological neurological outcome, which correlates with previously described studies. Additionally, the results of this study suggest that a pathological US finding has predictive value for later neurological deviations. A pathological US finding is statistically significantly more frequent in subjects who had CP as the final outcome ($p < 0.05$). All obtained results are consistent with Prechtl's studies on the predictive value of US brain findings. Prechtl concluded that the finding of increased echogenicity of brain tissue has a transient character and weak prognostic value, especially if it lasts less than two weeks. It is important to emphasize that despite the utility and necessity of US diagnostics, studies have described cases of children diagnosed with CP who had normal US brain findings in the first months of

life (29). Certainly, an abnormal US finding in most cases necessitates an MRI examination and further monitoring (13, 30).

Conclusion

The results of this study confirm the practical importance of assessing general movements and the need for developmental follow-up for all preterm infants. A finding indicating normal general movements during the 50–54 weeks of age, resulted in a normal outcome for all subjects after 24 months. Such a high predictive value of this finding suggests the need for wider application of this method and, consequently, the need for the education of professionals.

Early detection of any neurological deficit symptoms is crucial as it allows for the timely inclusion of children in neurodevelopmental treatment, contributing to the improvement of functional motor status at a later age, considering the biological phenomenon of brain plasticity.

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PROCENA SPONTANE MOTORIČKE AKTIVNOSTI U PREDIKCIJI NORMALNOG NEUROMOTORIČKOG RAZVOJA KOD PREMATURUSA

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Konvencionalne metode neurološke procene novorođenčadi i odojčadi upotrebljavaju se u svakodnevnoj kliničkoj praksi. Budući da kod prevremeno rođene dece postoji više faktora rizika za nastanak neuromotoričkih razvojnih poremećaja, cilj ovog istraživanja bio je da se utvrdi prediktivna vrednost spontane motoričke aktivnosti za normalan neurološki i funkcionalni ishod u uzrastu od 24 meseca kod prevremeno rođene dece u tzv. *fidgety* periodu.

Studija je sprovedena kao prospektivna klinička studija i obuhvatila je osamdesetoro prevremeno rođene dece. Procena spontane motoričke aktivnosti vršena je prema osnovnim principima Prechtlove metode u periodu od 50. do 54. nedelje postmenstrualnog uzrasta.

Svi ispitanici kod kojih su evidentirani normalni *fidgety* pokreti imali su i uredan neuromotorički nalaz u uzrastu od 24 meseca. Među decom koja su kao konačan neurološki ishod imala nalaz minimalne neurološke disfunkcije nakon 24 meseca, 73% njih pokazalo je abnormalne *fidgety* pokrete. U istraživanju nije bilo ispitanika kod kojih je uočena normalna prezentacija *fidgety* pokreta, a kod kojih su u uzrastu od 24 meseca evidentirani neurološki deficit i klinička slika koja ide u prilog kasnijem razvoju cerebralne paralize. Veće šanse za razvoj neurorazvojne devijacije imaju deca rođena pre termina sa (veoma) malom porođajnom težinom, prematurusi rođeni pre 30. gestacijske nedelje, kao i deca sa niskim vrednostima Apgar skora.

Visoka prediktivna vrednost nalaza normalne spontane motoričke aktivnosti u periodu od 50. do 54. nedelje postmenstrualne starosti potvrđuje praktičnu važnost procene spontane motoričke aktivnosti i potrebu za praćenjem razvoja sve prevremeno rođene dece.

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***Ključne reči**: prevremeno rođena deca, spontana motorička aktivnost, Prechtlov metod, neurorazvojni ishod*

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PREVALENCE OF BURNOUT AND DEPRESSIVE SYMPTOMS AMONG HEALTHCARE WORKERS IN THE CORONAVIRUS DISEASE 2019 PANDEMIC IN BELGRADE

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A cross-sectional study was conducted among all the employees of the "Barajevo" Health Center using the following questionnaires: Maslach Burnout Inventory-Human Services Survey (MBI-HSS) for measuring three aspects of the burnout syndrome (emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA)); Patient Health Quality 9 (PHQ-9) for self-assessment of depressive symptoms, and sociodemographic characteristics of respondents were collected through a general questionnaire. Only completely completed questionnaires were included in the study, which was 71. No statistically significant differences were found between the frequency of depressive symptoms based on the score of the PHQ9 questionnaire among both medical and non-medical personnel as well as among employees in the COVID-19 and non-COVID-19 zones. Based on the average values of the scores of the PHQ9 questionnaire, it was determined that the employees who worked in the COVID-19 zone had a significantly higher ($p < 0.05$) average value of the PHQ9 score (6.84 ± 5.73) compared to the average value of the PHQ9 score of employees in the non-COVID-19 zone (4.00 ± 3.70). A moderate to high level of emotional exhaustion was observed in more than 50% of respondents. Low level of depersonalization was noted in 70.4%, whereas the majority of employees, 53.5%, exhibited low levels of personal accomplishment. Only 1 patient (1.4%) met all three criteria for high burnout, while 67 (94.4%) of them belonged to the moderate overall burnout category.

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Key words: *burnout syndrome, coronavirus disease 2019, healthcare workers, symptoms of depression*

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Introduction

The spread of the SARS-CoV-2 virus and the resulting coronavirus disease 2019 (COVID-19) pandemic have been associated with burnout syndrome (BS), depression and anxiety among healthcare workers (HCWs) (1). In recent years, the effect of work on the physical and mental health of professionals has been an important subject (2). The term work stress was first introduced by McGrath in 1970 and defined as the imbalance perceived between a demand and the individual's capacity to fulfill it under certain conditions where failing to fulfill that demand entails significant consequences (3). Although the initial studies concerning the work satisfaction of health professionals were done by Donabedin in 1966, and later by Freebon and Greenlick in 1973, it was not until 1974 that psychoanalyst Herbert Freudenberger talked of work disease for the first time, defining the burnout syndrome as a state of exhaustion or frustration resulting from dedication to a cause, way of life, or relationship that does not result in the expected reinforcement (3). Christina Maslach, one of the first authors and researchers on this concept, developed the Maslach Burnout Inventory (MBI), which is considered the gold standard for evaluating burnout syndrome. According to Maslach, emotional excitement at work and the way of confrontation have significant consequences on the professional identity of employees and their behavior at work. The most important components of the burnout syndrome are feelings of emotional exhaustion (EE), depersonalization (DP), and perception of reduced personal accomplishment

(PA) (4). Burnout has been associated with impaired job performance and poor health issues, including headaches, sleep disturbances, irritability, marital difficulties, fatigue, hypertension, anxiety, depression, and myocardial infarction, and may contribute to alcoholism and drug addiction. Symptoms of burnout can lead to physician errors, and these errors can, in turn, contribute to burnout. Dissatisfaction and distress have significant costs for physicians and their families, patients and healthcare organizations (5). As we can see from the above, one of the symptoms that can cause burnout syndrome is depression, which, according to some studies, is the most common symptom among health workers (6). Burnout is a syndrome that occurs more frequently in professions that are closely related to helping people, such as social workers, healthcare professionals, teachers and police officers (4). According to Vieira, in health professionals, it occurs at a rate between 30% and 47% (2).

This study aimed to analyze burnout syndrome and depressive symptoms among employees of the healthcare facility "Barajevo" in Belgrade during the COVID-19 pandemic.

Materials and Methods

A cross-sectional study was conducted from June to September 2022 on the population of respondents represented by all employees of the primary Health Center "Barajevo" in Belgrade. The criteria for inclusion of respondents in the research were the following: adults (> 18 years), permanent employment in the mentioned sector and voluntary consent to participate in the study. Exclusion criteria: minors (< 18 years), discontinuity in work for more than a year, and persons who refused to participate. This study was approved by the Board of Directors of the Primary Health Center "Barajevo" in Belgrade on June 9, 2022. The data for this study were obtained by voluntary filling of anonymous questionnaires by the respondents. The representative sample size was 89, of which 71 participants filled out all questionnaires (7).

For this research, a general questionnaire was constructed, and two more were used: BMI-HSS and PHQ-9.

The general questionnaire consisted of 20 questions and was used to collect the basic sociodemographic data of the respondents (gender, age, marital status, education level, work zone (COVID-19 or non-COVID-19), children, length of service, satisfaction with working conditions, housing issue, income issue, illness from COVID-19, vaccination against COVID-19).

The Maslach Burnout Inventory Human Services Survey (MBI-HSS) contains 22 questions with 3 subscales that measure the level of EE, DP and PA. Respondents circled one of the provided answers on a seven-point Likert scale (0—never, 1—few times a year or less, 2—once a month or less, 3—several times a month, once a week, 5—several times a week, 6—every day). Table 1 shows the border values of emotional exhaustion (EE), depersonalization (DP), and personal accomplishment (PA).

Table 1. Border values of emotional exhaustion, depersonalization, and personal accomplishment

Emotional exhaustion	Depersonalization	Personal Accomplishment
Level Value	Level Value	Level Value
Low 0–16 points	Low 0–6 points	Low 0–31 points
Medium 17–26 points	Medium 7–12 points	Medium 32–38 points
High 27 points and more	High 13 points and more	High 39 points and more

The 9 questions contained in the PHQ-9, respondents answered by circling one of the provided answers. The answer to each of 9 questions on a four-point Likert scale was scored 0−3 (not at all = 0, a few days = 1, more than half a day = 2, almost every day = 3), the points were also added depending on the highest score, and the severity of assessed depressive episode (0−4 no depressive symptoms, 5−9 subclinical form of depression, 10−14 mild depressive episode, 15−19 moderately severe and > 20 indicated severe depressive episode).

Statistical analysis

The obtained test results were compared by statistical analysis using Microsoft Excel 2010, GraphPad Prism software, version 9.00 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com) and IBM SPSS Statistics 25 software. The chi-square test was used to compare frequencies between sociodemographic characteristics. Differences were considered significant if the observed value was $p < 0.01$ and $p < 0.05$. All values in tables and figures are presented as mean ± standard deviation. Spearman's correlation coefficient (ρ) was used for measurement of the strength and direction of association between two ranked variables.

Results

A total of 71 respondents (13 male and 58 female) participated in the research. The response

rate was 62.28%. Significantly more ($p < 0.01$) employees were women (81.69%), older than 40 years (75%), medical staff (including technicians, nurses, physiotherapists) (57.35%), in either a marital or extramarital union (80.60%), working in shifts and partially satisfied with working conditions (64.79%), having 6–8 hours of sleep (80.28%), length of vacation 31–40 days (70%) and working in the COVID-19 zone (71.43%). More than half of the participants (60.56%) completed primary and secondary school, while 39.44% completed college. There was no statistically significant difference in the level of education in our study population ($p = 0.075$). Significantly fewer ($p < 0.01$) employees had managerial positions (15.38%) and less than 5 years of service (17.91%) (Table 2). The average values of age, length of working hours, length of sleeping hours, years of employment and length of vacation were (47.5 ± 10.33; 7.33 ± 1.26; 6.80 ± 1.29; 18.61 ± 12.9; 32.98 ± 6.53 days). Monthly incomes above the minimum wage had 61.97% employees, less than three-fifths were house owners and 60 (84.50%) had children. Less than three-quarters of respondents were vaccinated against COVID-19 and 43 (60.56%) of them were infected with this disease.

After analyzing the answers received (Figure 1), it was determined that there were 26 medical staff respondents without depressive symptoms (48%), which is significantly more ($p < 0.01$) than the group of medical staff who had mild depressive episodes, (11%) 6 respondents, moderately severe depressive episode, (7%) 4 respondents, and severe depressive episode, (2%) 1 respondent. Further, it was found that there were significantly more respondents who had a subclinical form of depression, (32%) 17 respondents, compared to medical staff with a mild depressive episode ($p < 0.05$), as well as those with moderately severe and severe depressive episode ($p < 0.01$). The average score of the PHQ9 questionnaire for medical staff was 6.15 ± 5.54.

There were no non-medical staff who showed a severe depressive episode according to this questionnaire ($n = 0$), which was significantly less ($p < 0.05$) compared to respondents without depressive symptoms according to the score in the PHQ9 questionnaire, (43%) 6 respondents, and those with a subclinical form of depression, (36%) 5 respondents (Figure 2). The average score of the PHQ9 questionnaire for non-medical staff was 6.00 ± 5.00. No statistically significant differences were found between the frequency of depressive symptoms based on the score of the PHQ9 questionnaire among medical and non-medical staff.

Analyzing the responses of working staff in COVID-19 zone, it was determined that significantly more ($p < 0.01$) respondents were without depressive symptoms (44%; 22) compared to those whose questionnaire score indicated mild (10%; 5), moderately severe (12%; 6) and severe depressive episode (2%; 1). Further, significant differences were found between respondents with a score 5–9 (32%; 16) compared to those with a score of 10–14 and 15–19 ($p < 0.05$), as well as respondents with a score ≥ 20 ($p < 0.01$) (Figure 3). The average value of the PHQ9 questionnaire score for staff in the COVID-19 zone was 6.84 ± 5.73.

There were 60% (12) of employees in the non-COVID-19 zone without symptoms of depression, which was significantly more ($p < 0.01$) than employees who had a score of 10–14 (10%; 2), 15–19 (0%) and ≥ 20 (0%). Further, there were significantly more ($p < 0.05$) employees in the non-COVID-19 zone with a score 5–9 (30%; 6) compared to respondents with a score of 15–19 and ≥ 20 (Figure 4). The average PHQ9 questionnaire score in employees in the non-COVID-19 zone was 4.00 ± 3.70. No statistically significant differences were found between the frequency of depressive symptoms among employees in the COVID-19 and non-COVID-19 zones. No statistically significant correlation was found between the PHQ9 score and the age of the respondents ($p = 0.45$; $r = -0.093$), the length of work experience ($p = 0.90$; $r = 0.01$), as well as the length of vacation ($p = 0.76$; $r = -0.04$), i.e., correlation relationship does not exist. Among the employees who worked in the COVID-19 zone, a significantly higher ($p < 0.05$) average value of the PHQ9 score (6.84 ± 5.73) was found compared to the average value of the PHQ9 score (4.00 ± 3.70) in employees who worked in the non-COVID-19 zone.

After analyzing the answers received from our respondents about presence and level values of burnout syndrome, it was found that the mean score for emotional exhaustion was 17.8 ± 15.5. Moderate to high levels of emotional exhaustion were observed in more than 50% of patients (Table 3). Additionally, the mean score for depersonalization was 4.8 ± 6.6, with scores distributed as 70.4% in the low range, 22.5% in the moderate range, and 7.0% in the high range of burnout. The average personal accomplishment score was 24.1 ± 15.9. Based on these subscale outcomes, it is noteworthy that most patients exhibited low levels of burnout, accounting for 53.5% of the participants.

Overall, only 1 patient (1.4%) met all three criteria for high burnout (high emotional exhaustion, high depersonalization, and low personal accomplishment) and 4.2% of patients met all three criteria for low burnout (low emotional exhaustion, low depersonalization, and high personal accomplishment) revealing that 94.4% of our study population belonged to moderate overall burnout category.

Table 2. Sociodemographic characteristics of employees

Parameter		N	(%)
Gender	Male	13	18.31[A]
	Female	58	81.69[A]
Age*	< 40	17	25.00[A]
	≥ 40	51	75.00[A]
Marital status*	Union (married/extramarital)	54	80.60[A]
	Single	13	19.40[A]
Education*	Primary/Secondary school	43	60.56
	High education	28	39.44
Occupation*	Non-medical staff	14	20.59[A]
	Medical staff (technicians, nurses, physiotherapists)	39	57.35[AB]
	Medical staff (doctors, specialists)	15	22.06[B]
Higher position in company*	Yes	10	15.38[A]
	No	55	84.62[A]
Working in shifts*	Yes	46	64.79[A]
	No	19	35.21[A]
Duration of working hours*	7	42	93.33[A]
	12	3	6.67[A]
Satisfaction with working condition	Yes	10	14.08[A]
	No	15	21.13[B]
	Neither	46	64.79[AB]
Hours of sleep	< 6 hours	9	12.68[A]
	6–8 hours	57	80.28[AB]
	> 8 hours	5	7.04[B]
Length of vacation per day*	Up to 30	18	30.00[A]
	31–40	42	70.00[A]
Years of employment*	Up to 5	12	17.91[AB]
	5–20	24	35.82[A]
	≥ 20	31	46.27[B]
Work zone*	COVID-19	50	71.43[A]
	Non-COVID-19	20	28.57[A]

*If the number of the answer (n) is less than 71, the difference in the number is respondents who did not want to answer the question

A, B–statistically significant difference at the significance level $p < 0.01$

Table 3. Levels of emotional exhaustion, depersonalization, personal accomplishment and overall burnout syndrome

Domain	Mean ± SD	Low, n (%)	Moderate, n (%)	High, n (%)
Emotional exhaustion	17.8 ± 15.5	35 (49.3)	15 (21.1)	21 (29.6)
Depersonalization	4.8 ± 6.4	50 (70.4)	16 (22.5)	5 (7.0)
Personal accomplishment*	24.1 ± 18.9	38 (53.5)	19 (26.8)	14 (19.7)
Overall burnout		3 (4.2)	67 (94.4)	1 (1.4)

* The accomplishment subscale is interpreted in the opposite direction as the emotional exhaustion and depersonalization subscales. High burnout: high emotional exhaustion, high depersonalization, and low personal accomplishment; low burnout: low emotional exhaustion, low depersonalization, and high personal accomplishment.

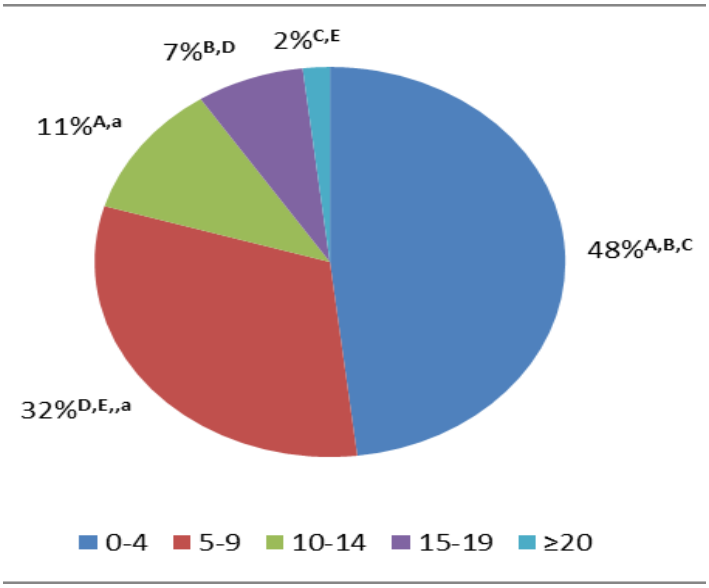

Figure 1. Frequency of depressive symptoms among medical staff according to the score in the PHQ9 questionnaire

A, B, C, D, E–$p < 0.01$; a–$p < 0.05$

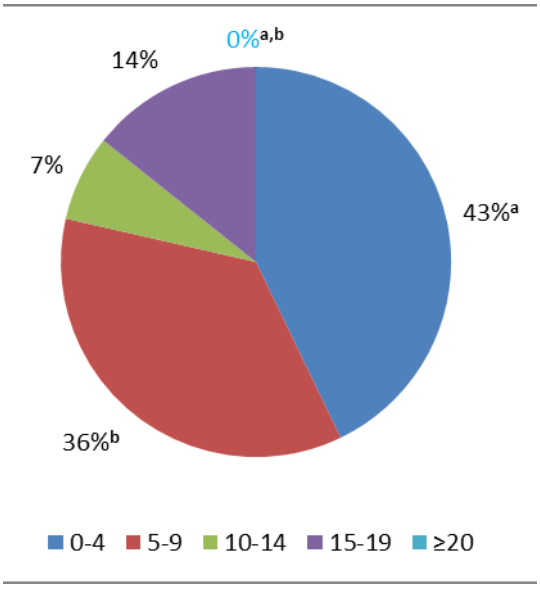

Figure 2. Frequency of depressive symptoms among non-medical staff according to the score in the PHQ9 questionnaire

a, b–$p < 0.05$

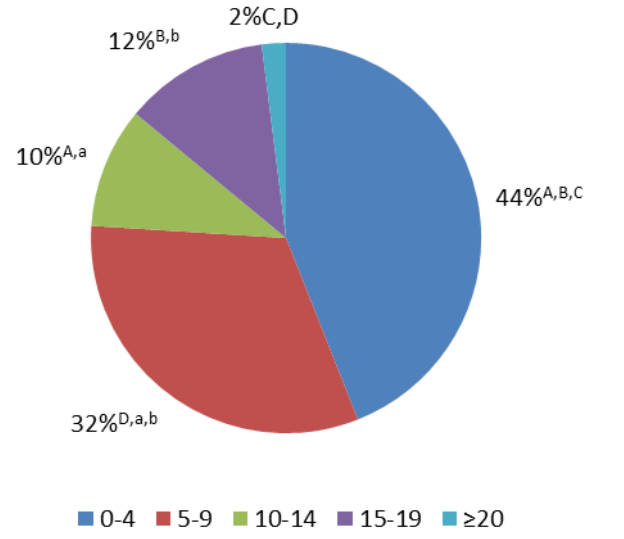

Figure 3. Frequency of symptoms of depression among employees working in the COVID-19 zone according to PHQ9 questionnaire score

A, B, C, D–$p < 0.01$; a, b–$p < 0.05$

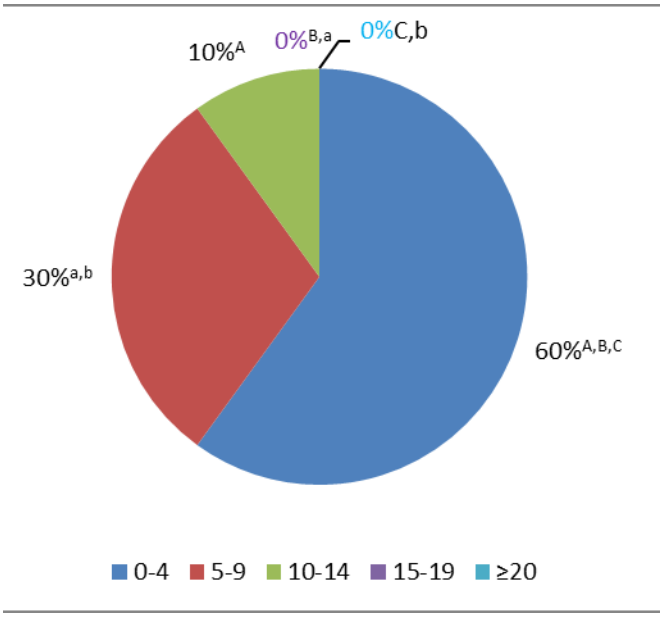

Figure 4. Frequency of symptoms of depression among employees working in the non-COVID-19 zone according to the score of the PHQ9 questionnaire

A, B–p < 0.01; a, b–p < 0.05

Discussion

Burnout syndrome has recently been included in the International Classification of Diseases, 11th Issue (ICD-11) as an occupational phenomenon (8). In general, burnout syndrome (BS) and depression are considered diseases of modern society (5). Many studies have been done related to the mental health of HCWs both during (1, 6, 9–13) and before (14–16) the COVID-19 pandemic. Some of them, such as a multicenter longitudinal descriptive study conducted among Catalonia physicians in October 2020, showed a percentage of high burnout for all domains (EE 77.5%; DP 70.0%; PA 67.5%), unlike the values obtained in the present study where these values were as follows: EE—29.6%, DP—7.0% and PA—19.7% (11). Others, like a cross-sectional study conducted in primary HCWs in Iran, showed that 36% of participants had major depressive disorder, while the present study found that only 2% of medical staff had severe depressive episodes, and 7% of them moderately severe depressive episodes (12). A survey with a focus on the levels of BS in HCWs in Italy during the COVID-19 pandemic using the MBI–HSS questionnaire as a research instrument revealed high levels of EE in 41% and high levels of DP in 27% of respondents (17). To understand the impact of COVID-19 on HCWs around the world, a study was conducted among 2707 participants from 60 countries, and results showed that 51% of HCWs reported burnout (18). A cross-sectional study done among primary care physicians working in Portugal with the purpose of assessing levels of BS using questionnaire Copenhagen Burnout Inventory (CBI), also showed high levels of burnout in 3 dimensions (65.9%—personal burnout, 68.7%—work-related, 54.7%—patient-related) (19). Besides levels of burnout, the study conducted in Portugal also evaluated levels of depression in HCWs by using DASS-21. Normal levels of depression were reported by 67.3% of respondents, while severe levels of depression were found in 65% of HCWs, three times higher values compared to our study where severe depressive episodes were reported by 2% of respondents (19). Finally, in October 2021, a cross-sectional online anonymous survey was conducted among 286 HCWs from all regions of Serbia to assess levels of BS and depressive symptoms. High or moderate levels of emotional exhaustion (91.9%) and compassion fatigue (60.8%) were reported and lower levels (23.8%) of self-efficiency (20).

Conclusion

The study included significantly more participants of female gender, women older than 40 years, medical staff and those working in the COVID-19 zone. No significant differences were found between the frequency of depressive symptoms based on the score of the PHQ9 questionnaire among medical and non-medical staff, as well as among employees in the COVID-19 and non-COVID-19 zones. However, the average value of the PHQ9 score of employees in the COVID-19 zone was significantly higher compared to the average value of the PHQ9 score employees in the non-COVID-19 zone.

Levels of burnout in participants of the study showed moderate to high emotional exhaustion (› 50%), low depersonalization

(70.4%) and low personal accomplishment (53.5%). According to values of overall burnout, we can conclude that most participants (94.4%) in our study experienced a moderate level of burnout. More detailed studies are needed to examine the factors that influence the level of burnout syndrome (BS) in primary healthcare workers (HCWs) so that measures can be implemented to reduce the level of BS in primary HCWs.

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PREVALENCIJA SIMPTOMA SAGOREVANJA I DEPRESIJE MEĐU ZDRAVSTVENIM RADNICIMA U TOKU PANDEMIJE COVID-19 U BEOGRADU

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Širenje virusa SARS-CoV-2 i posledična pandemija COVID-19 povezani su sa sindromom sagorevanja (engl. *burnout syndrome* – BS), depresijom i anksioznošću među zdravstvenim radnicima (ZR). Sprovedena je studija preseka kod zaposlenih u Domu zdravlja „Barajevo" primenom upitnika *Maslach Burnout Invetory–Human Services Survey* (MBI–HSS), koji služi za merenje tri aspekta sindroma sagorevanja na poslu (emotivna iscrpljenost (engl. *emotional exhaustion* – EE), depersonalizacija (engl. *depersonalization* – DP) i lična postignuća (engl. *personal accomplishment* – PA)), upitnika *Patient Health Quality* 9 (PHQ-9), koji služi za samoprocenu depresivnih simptoma, i opšteg upitnika, pomoću kojeg su prikupljeni sociodemografski podaci ispitanika. U studiju je uključen samo 71 kompletno popunjen upitnik. Kada je reč o učestalosti simptoma depresije, na osnovu skora upitnika PHQ-9 kod medicinskog i nemedicinskog osoblja, kao i kod zaposlenih u kovid i nekovid zoni, nisu utvrđene statistički značajne razlike. Na osnovu prosečnih vrednosti skorova PHQ-9 upitnika utvrđeno je da kod zaposlenih koji su radili u kovid zoni postoji značajno veća ($p < 0,05$) prosečna vrednost skora PHQ-9 upitnika (6,84 ± 5,73) nego kod zaposlenih u nekovid zoni (4,00 ± 3,70). Umeren do visok nivo emocionalne iscrpljenosti primećen je kod više od 50% ispitanika. Nizak nivo depersonalizacije zabeležen je kod 70,4% ispitanika. Većina zaposlenih (53,5%) ispoljila je nizak nivo ličnog postignuća. Samo je jedan ispitanik (1,4%) ispunio sva tri kriterijuma za kategoriju visokog nivoa sagorevanja, a 67 ispitanika (94,4%) svrstano je u umerenu kategoriju opšteg sagorevanja.

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***Ključne reči**: sindrom sagorevanja, COVID-19, zdravstveni radnici, simptomi depresije*

Review article

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WHAT IS BENTA DISEASE?

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B cell expansion with NF-κB and T cell anergy (BENTA) represents a newly defined entity in immunology. It is a primary immunodeficiency (PID). This rare genetic disorder is transmitted in an autosomal dominant manner and classified as a predominantly antibody deficiency by the International Union of Immunological Societies (IUIS). The cause of the disease is a gain-of-function mutation in the Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1 (CARMA1 (CARD11)) gene. Clinically, the disease is manifested at an early age with hepatosplenomegaly, lymphadenopathy, anemia, susceptibility to frequent respiratory tract infections, and a low response to certain vaccines. Lymphadenopathies can be part of the clinical spectrum of several PIDs and can pose a significant diagnostic dilemma. Patients with this disease carry a risk of developing chronic B cell leukemia. Thorough family history is an important element in the assumption of diagnosis of BENTA disease. Treatment options of BENTA disease are still being considered. They can include splenectomy, application of monoclonal antibodies such as rituximab to deplete B cell reserve, wearing special spleen guards when playing sports, and antibiotics for infections. Because it can present a burden for families, psychological support and counseling may be necessary. Each physician should be informed about the existence of this disease so they can eventually recognize it in their medical practice.

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Key words: *B cell expansion with NF-κB and T cell anergy, lymphadenopathy, Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1, primary immunodeficiency diseases*

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Introduction

Primary immunodeficiency diseases (PID) are a group of hereditary and genetic disorders characterized by immune system dysfunction, leading to increased susceptibility to infections, autoimmunity, organ damage, and eventual malignancy (1). Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1 (CARMA1), also known as CARD11, is a member of the CARD-CC protein family and plays a critical role in T and B cell function. CARMA1 is activated following stimulation of the B cell receptor (BCR) or T cell receptor (TCR). CARMA1 is organized into several distinct domains, including an N-terminal CARD domain, a central coiled-coil (CC) domain, a PDZ homology domain, an SH3 domain, and a C-terminal guanylate kinase (GUK) domain (1, 2). Several heterozygous missense gain-of-function (GOF) mutations in this gene have been reported, including C49Y, G123S, G123D, E134G, K215del, and H234Ldel235–238. Dysfunction of this gene, which is highly sensitive to mutations and genetic variation (3), can lead to atopic disease, immunodeficiency, and cancer (4–6). Activation of CARMA1 subsequently leads to activation of transcription factor NF-κB, an important factor for lymphocyte activation, survival, and proliferation (7, 8). Dysregulation of NF-κB could lead to autoimmunity, septic shock, and cancer (9), and increased NF-κB activity is found in oropharyngeal, prostate, and pancreatic cancer. This kind of dysfunction protects cells from apoptosis and promotes cell mitosis and angiogenesis (9). Increased access to the next-generation sequencing (NGS) has contributed to the discovery of the genetic footprint of many primary immunodeficiencies and their subsequent classification. B cell expansion with NF-κB and T cell anergy (BENTA disease, see Figure 1) is newly revised and classified as a predominantly antibody deficiency by the International Union of Immunological Societies (IUIS) (1). BENTA disease is an extremely rare genetic, autosomal dominant disorder (Figure 2) caused by gain-of-function mutation in the CARMA1 gene important

in T cell and B cell function (10). The disease is characterized by polyclonal B lymphocyte expansion, splenomegaly and lymphadenopathy at an early age, mild immunodeficiency, and an increased risk for the development of lymphoma (4). Due to its extreme rarity and complexity, there are no established guidelines or standardized protocols for the treatment of this disease.

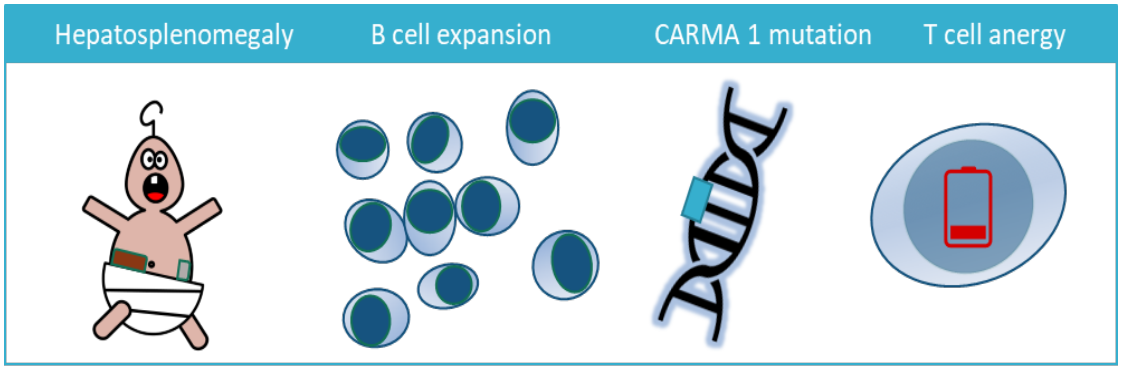

Figure 1. BENTA disease features

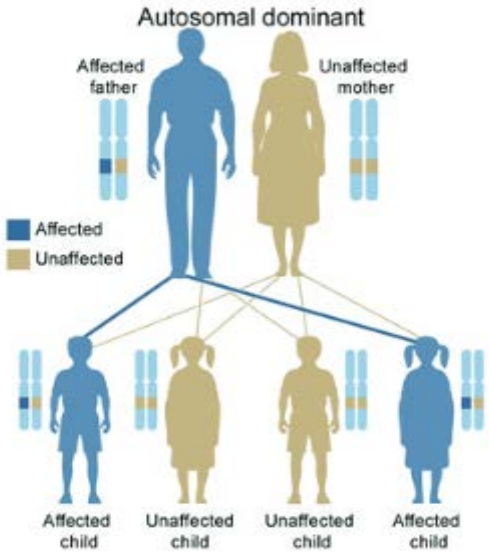

Figure 2. Autosomal dominant nature of inheritance of BENTA disease

Materials and Methods

A thorough search of the literature and the MEDLINE database was conducted using the following search terms: CARD11, BENTA disease, primary immunodeficiency, and NF-κB.

Discussion

Immunological aspects

B cells play an important role in adaptive immunity. They are activated in secondary lymphoid organs (spleen, lymph nodes) and are involved in the pathogenesis of many autoimmune, malignant, and infective diseases (11, 12). BENTA patients show an increased production of B cells in bone marrow. Immunological phenotyping may show that ~50–80% of peripheral blood mononuclear cells are $CD19^{+}CD20^{+}CD5^{int}$ polyclonal naïve mature B cells (above normal range), representing mainly polyclonal, IgD^{hi} naïve mature B cells, with a significant elevation of $CD10^{+}CD24^{hi}CD38^{hi}$ transitional B cells (13). This is because B cell differentiation to plasma cells is impaired in patients with BENTA, even with additional in vitro cytokine stimulation (14). Therefore, patients could have an extremely low number of class-switched B cells, as well as a low number of

memory B cells. Circulating B cells in these patients are also more prone to apoptosis, and their increased number is not a consequence of increased turnover or survival, as Snow et al. mentioned (15). NK cells are important in antiviral immunity and the removal of tumor cells. They are part of the innate immune system, and their function is analogous to cytotoxic T cells of adaptive immunity. NK cells are important in the pathogenesis of autoimmune diseases and can be used therapeutically in the treatment of malignancies (16, 17). BENTA patients may exhibit decreased natural killer (NK) cell activity, as demonstrated in vitro for the G126D mutation using immortalized HeLa cell lines (16, 17). This mutation also induces antigen receptor–independent immune activation (18). Several patients have been reported to show low serum levels of IgM antibodies, with IgA and IgG levels at the lower end of the normal range, while the total number of T cells generally remains within normal limits (19). CARMA1 aggregates can be detected, and their quantification may reveal marginally elevated levels. Affected individuals often exhibit a weak immune response to polysaccharide-conjugate vaccines; some also display diminished responses to varicella and measles vaccines (20, 21). The spleen may be enlarged, resembling the splenic architecture of an older individual (21), or it may show characteristics of splenic marginal zone lymphoma, which include the expansion of white pulp follicles and significant infiltration of red pulp with minimal cytological atypia and occasional binuclear lymphocytes (22). Individuals with a C49Y mutation in the CARMA1 (CARD11) gene, located outside the LATCH-CC region, exhibit a milder form of adult BENTA disease. Predisposition to mild respiratory infections and low Candida albicans antigen-specific proliferation were noted in three patients with this mutation (23). As mentioned, CARMA1 mutation causes NF-κB overactivity despite a lack of stimulation by T cell and B cell receptors that are usually triggered by a pathogen (18). Inadequate activation of NF-κB leads to activation of genes involved in the survival of transitional and naïve B lymphocytes and, paradoxically, to a weaker T cell responsivity to IL-2, which causes T cell anergy in the states of inflammation (24). Although NF-κB is involved in the pathogenesis of BENTA disease, the downstream signaling itself is preserved with CD40 stimulation and plasmablast differentiation after CD40 and IL-21 stimulation *in vitro*. The said cannot explain severe antibody deficiency, and some other mechanism of T and B cell interaction may play a role *in vivo* antibody deficiency (13). Elevated double negative T cell count could present a potential problem in differential diagnosis. Namely, T cell elevation with lymphadenopathy is also encountered in Autoimmune lymphoproliferative syndrome (ALPS), but absolute T cell count remains in the normal range in BENTA patients and shows weak response to *in vitro* stimulation with impaired IL-2 secretion and proliferation. The main early distinction between the two remains the CARMA1 genetic mutation, which is detected only in BENTA patients (13, 20, 25).

Clinical aspects

Clinically, the disease begins to manifest itself with lymphadenopathy and hepatosplenomegaly in infancy. The cause of this manifestation of BENTA disease is in lymphocyte tendency to sequestrate in these organs (26, 27). Lymphadenopathies can be part of the clinical spectrum of several PIDs and can pose a significant diagnostic dilemma (28). Some rare diseases that manifest with lymphadenopathy at an early age are shown in Figure 3. Hemophagocytic lymphohistiocytosis (HLH) can also be included in differential diagnosis. HLH is characterized by some overlapping features such as lymphadenopathy, splenomegaly, and hepatomegaly (29). As in ALPS, some patients can be prone to certain autoimmune phenomena such as autoimmune hemolytic anemia, immune thrombocytopenia, and hives (25). Mild immunodeficiency could predispose these patients to episodes of recurrent sinusitis, pneumonias, and in some cases towards infection to certain pathogens such as Epstein–Barr virus (EBV), molluscum contagiosum virus (MCV), and BK virus (15, 30). Nonspecific symptoms such as fatigue, night sweats, and loss of body mass with loss of appetite could suggest a development of complication of BENTA towards B cell lymphocytic leukemia (31). A thorough family history is a crucial component in the initial suspicion of BENTA disease. Laboratory findings, supplemented by genetic testing, are essential for establishing a definitive diagnosis. The autosomal dominant nature of inheritance means that the offspring will have a 50% chance of getting the disease (Figure 2). Splenectomy could potentially cause complications due to lymphocytosis and increased risk for infection with encapsulated pathogens because splenic macrophages play an important role in protection against these bacteria (32, 33). It can also increase the risk for B cell malignancy (25). In some cases, a low number of NK cells (caused by CARMA1 mutation) could predispose BENTA patients to persistent Epstein–Barr virus (EBV) viremia (34–36). Following splenectomy, the number of NK cells and T cells could increase, which can point to an important role of splenic tissue as a niche for these cells (30). Because of weak response to certain vaccines, a potential splenectomy could increase the risk of infection without the possibility of protecting these individuals with usual immunization against *Haemophilus influenzae, Streptococcus pneumonia,* etc. (37, 38). Clinical manifestations of BENTA disease may depend on additional genetic mutations, interaction with environmental factors and exposure to infections (23).

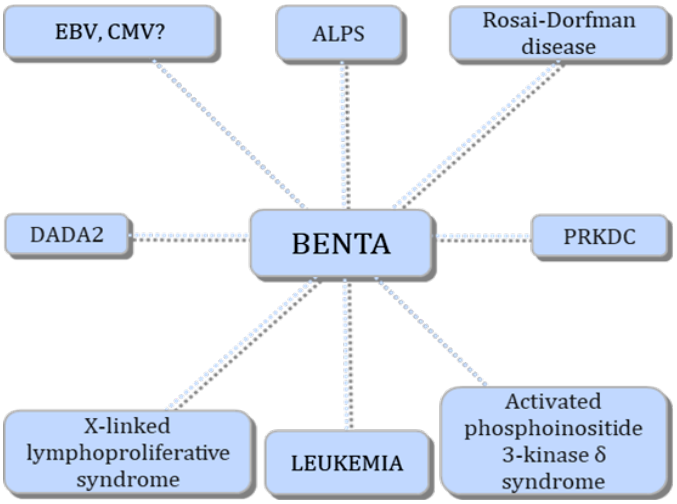

Figure 3. Example of disorders with lymphadenopathy in infancy

Many rare diseases present with lymphadenopathy in infancy, and congenital infections with CMV, EBV, and others are another possible cause of lymphadenopathy. Autoimmune lymphoproliferative syndrome (ALPS) is caused by lymphocyte apoptosis/homeostasis dysregulation. Rosai-Dorfman disease is characterized by the presence of excess histocytes in lymph nodes. Deficiency of Adenosine Deaminase 2 is an autosomal recessive disorder characterized by systemic inflammation, cytopenia, immunodeficiency, and early onset stroke. PRKDC mutation causes defects in the DNA repair mechanism and impairs the V(D)J recombination process. This is known to be one of the rare causes of severe combined immunodeficiency (SCID). X-linked lymphoproliferative syndrome (XLA) is characterized by immunodeficiency and a predisposition to hemophagocytic lymphohistiocytosis. It predominantly affects males. Leukemia in infancy is a rare cause of lymphadenopathy at an early age. Activated PI3K delta syndrome is characterized by lymphadenopathy but low circulating T and B lymphocytes (1, 39).

Treatment options

Treatment options for BENTA disease are still under investigation. One possible role is given to monoclonal antibodies such as rituximab, which could deplete B cell reserve. This approach is already used in the treatment of autoimmune diseases (13, 40). Methotrexate can also be used to reduce and control lymphocytosis after splenectomy (20). Sirolimus (Rapamycin), an mTOR inhibitor, is used in ALPS patients and can be used in BENTA patients as well to reduce lymphocyte burden (25, 39). In all patients, a regular follow-up is a essential. MALT1 protease is a paracaspase involved in the activation of NF-κB and, therefore, in the production of IL-2 and the development of T cells and B cells. MALT1 protease inhibitors may have a potential role in the management of BENTA disease (41, 42). Transfusions of blood and blood products may be needed if anemia and thrombocytopenia occur (43). Splenomegaly is a potential risk for spleen rupture, and patients with BENTA are sometimes required to wear spleen guards when playing sports. Counselling may be beneficial because of potential high psychological stress encountered by individuals with BENTA disease and their families. Families may also benefit from meeting or talking to other families affected by the same rare disease. Hematopoietic stem cell transplantation could be curative and is effectively used in other immunodeficiency states (44). In case of disease complications with the development of leukemia, treatment would involve chemotherapy with stem ce ll transplantation (31). There are still no studies to prove the eventual benefit of prophylactic antibiotic use in PID patients, although this kind of practice is common (45, 46). Antiviral treatment of EBV and Chronic active Epstein–Barr virus (CAEBV) infection is generally ineffective. Immunomodulatory treatment (IFN-α, IFN-γ) has also shown small success in CAEBV (47, 48). In such cases, allogeneic hematopoietic stem cell transplantation (HSCT) may be considered, as it is an established therapeutic option for certain forms of PID (49).

Conclusion

BENTA disease is a recently characterized, incompletely understood, but clinically significant immunological disorder. Its wide spectrum of clinical manifestations, combined with its rarity, contributes to frequent underrecognition. The limited number of reported cases likely reflects a lack of awareness among clinicians rather than true incidence. Enhancing physician familiarity with BENTA disease is essential to improve early recognition, diagnosis, and appropriate management in clinical practice.

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ŠTA JE BENTA BOLEST?

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BENTA (engl. B-cell expansion with NF-jB and T-cell anergy – BENTA) bolest predstavlja pojavu koja je nedavno definisana u imunologiji. BENTA bolest spada u primarne imunodeficijencije (engl. *primary immunodeficiency* – PID). Karakteriše je B-ćelijska ekspanzija sa NF-kB i T-ćelijskom anergijom. Ovaj retki genetski poremećaj prenosi se autozomno dominantnim putem. Internacionalno udruženje imunoloških društava (engl. *International Union of Immunological Societies* – IUIS) svrstalo ga je u predominantne deficijencije antitela. Uzrok ove bolesti jeste *gain-of-function* mutacija u CARMA1 (engl. *Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1* – CARMA1) (CARD11) genu. Ova bolest klinički se prezentuje u ranom dobu hepatosplenomegalijom, limfadenopatijom, anemijom i skonošću ka čestim respiratornim infekcijama, kao i smanjenim odgovorom na određene vakcine. Limfadenopatija može biti deo kliničkog spektra ispoljavanja nekolicine PID-a i može predstavljati dijagnostičku dilemu. Kod osoba sa ovom bolešću postoji rizik od razvoja hronične B-ćelijske leukemije. Temeljna porodična anamneza predstavlja važan element kada postoji sumnja na BENTA bolest. Kao načini lečenja BENTA bolesti, koji se i dalje ispituju, navode se splenektomija, primena monoklonskih antitela poput rituksimaba radi smanjenja broja B-limfocita, nošenje specijalnih štitova za slezinu prilikom bavljenja sportom, kao i antibiotici za lečenje infekcija. Budući da oboleli mogu predstavljati teret za čitavu porodicu, psihološko savetovanje može biti neophodno. Verujemo da svaki lekar treba biti svestan postojanja ove bolesti kako bi je mogao prepoznati u svojoj praksi.

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***Ključne reči**: B-cell expansion with NF-jB and T-cell anergy, limfadenopatija, Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1, primarna imunodeficijencija*

Review article **UDC: 61:004.8**
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ARTIFICIAL INTELLIGENCE IN DRUG DEVELOPMENT, CLINICAL TRIALS, AND HEALTHCARE

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The use of artificial intelligence (AI) in drug development, clinical trials, and clinical practice represents a transformative advancement in healthcare. AI technologies offer unprecedented capabilities to analyze vast datasets, identify patterns, and generate actionable insights, thereby revolutionizing various aspects of the healthcare ecosystem. This review aims to offer a thorough overview of current research on AI applications in healthcare. In drug development, AI-driven approaches rationalize the process of identifying potential therapeutic compounds, accelerating the route from discovery to market approval. Within clinical trials, AI-powered analytics optimize trial design, reduce sample size, patient recruitment, and data analysis, increasing statistical power and efficiency. Moreover, in clinical practice AI applications empower healthcare providers with decision support systems, personalized treatment recommendations, and predictive analytics, leading to more effective and personalized patient care. While challenges such as ethical considerations and regulatory frameworks remain, the potential benefits of AI in driving medical innovation and improving patient outcomes are substantial, underlining the importance of continued research, collaboration, and responsible application of AI in healthcare.

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Key words: *artificial intelligence, drug development, clinical trials, healthcare, machine learning, deep learning*

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Artificial intelligence

Introduction

Artificial intelligence (AI) refers to the imitation of human intelligence within computer systems. This field focuses on creating machines that can perform tasks on par with or even exceeding human capabilities (1). The methodology involves gathering data, establishing rules for its application, making either tentative or final decisions, and continuously refining the process through self-correction. The fields of AI and its subset, machine learning (ML), have produced considerable interest across diverse industries, with pharmaceutical sciences being no exception. The exponential growth in data from myriad sources, coupled with advancements in analytical tools and the continuous refinement of ML algorithms, has led to a rapid proliferation of ML applications within pharmaceutical sciences. From revolutionizing drug discovery and development processes to enabling the realization of personalized medicine, ML applications in this domain highlight the transformative potential of AI. Throughout history, the quest of AI has been characterized by four primary approaches, each supported by distinct groups using specific methodologies (2). These approaches refer to: a) Act humanly, b) Think humanly, c) Act rationally, and d) Think rationally.

In this context, the intersection of AI and healthcare has sparked a paradigm shift in how we approach drug development, clinical trials, and healthcare. In recent years, AI technologies have emerged as powerful tools capable of analyzing vast quantities of data, identifying intricate patterns, and generating actionable insights with unprecedented speed and accuracy (3). Within the fields of drug discovery and development, AI algorithms are revolutionizing the identification of potential therapeutic compounds, expediting the research process from bench to bedside. In parallel, AI-driven analytics are reshaping the landscape of clinical trials, optimizing trial design, patient recruitment, and data analysis to enhance efficiency and efficacy. Moreover, within healthcare, AI applications are empowering healthcare providers with decision support systems, personalized treatment

recommendations, and predictive analytics, thereby revolutionizing patient care delivery. As we delve deeper into the field of AI in healthcare, it becomes increasingly evident that these technologies hold immense promise in accelerating medical innovation, improving patient outcomes, and ultimately transforming the way we approach healthcare delivery.

Historical background

The ancient Greeks held reasoning faculties in high regard, viewing them as the hallmark of human uniqueness that set humans apart from other creatures (1). They honored the ability to think logically and critically as a defining characteristic of humanity, shaping the foundation of Western philosophy and science. The ancient Greek philosopher Plato (5th BC century), as well as religious thinkers many centuries later, expanded upon this notion by introducing the concept of the soul (1). Beyond mere reasoning, humans were believed to possess a soul—a divine essence imparted by their creator—which granted them a unique position in the cosmic order. This synthesis of reason and soul provided a holistic framework for understanding human nature, blending philosophical inquiry with theological reflection. His student, Aristotle, codified laws governing logical thought (1). His development of syllogistic reasoning laid a solid foundation for subsequent philosophical and scientific quests, shaping scholarly discourse on the human mind for centuries. In the 16th century, the polymath Leonardo da Vinci, conceptualized a mechanical calculator; a testament to his approach to engineering and mathematics (1). Although da Vinci never constructed the device himself, modern reconstructions based on his designs have validated its feasibility, showcasing his remarkable foresight and contributions to the early development of mechanical computing.

In the 20th century, Alan Turing introduced the concept of "effective calculability" as a solution to this fundamental challenge (4). Turing's work laid the basis for computational models, establishing the concept of algorithms, as step-by-step procedures for calculations. The genesis of artificial neural networks (ANNs) can be traced back to 1943, with the development of an initial neural network composed of electrical circuits (5). This research aimed to replicate the intricate interactions between neurons in the human brain, laying the foundation for the burgeoning field of neural networks and their applications in AI. The formal establishment of AI as a distinct field occurred in 1956 during a historic conference held at Dartmouth College (6). This landmark event brought together prominent researchers to explore the potential of creating machines capable of simulating various aspects of human intelligence. The Dartmouth conference marked the official birth of AI, heralding decades of intensive research and development in the field.

The computer stands as one of the most monumental technological advancements since the advent of the printing press in the 15th century (1, 7). During World War II, early iterations of computers were utilized by the military forces of Germany and the western allies, although these machines exerted little resemblance to modern computers. For example, America's ENIAC, weighing 30 tons and spanning an entire basement, relied on 17,000 vacuum tubes. In the 1950s, IBM embarked on the development of business computers, which were notably smaller than their military counterparts, occupying only a fraction of a room space. Over the subsequent two decades, computers evolved into forms more akin to those familiar today, albeit still considerably large. By the late 1980s, the personal computer had become a ubiquitous presence, with approximately 20% of US households owning at least one (1). This widespread integration signified a pivotal moment, as artificial intelligence began to permeate homes and workplaces nationwide, underscoring the swift assimilation of advanced computing technologies into everyday life.

AI classification

AI can be classified into several main types based on the learning approach used (Table 1):

Supervised learning: The AI system is trained on labeled data, where the inputs and desired outputs are provided (8). The system then learns to map the inputs to the outputs, allowing it to make predictions on new, unseen data. Examples include image classification, spam detection, and predictive analytics.

Unsupervised learning: The AI system is given unlabeled data and must find patterns and structure within it on its own (8–11). The goal is to discover hidden insights and groupings in the data. Examples include customer segmentation, anomaly detection, and recommendation systems.

Reinforcement learning: The AI system learns by interacting with an environment and receiving feedback (rewards or penalties) based on its actions (12). It then adjusts its behavior to maximize the rewards, allowing it to learn complex tasks through trial and error. Examples include game-playing AIs, robotics, and autonomous vehicles.

Table 1. Popular machine learning algorithms

Linear Regression	K-Means Clustering	Reinforcement learning
Logistic Regression	Hierarchical Clustering	Q-Learning
Decision Trees	Density-Based Spatial Clustering of Applications with Noise (DBSCAN)	Deep Q-Networks (DQN)
Random Forests	Gaussian Mixture Models (GMM)	State-Action-Reward-State-Action (SARSA)
Support Vector Machines (SVM)	Principal Component Analysis (PCA)	Policy Gradient Methods
K-Nearest Neighbors (KNN)	Independent Component Analysis (ICA)	Actor-Critic Methods
Naive Bayes	t-Distributed Stochastic Neighbor Embedding (t-SNE)	Deep Deterministic Policy Gradient (DDPG)
Neural Networks	Self-Organizing Maps (SOM)	Proximal Policy Optimization (PPO)
Gradient Boosting Machines (GBM)	A priori Algorithm	Advantage Actor-Critic (A3C/A2C)
Adaptive Boosting (AdaBoost)	Association Rules	Monte Carlo Methods

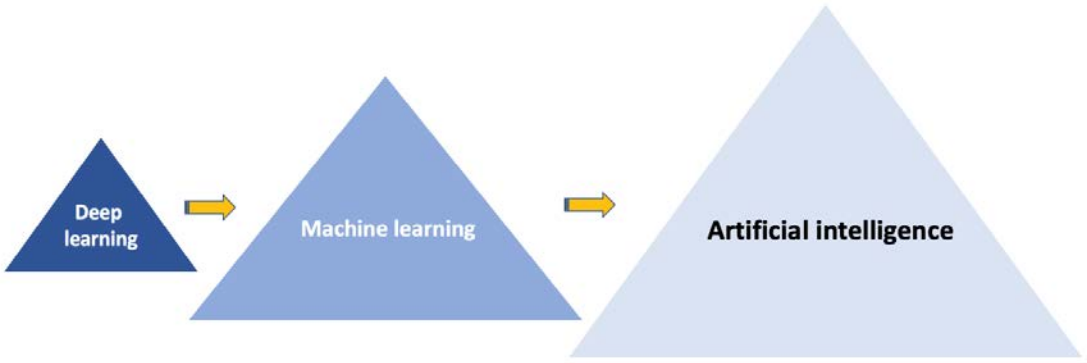

Figure 1. Association among the terms deep learning, machine learning, and artificial intelligence

Deep learning (DP) is a powerful subdivision of machine learning (Figure 1) that utilizes ANNs with multiple hidden layers to learn complex patterns in data (13, 14). Unlike more traditional ML algorithms that rely on manual feature engineering, DP models can automatically extract relevant features from raw data, enabling them to tackle increasingly complex problems. Deep learning has been particularly successful in areas like computer vision, natural language processing, and speech recognition, where it has outperformed previous state-of-the-art methods (2). By using the hierarchical structure of neural networks, DP models are able to learn high-level abstractions from low-level inputs, allowing them to make highly accurate predictions and classifications. While DP models require large amounts of training data and significant computational resources, they have become an invaluable tool in the field of AI, powering many of the most advanced intelligent systems and applications we see today. As the field continues to evolve, DP is likely to play an even more central role in the development of increasingly capable and versatile AI systems.

AI in Drug Development

Over the past two centuries, the field of medicine has undergone a remarkable evolution, progressing from reliance on simple herbal remedies to the development of intricate pharmaceutical formulations and dosage forms (15). However, the process of bringing a new drug to market remains a lengthy and complex journey, often spanning several years and involving substantial financial investments, largely due to the high attrition rate inherent in drug development. Consequently, there is a pressing need to streamline this process by using state-of-the-art technologies, including AI.

Machine learning, plays a significant role in pharmaceutical sciences, particularly in drug research and development, where techniques like

high-throughput screening and combinatorial chemistry are extensively utilized (16–18). As the volume of such research continues to escalate, the importance of ANNs in facilitating drug discovery processes has grown exponentially (19, 20). Moreover, the advent of extensive datasets pertaining to potential medicinal compounds has heralded the era of big data in medicine (21). This paradigm shift necessitates the adoption of AI technologies capable of effectively modeling dynamic, heterogeneous, and vast repositories of drug-related data.

Deep learning models in computational chemistry have transformed drug development, notably in terms of predicting drug-target interactions, creating novel compounds, and anticipating ADMET properties for translational research (22). Machine learning techniques, instrumental in target development and drug discovery, have been integrated into various research and development pipeline stages , using advancements in ML theory and pharmacological data accumulation (23, 24). Machine learning accelerates virtual screening, reducing costs and enhancing accuracy using web-based tools (25, 26).

Utilizing an established treatment for a novel condition presents a favorable scenario wherein the new medication can bypass Phase I clinical trials and proceed directly to Phase II trials (27). This approach offers the potential for expedited development timelines and reduced overall costs, rendering drug repurposing an increasingly attractive strategy. In the era of big data, the convergence of AI and network medicine leads to innovative data science applications in disease characterization, medication evaluation, treatment selection, and target identification with unprecedented precision (28). Emerging systems biology methodologies use ML algorithms to analyze medication effects, separating from traditional reliance on chemical similarity and molecular docking. Notably, such studies have been exemplified in remdesivir trials for COVID-19 treatment (28). Similarly, in the fight against the Hepatitis C virus (HCV), network-based medication repurposing efforts have led to the discovery of 16 potentially repurposable medicines (29). These innovative approaches underline the transformative potential of AI-driven strategies in drug repurposing, offering novel avenues for accelerating therapeutic discoveries and optimizing treatment outcomes.

During the pre-formulation stage of drug development, assessing the physicochemical properties of a medicinal substance is pivotal (30). These properties govern critical aspects such as solubility, stability, excipient interactions, and ultimately, bioavailability. Determining the water solubility of a new drug compound is particularly crucial as it directly impacts absorption across various administration routes (31). Techniques like surfactants, complexation, and cocrystal formation are used to enhance aqueous solubility (31). Predicting drug solubility in silico using AI is of paramount importance (31, 32). Additionally, substantial progress has been made in utilizing ML, particularly transfer learning, in pharmaceutical settings (33). Integrated techniques combining transfer learning and multitask learning have shown promise in predicting various pharmacokinetic parameters with strong generalization ability (33). ANNs have been extensively used to predict formulation and process-related characteristics such as drug dissolution and release, showcasing remarkable success and potential for rapid and efficient manufacturing optimization (34). In the same vein, early consideration of interactions among materials and conditions during drug manufacturing is vital to prevent subsequent losses in time and resources (35). AI is increasingly applied in pharmaceutical technology to streamline operations and gain insights into formulation-process interactions. Quality-by-Design is a systematic approach integrating quality into product development through a well-defined framework (36). ANNs play a crucial role in drug development, linking material related parameters to *in vivo* performance (36).

AI in Clinical Trials

The use of AI in clinical trials represents a transformative advancement in healthcare research, since it can give unprecedented capabilities to rationalize various aspects of clinical trial management and analysis (37). From patient recruitment and selection to data monitoring and analysis, AI enhances efficiency and accuracy throughout the trial lifecycle. AI-driven predictive models aid in identifying suitable patient populations, optimizing trial protocols, and predicting patient outcomes, thereby expediting trial timelines and reducing costs. Furthermore, AI facilitates real-time data monitoring, enabling early detection of adverse events and protocol deviations.

Quite recently, generative AI algorithms were proposed as an innovative way to reduce the actual human sample size by using AI-synthesized virtual patients instead (38, 39). Thus, AI-driven algorithms have been proposed for data augmentation in clinical trials. Data augmentation techniques have primarily focused on image analysis, particularly in computer vision, with methods like random rotation, noise addition, and generative adversarial networks being explored (40–43). While some studies have applied data augmentation to generate synthetic fetal ultrasound images, the present study primarily deals with numerical data augmentation (44). Variational autoencoders (VAEs) have been recognized as effective in developing generative models to produce novel synthetic data, offering advantages over conventional autoencoders by generating data from the same distribution as input data (45).

Besides, sample size estimation is pivotal in clinical trials, ensuring safety and efficacy (46). Obtaining a representative sample is essential for understanding a population, yet collecting extensive data can be challenging and resource-intensive. Each trial requires meticulous planning, including outlining objectives, endpoints, data collection, and statistical methods (46). A recent study aimed to reduce required sample sizes in clinical trials using a VAE (47). That study explored the application of VAEs to virtually increase sample sizes in clinical trials, demonstrating the feasibility of using only 20% of the original dataset without altering study outcomes (45). Even for data with high variability, VAEs substantially reduce sample size requirements, accelerating trials, cutting costs, and minimizing human exposure (45). Moving one step ahead, a subsequent study proposed the utilization of ANN specifically VAEs, to reduce the need for recruiting large participant populations in bioequivalence investigations (39). In that study, the suitability of utilizing VAEs to virtually expand the sample size in the context of a typical 2 x 2 crossover design bioequivalence study was investigated. The aim was to generate realistic synthetic data that can supplement the original trial data, potentially reducing the burden of recruiting a large number of participants (39). Both these two studies represent an important step forward in the integration of advanced AI techniques into the clinical trial process. By demonstrating the feasibility and potential benefits of using VAEs to augment bioequivalence data, they pave the way for further exploration and adoption of generative AI algorithms in various aspects of clinical research.

Machine learning approaches have also been used in the field of pharmacokinetics, aiming to address the old problem of finding an appropriate metric for absorption rate (48, 49). In recent studies, several ML approaches have been used to solve the ongoing difficulty of establishing an adequate absorption rate measure (50–52). Using Cmax as an absorption parameter presented many problems (53–55). Alternative metrics, such as Tmax and the Cmax/AUC ratio, were proposed to better characterize absorption rate features, particularly in immediate-release formulations (55). Studies comparing these measurements discovered that the Cmax/AUC ratio provided higher statistical precision and ease of use than Tmax (55, 56). However, the choice of a parameter to describe absorption rate should be based on theoretical considerations, particularly the units (51). A good absorption rate measure should represent variations in concentration over time and indicate a concentration per time unit. Unfortunately, several proposed metrics lack proper units, such as AUC, Cmax, Tmax, and even the Cmax/AUC ratio, which is measured *in time-1*.

In this context, a unique measure known as average slope (AS) was introduced by applying several computational interdisciplinary techniques (51, 52). It was shown that the usual metric, Cmax (peak plasma concentration), is insufficient to reflect the absorption rate. In contrast, the newly suggested metric, average slope, has the requisite absorption rate features, suitable units of measurement (concentration units per time), and is simply computed directly from drug concentration-time data. All ML algorithms revealed that the average slope measure outperformed other metrics used or suggested in bioequivalence studies (50–52). Simplicity and applicability are crucial for pharmacokinetic measures. Metrics like AS can be easily estimated using simple, reproducible methods without complex modeling, making them more reproducible and straightforward compared to model-based approaches (50–52). The estimation of AS can even be done manually using tools like Excel®, enhancing its accessibility. These findings highlight the necessity of reevaluating established measurements and investigating novel solutions, with ML providing a fresh viewpoint on long-standing pharmacokinetic issues.

AI in Healthcare

AI has become increasingly important in clinical practice because of its ability to efficiently handle massive datasets, resulting in better patient care and a lower burden on healthcare staff (6). This growth prepared the path for personalized medicine, which goes beyond typical computational procedures. Predictive models, in particular, have enormous potential for diagnosing diseases, forecasting treatment outcomes, and influencing the future of preventative healthcare. AI can improve diagnostic accuracy, streamline healthcare operations, facilitate more effective disease and therapy monitoring, and modify medical procedures.

In cardiology, the integration of advanced AI algorithms, collectively known as AI, revolutionizes the analysis of cardiac data. AI systems aim to interpret data more efficiently, offering insights for diagnosing, treating, and managing cardiovascular conditions. In cardiovascular imaging, AI serves two main purposes (57). Firstly, it automates tasks like image segmentation and parameter assessment, reducing the need for human involvement. Secondly, it identifies clinically significant insights. While most applications focus on task automation, there are also advancements in algorithms for acquiring cardiac measurements. Also, the AI use in anesthesia has made tremendous progress (58, 59). Various activities are efficiently done using a variety of strategies throughout all phases of operation (60, 61). For example, while a neural network built to detect esophageal intubation is efficient, continuous capnography makes it unnecessary, disclosing previously unknown difficulties (62, 63).

In addition, the use of AI algorithms for image analysis has enormous potential in pulmonary medicine (64, 65). Lung cancer, a

common and fatal illness, frequently appears as lung nodules on early imaging, making manual interpretation difficult (66). AI recognition technology can speed up picture processing, allowing for multi-parameter cluster analysis and diagnosis support (67). New results show that AI systems are effective at recognizing malignant pulmonary nodules from chest CT scans, employing deep learning technology for analysis, and assisting medical personnel in screening for lung cancer with greater accuracy (68). Another study found that a predictive approach including logistic regression analysis and particular tumor markers outperformed basic combination detection.

AI plays an important role in urology, notably in genitourinary cancers. For example, in a study on prostate cancer, AI was used to predict biopsy results (69). AI has the capacity to stage and predict disease recurrence in kidney and testicular cancer cases. Recent applications include non-oncological illnesses such as stones and functional urology. Over the last few decades, various research has looked into the use of AI in prostate cancer management, in line with the precision medicine paradigm (69). Prostate cancer diagnostics, which encompasses a variety of applications, has made substantial advances (70). In 1994, a critical study investigated the ability of ANNs to predict biopsy outcomes and treatment outcomes following radical prostatectomy (70). Another study assessed the predicted accuracy of two AI systems developed using data from a European referral database, with the goal of detecting prostate cancer early (71).

Skin disorders are often characterized by the visual characteristics of the lesions they cause. However, dermatology faces a hurdle because there are over 2,000 different dermatological disorders, some of which present identical symptoms, complicating correct diagnosis and therapy (72). This difficulty is aggravated by a dermatological scarcity, particularly in underdeveloped nations and isolated places with few medical resources (73). The convergence of big data, advancements in image recognition, and widespread smartphone usage has the potential to transform skin disease diagnosis and treatment (74). AI, in particular, holds promise for providing rapid diagnoses, expanding treatment options, and improving accessibility, especially in underserved areas and resource-constrained settings (75). The integration of AI technology and algorithms is set to become a standard approach in dermatological diagnosis and assessment, offering increased reliability in analyzing the structure and appearance of skin abnormalities, with significant progress made in facial recognition and aesthetic analysis (76).

Neuroimaging is crucial in healthcare and research, enabling the study of the brain in different conditions (77−79). Advanced analysis methods help extract meaningful insights from imaging data, aiding in understanding brain function and pathology. It has notably contributed to the rapid association of conditions in brain imaging, advancing our understanding of brain function. AI also has potential in neuro-oncology. AI algorithms are likely to advance our understanding of brain cancers and therapy. Neuro-oncology has made significant progress by integrating molecular indicators into therapy. AI systems excel at identifying these indicators from imaging data with great accuracy, especially in small patient groups. They successfully assessed the mutational status of numerous markers using distinct institutional databases (77—79).

Imaging techniques are critical for treating pediatric neurological, neurosurgical, and neuro-oncological diseases (80). Multiparametric MRI, when paired with radiogenomic analysis, links imaging features with molecular biomarkers, which aids in illness diagnosis. However, implementing this method into everyday healthcare remains difficult. AI approaches can model large datasets linked to childhood neurological illnesses, allowing for early inclusion into prognostic modeling systems and providing a solution to this difficulty (80). ANNs have demonstrated substantial effectiveness in pediatric neuroradiology, particularly in categorizing children based on ventricular size to distinguish between normal and hydrocephalic conditions. A recent study examined hydrocephalus and controls, reaching a very high accuracy level for hydrocephalus and for controls using T2-weighted MRI scans from 399 children (81). Previous research has indicated similar effectiveness in pediatric hydrocephalus diagnosis using evolutionary adjustments to ANN techniques (82). Ultrasound has become widely adopted in clinical settings due to technological advancements and digital health infrastructure (83, 84). Breast cancer, a leading cause of cancer-related mortality, has seen significant DL utilization for diagnosing and categorizing breast masses. DL techniques applied to abdominopelvic imaging, particularly liver examination, have shown superior accuracy in evaluating liver fibrosis compared to traditional methods. In muscle illness detection and imaging segmentation, ANN-based approaches have increased diagnosis accuracy, particularly for inflammatory muscle diseases (85, 86). Digitalized image datasets, open-source algorithms, computer power increases, cloud services, and ongoing DL technique research all contribute to the rapid evolution of AI/ML tools for imaging interpretation.

Clinical decision-support systems (CDSSs) are designed to enhance the quality of clinical decision-making and, consequently, the treatment provided by healthcare organizations (87). The underlying principle is that the integration of AI-powered support systems can help address the challenges faced by clinicians in their decision-making processes (Figure 2) (88).

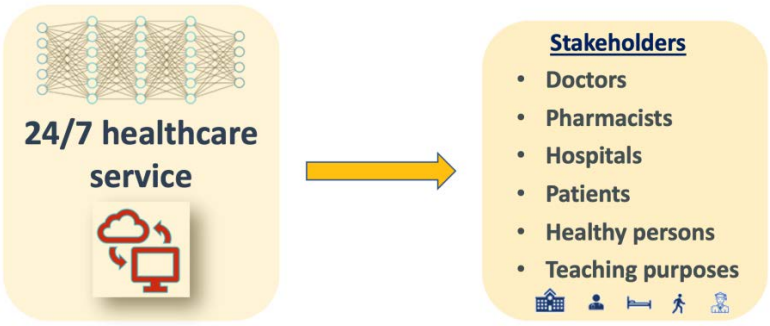

Figure 2. The benefits and stakeholders of a clinical decision support system (CDSS)

These AI-driven strategies for CDSSs can be broadly categorized into two main approaches (89):

1. *Knowledge-based approaches*: These systems rely on a comprehensive knowledge base, typically curated by domain experts, which contains clinical guidelines, rules, and best practices (89). The AI algorithms then apply this knowledge to analyze patient data and provide recommendations or alerts to clinicians.

2. *Data-driven approaches*: These systems use ML and other data-centric techniques to identify patterns and insights from large datasets of clinical information, such as electronic health records, diagnostic test results, and patient outcomes (89). The AI models can then use these data-driven insights to generate personalized recommendations and support clinical decision-making.

By incorporating these AI-powered CDSS strategies, healthcare organizations can enhance the consistency, accuracy, and timeliness of clinical decision-making, ultimately leading to improved patient outcomes and more effective treatment plans. As the field of AI in healthcare continues to evolve, the integration of these advanced decision-support systems is poised to become an essential component of modern healthcare.

Concerns and future perspectives

The incorporation of AI technologies into clinical settings represents a significant advancement in improving diagnostic precision and treatment effectiveness (90). By exploiting the power of ML and data-driven approaches, AI-powered systems can enhance various aspects of healthcare delivery, from early disease detection to personalized therapy recommendations. AI-based tools have the potential to assist clinicians in making more accurate and timely diagnoses by analyzing medical images and identifying subtle patterns that may be overlooked by human observers. This enhanced diagnostic capability can lead to earlier intervention, improved patient outcomes, and more efficient utilization of healthcare resources.

Furthermore, AI algorithms can be trained to predict disease progression, identify high-risk individuals, and recommend personalized treatment plans tailored to a patient's unique medical history and genetic profile. This personalized approach to healthcare can help healthcare providers deliver more effective and targeted therapies, minimizing the risk of adverse reactions and improving overall patient well-being. The integration of AI into healthcare also has the potential to streamline administrative tasks, automate routine workflows, and free up clinicians' time, allowing them to focus more on direct patient care. By automating tasks such as appointment scheduling, medication management, and data entry, AI can enhance the efficiency and productivity of healthcare organizations.

As the adoption of AI in clinical settings continues to grow, it is crucial to address the ethical and regulatory considerations surrounding the use of these technologies. Ensuring data privacy, algorithmic transparency, and human oversight will be essential to maintaining patient trust and upholding the highest standards of healthcare. Overall, the integration of AI into healthcare represents a significant step forward in improving diagnostic accuracy, treatment outcomes, and the overall quality of healthcare delivery. As the field continues to evolve, the synergistic collaboration between clinicians and AI-powered systems will pave the way for a more personalized, efficient, and effective healthcare landscape.

As the integration of AI into healthcare becomes more widespread, it is crucial that healthcare professionals receive comprehensive training and education on the capabilities, limitations, and ethical considerations of these emerging technologies (91). Effective training programs should prepare clinicians, nurses, and other healthcare staff with a fundamental understanding of AI principles, including ML algorithms, data preprocessing, and model interpretability. Healthcare professionals should be trained to critically evaluate the inputs, outputs,

and decision-making processes of AI-powered systems, ensuring that they can make informed judgments about the reliability and appropriateness of the recommendations provided. Additionally, training should address the ethical implications of AI in healthcare, such as data privacy, algorithmic bias, and the maintenance of human oversight and accountability. By investing in the training and upskilling of healthcare professionals, organizations can foster a culture of AI-readiness and empower their staff to effectively use these advanced tools to enhance diagnostic accuracy, treatment planning, and patient outcomes. Ongoing education and collaborative learning opportunities will be essential as the field of AI in healthcare continues to evolve rapidly. Ultimately, the successful integration of AI will depend on the ability of healthcare professionals to understand, trust, and responsibly utilize these transformative technologies.

While AI systems become more integrated into clinical decision-making processes, it is crucial that these technologies adhere to principles of transparency, traceability, and explainability (92). Healthcare professionals and patients must be able to understand how AI-powered algorithms arrive at their recommendations and predictions, in order to build trust and ensure responsible deployment. Transparency refers to the need for AI systems to be open and accountable, with clear documentation on the data sources, model architectures, and training procedures used. Traceability involves maintaining detailed logs of the AI system decision-making process, allowing for retrospective auditing and debugging. Explainability, on the other hand, focuses on the ability to interpret the reasoning behind an AI system outputs, enabling healthcare providers to validate the logic and make informed decisions. By prioritizing these key attributes, AI developers and healthcare organizations can foster greater trust and acceptance of these transformative technologies. Clinicians must be able to understand the strengths, limitations, and potential biases of AI systems, and patients should have confidence that their personal health data is being handled ethically and responsibly. Upholding principles of transparency, traceability, and explainability will be essential as AI continues to shape the future of healthcare delivery.

Regulatory bodies overseeing medical device certification and approval have been slow to address the issue of explainable AI and its implications for product development and marketing. While the FDA takes a comprehensive approach to advancing AI-based medical products, explicit mention of explainability is lacking (93, 94). Instead, there is an emphasis on ensuring transparency and clarity in the output and algorithms provided to users, with a focus on understanding the software's functionalities and its evolutionary changes. Similarly, the Medical Device Regulation (MDR) does not directly address the need for explainability in AI and ML-based medical devices (95). However, accountability and transparency remain crucial, particularly concerning the information provided about the development process of machine learning and deep learning models used in medical treatment. Future regulations will likely require manufacturers to provide detailed insights into model training and evaluation, data usage, and overall methodologies used in their creation.

The legal landscape for AI in healthcare is constantly changing, with new rules and regulations expected to address liability concerns. Healthcare practitioners must be aware of these shifts as legislative frameworks evolve to promote ethical, transparent, and responsible practices in the development and deployment of AI technologies. There are disparities between Europe and the United States in terms of international guidelines on legal difficulties resulting from the use of AI in healthcare, with each region taking its own approach. The European Union has adopted a proactive approach, recognizing the particular issues AI brings to liability regimes and enacting the Artificial Intelligence Act to ensure coherence and legal clarity for AI use, notably in healthcare (96).

The EU intends to promote safe AI use while also encouraging technological innovation. In comparison, the USA lacks a complete legal structure. However, the FDA acknowledges the regulatory implications of AI in healthcare and is aiming to maintain continued oversight of AI as a medical device through strategic planning (97). The FDA's measures include increasing transparency by mandating makers to provide extensive descriptions of the operational mechanisms of AI devices in order to promote a comprehensive understanding of device advantages and hazards. In addition, attempts are underway to eliminate potential bias in AI systems by taking into account aspects such as training data sources and demographics. The FDA has issued a discussion paper proposing a regulatory framework for changes to AI-based medical software to assure the safety of AI technology in healthcare (98).

Conclusion

In conclusion, the utilization of AI across the spectrum of drug development, clinical trials, and healthcare heralds a new era in healthcare innovation. The capacity of AI to analyze through huge volumes of data, identify patterns, and generate insights at unprecedented speeds has reshaped how we approach medical research and patient care. In drug development, AI algorithms streamline the process of identifying promising drug candidates, accelerating the journey from discovery to market availability. Likewise, in clinical trials, AI-powered analytics optimize trial design, patient recruitment, and data analysis, fostering greater efficiency and precision. Moreover, within healthcare, AI-driven tools enable healthcare providers to make more informed decisions, tailor treatments to individual patients' needs, and predict disease progression

with greater accuracy. Nevertheless, the incorporation of AI in healthcare comes with its own set of challenges and considerations. Ethical concerns surrounding data privacy, algorithm bias, and transparency in decision-making must be carefully addressed to ensure the responsible and equitable deployment of AI technologies. Additionally, regulatory frameworks need to evolve to keep pace with the rapid advancements in AI-driven healthcare solutions, striking a balance between fostering innovation and safeguarding patient safety. Despite these challenges, the potential benefits of AI in transforming healthcare delivery are profound. By harnessing the power of AI to augment human expertise, we can unlock new frontiers in medical research, improve clinical outcomes, and ultimately enhance the quality of life for patients worldwide. Moving forward, sustained investment in research, interdisciplinary collaboration, and stakeholder engagement will be key to realizing the full potential of AI in revolutionizing drug development, clinical trials, and healthcare.

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VEŠTAČKA INTELIGENCIJA U RAZVOJU LEKOVA, KLINIČKIM ISTRAŽIVANJIMA I ZDRAVSTVU

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Primena veštačke inteligencije (engl. *artificial intelligence* – AI) u razvoju lekova, kliničkim istraživanjima i zdravstvenoj zaštiti predstavlja transformativno napredovanje zdravstvene nege uopšte. Tehnologije bazirane na AI-ju pružaju neprocenjive mogućnosti za analizu ogromnih skupova podataka i identifikaciju primenljivih obrazaca pošto revolucionarno modifikuju različite aspekte eko-sistema zdravstvene zaštite. Cilj ovog revijalnog rada bio je da pruži pregled aktuelnih istraživanja o primeni veštačke inteligencije u zdravstvu. Pristupi bazirani na AI-ju u razvoju lekova racionalizuju proces identifikacije potencijalnih terapijski aktivnih supstanci i ubrzavaju put od otkrića do odobrenja za promet. U kliničkim istraživanjima, analitika ojačana primenom AI-ja optimizuje dizajn studija, smanjuje veličinu uzorka, regrutovanje bolesnika i vreme potrebno za analizu podataka, povećavajući pritom statističku relevantnost i validnost rezultata. Pored toga, aplikacije bazirane na upotrebi AI-ja u kliničkoj praksi osnažuju pružaoce zdravstvenih usluga sistemima za podršku u donošenju odluka, personalizovanim preporukama za lečenje i prediktivnoj analitici, što vodi do nege bolesnika koja je znatno efikasnija i personalizovana u većoj meri. Premda ostaju izazovi poput etičkih razmatranja i regulatornih zakonskih okvira, značajna je potencijalna dobrobit od upotrebe AI-ja u medicinskim inovacijama i poboljšanju ishoda lečenja bolesnika. Naglasak treba staviti na važnost kontinuiranih istraživanja, saradnje i odgovorne primene veštačke inteligencije u zdravstvu.

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***Ključne reči**: veštačka inteligencija, razvoj lekova, klinička istraživanja, mašinsko učenje, dubinsko učenje*

Review article

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MEDICO-LEGAL ASPECTS OF THE PHYSICIAN'S RESPONSIBILITY EXPERTISE

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Legal medicine, an independent scientific medical discipline, is crucial in studying and resolving numerous health, legal, and social issues that can harm health or destroy lives. The institution of medico-legal expertise intricately links this science with the field of law. Questions related to medical ethics and the professional, criminal, and civil liability of doctors and other medical personnel are prevalent in forensic medical expertise. The nature of the medical profession implies that healthcare workers perform activities according to the valid healthcare doctrine and the code of professional ethics, which presuppose the assumption of profound professional, ethical, criminal, and material responsibility for their actions. Part of the regulations for malpractice are implemented through the competencies of the health institutions where the health worker is employed, and the work is done through the competencies of the state or public powers transferred by the state to the chambers of health workers, which regulate the obligations and responsibilities in the actions of healthcare workers. In the broadest sense, doctors and medical staff can be held responsible if they break humanitarian principles, universal human rights, established and generally accepted scientific medical achievements and rules of the professional code at a given time (lat. *Vitium Artis*).

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Key words: *medical malpractice, physician's responsibility, forensic medicine, medicolegal expertise*

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Introduction

Medicine and law have a long comparative history whose flows are congruent with the rise of technological, cultural, and civilizational achievements. Forensic medicine, or legal medicine, is an independent scientific medical discipline that, using a specific methodology, studies and resolves numerous health, legal, and social issues related to harming or destroying people's lives. As a result, the establishment of medico-legal expertise inextricably links forensic medicine with legal science. The dynamic nature of modern life and the uncontrolled development of modern technologies and innovations in almost all spheres of life increasingly force current forensic medicine to incorporate the expertise of doctors and other medical personnel. This paper apostrophizes the basic medico-legal principles of expertise based on violations of the medical profession's rules and regulations.

The doctor-patient interconnection

The doctor-patient relationship involves a complex connection where both parties make collaborative decisions about medical requirements and health objectives through mutual respect, information exchange, and agreements (1). When a patient and a doctor establish mutual rights and obligations, the patient requests medical assistance and agrees to provide it. This specific relationship can potentially establish a contractual medical treatment relationship between the patient, the doctor, and the health institution where the doctor works. Although the doctor and the patient share the same goal of providing or receiving medical treatment, their obligations are not of equal quality, as the doctor's obligations are in the patient's best interest while the patient's duties are in their interests. The doctor's dominance over the patient, who entrusts him with his greatest wealth—life and health—conditions the relationship's asymmetry. Therefore, the patient is subordinate to the doctor, and the patient's trust in the doctor is the foundation of the doctor-patient relationship. That trust rests on humanity, the essence of which is the medical profession's

promise that its members will take care of each patient indefinitely, selflessly, and immeasurably, respecting the primary principle of health care, *primum nil nocere* (first of all, do not harm) (1, 2).

However, the doctor's professional knowledge, compassion for the patient, and commitment to viewing the patient as an active participant in the healing process rather than an object or recipient of medical care underpin this trust, making it impossible to order or establish through legal penalties. The patient's faith in the doctor and the expectation that the doctor will use all his attention and knowledge to choose the most effective and, therefore, the best, safest, harmless, and least unpleasant methods put the doctor in a typical relationship of supremacy over the patient. That is why medical ethics recognizes the patient's right to freely choose a doctor to whom he will entrust his health, as well as the doctor's capacity to freely make decisions in the patient's medical treatment, not unthinkingly following the instructions of some higher authorities or instances. Even though human actions and trust characterize the doctor-patient relationship, legal regulation of this specific liaison is necessary (2, 3).

The doctor's ligation

The history of medicine has shown that the medical profession cannot ensure the fulfillment of the doctor's ethical duties towards the patient (1, 2). That is why the state authority has supported these duties by legalizing a limited number of ethical and professional responsibilities, transforming them into legal obligations governed by articles of the Criminal Code of the Republic of Serbia (CC) (4). It means that the legislation covers only the "ethical minimum", considering that it is neither necessary nor possible to legislate all of the doctor's moral, ethical, and professional obligations to the patient (1, 5). Violating rules and regulations in providing medical assistance and health services entails the responsibility, which can be individual or institutional, of one or more persons, the management of a health institution, or the entire organization of the health system or some of its units. A critical aspect of medical personnel's responsibility is consolidating their work while maintaining individual accountability. This implies that many medical workers typically participate in providing health services to the patient, with each individual solely responsible for actions within the scope of their professional work while respecting the principle of supervision (6). In the hierarchy of medical assistance, the doctor oversees subordinates, yet he bears sole responsibility for his actions. If it is about faulty equipment and devices, the responsibility falls on the management of the health institution (hospital, clinic) or the appropriate ministry (7). However, in such cases, in addition to the institutional responsibility, there is also the individual responsibility of health workers who knew unsafe working conditions but agreed to work in such situations, i.e., with defective or inadequate equipment, regarding the so-called shared responsibility. The doctor's obligations are to provide medical treatment and professional and timely information about the facts related to the patient's health in a way that is understandable to him, considering his age, education, and mental abilities, as well as obtaining consent for medical treatment (informed consent) (1, 5–8).

The patient must accurately declare information about his general health, habits, and symptoms of illness, follow the doctor's orders, and respect his person's dignity. The health institution's responsibilities include obtaining a work permit from the competent ministry and ensuring appropriate working conditions. The nature of the medical profession implies that health workers perform health activities according to the current health doctrine and the code of professional ethics, which presupposes the assumption of professional, ethical, criminal, and material responsibility for their actions. In this way, part of the regulations for work failure is implemented through the competencies of the health institutions where the health worker is employed and partly through the competencies of the state (court) or public powers transferred by the state to the chambers of health workers, which regulate obligations and responsibilities in their regulations (7, 8).

From a broad perspective, we can hold the medical staff accountable for violations of 1) humanitarian principles (universal human rights), 2) non-observance or violation of established and generally accepted scientific medical achievements and rules of the profession at a particular time (lat. *Vitium Artis*), and 3) failure to act with due care (5, 9).

Human rights are universal rights that apply to all people in all situations. These moral rights, defined as universal rights based on the principles of "natural law", do not require codification within valid legal norms, making them supra-juridical or "above the law". The right to life is a universal human right and one of the most essential. Since health is the fundamental foundation of life, the right to life entails the right to treatment, thereby establishing a close relationship between the medical profession and universal human rights through health protection. According to domestic legislation, health protection is also a constitutional human right. The legal position of medicine significantly aligns with other universal individual human rights, particularly the right to self-determination and consent, the right to information, the right to privacy, and the protection of information. That includes the obligation to maintain medical secrets, equivalent to the responsibility to maintain official secrets, and the right to respect the person's dignity, encompassing the patient's religious and customary specifics. However, discrimination in

the broader social context may restrict certain individual rights, such as exemption from criminal offenses, to safeguard collective rights when society's general interest surpasses an individual's well-being. The disclosure of official secrets at the request of judicial authorities, the obligation to report serious infectious diseases, the number of patients handling food, the introduction of forced treatment, and mandatory hospitalization in cases where the wider community may endanger the patient's mental or physical health are typical examples of the narrowing of individual rights at the expense of collective rights (9).

The Law on Health Care and the Law on Patients' Rights of the Republic of Serbia also uphold universal human rights and values in patient health care (7). These include the right to access health care, the freedom to choose a doctor, the right to privacy and confidentiality of information, the right to self-determination and consent, the right to observe medical documentation, the right to privacy of data, the special rights of patients undergoing medical examinations, and the right to compensation. The public's right to information is also defined as respecting collective rights (expert instructions on preserving one's health based on the dangers of spreading infectious diseases or major environmental incidents). The patient, as a claimant in a civil law court, obtains compensation for the damage suffered due to the violation of personal rights and universal human rights (7, 9).

Medical malpractice

Malpractice is defined as non-compliance with or violation of specific, established, and generally accepted medical profession and science standards. It refers to non-compliance with the rules of good practice (1, 10). The doctor must use the most excellent knowledge and skill in medical treatment (diagnosis and therapy) because this obligation primarily stems from medical ethics, deontology, and legal regulations. The "standard of care" (1) and the rules of scientifically based and widely accepted modern medical doctrine and practice determine the distinction between proper and incorrect practice in each case. It is not even possible to standardize due diligence. Therefore, we view each malpractice case within its unique circumstances and time frame. Different specialized knowledge, skills, and techniques also contribute to the variability of the standard of care, requiring the assessment to consider the complexity and risks of performed medical procedures, the patient's general state of health, and his characteristics such as co-morbidities, idiosyncrasies, and body anomalies. Acting contrary to the generally accepted rules of the profession results in a complex amount of damage to the patient's health, and these harmful consequences are the basis for determining the responsibility of doctors and other medical personnel (4, 7, 11).

Throughout human history, specific legal mechanisms have called for doctors to take responsibility for transgressions during professional activities. We should view medical personnel's duties through the lens of social and legal obligations. Moral obligations and principles mirror social obligations, reflecting the time's prevailing social circumstances and conditions. Favorable legal regulations adjust legal obligations and their violation results in legal and judicial repercussions. A doctor's professional work includes pre-assumed and accepted responsibilities. Therefore, we should analyze the doctor-patient relationship within the framework of social (ethical and deontological or disciplinary) and legal (criminal and civil) responsibilities.

The Serbian Laws on Health Care, Patients' Rights, Health Insurance, Health Documentation and Records, Medicines and Medical Devices, Chambers of Health Workers, and the Code of Medical Ethics regulate the social responsibility of doctors and medical personnel (3, 7, 12). A doctor's ethical responsibility stems from violating the ethical and moral principles of medical ethics based on the Hippocratic Oath, which has survived for centuries and remains the basic ethical norm for all health workers. Medical deontology is a particular scientific discipline that studies health workers' professional duties and rights (1, 2). Medical personnel's moral and professional obligations, stemming from a duty violation in their workplace or harm to a chamber member's reputation, typically lead to disciplinary action. The Court of Honor of the Medical Chamber of Serbia can impose one of the following disciplinary measures: a public warning and a fine for a period of one to six months (for minor offenses), as well as a temporary ban on independent work in the performance of specific tasks in the health sector and a temporary ban on independent work in the performance of health activities (for severe offenses). These measures can last up to six months, one year, and, in exceptional cases, up to five years (12).

Legal (court) responsibility arises from the professional actions of doctors and medical staff (in the broadest sense, from applying medicine). When broader social interests protect the patient's interest, this type of responsibility can be criminal, and it can also be civil when the patient seeks compensation for damages caused by the doctor's negligence. Criminal responsibility entails violating specific laws outlined in the CC (4).

Criminal protection is only necessary for severe endangerment or impairment of people's health (5). It refers to cases where there are elements of a criminal offense in the professional work of health workers. For an action by a doctor or member of the medical staff to meet the criteria for a criminal offense, it must meet three criteria: 1) it must be illegal, as no criminal offense exists without an unlawful act or culpability; 2) it must pose a social danger; and 3) it must result in an adverse consequence. During the criminal act, the

perpetrator must be sane, act, and know explicitly or implicitly that his actions were prohibited. If the law expressly provides for negligence, the perpetrator is also guilty. A criminal offense is committed negligently if the perpetrator is aware that his action could commit a criminal offense. However, he carelessly assumed that the offense would not occur or that he would be able to prevent it. Alternatively, he was unaware that he could commit the offense despite the circumstances and personal characteristics that obliged him to be aware of this possibility. Furthermore, by taking voluntary action, he aimed to achieve a different outcome than the one that occurred. That was due to his imprudent belief that the consequences would not happen or that he could prevent unwanted consequences (conscious negligence). However, given the circumstances surrounding the act and his traits, he had a duty to be aware of this possibility (unconscious negligence) (4, 5).

Essential evidence in criminal proceedings includes: 1) an obligation that confirms that the patient has been accepted for medical treatment by a health institution or a doctor of private or state practice, which establishes a "contractual" relationship that lasts until the end of the treatment or until the termination of the contract by a patient or a doctor, which can be the basis for initiating a criminal or civil process if it was carried out by a medical institution or a doctor of private or state practice without the patient's will or without ensuring his further treatment in another institution with the provision of all previous medical documentation; 2) that there is a somatic and psychic impairment of the patient's health, which is considered to be a consequence of failure in treatment in terms of action or inaction; 3) bringing into causation, i.e., cause-and-effect unintended consequences (damage to the patient's health) with an omission in the course of treatment, which, as a rule, is carried out through medico-legal expertise. The cause-and-effect relationship, as well as other evidence for determining the liability of a doctor or other healthcare worker in criminal law, must be "beyond reasonable doubt", and this assessment belongs to the court. The state appears as the bearer of damage due to the civilizational achievement that the punishment inflicted for impairing an individual's health belongs to the organized society, not the individuals. Criminal sanctions aim to stifle actions that violate or jeopardize the values protected by criminal laws, safeguarding societal interests and judgments. This process reinforces specific moral and fundamental social values by isolating the offender from society and promoting rehabilitation to curb crime within society. By defining criminal offenses against people's health as a particular good, the legislator sought to protect the physical integrity of the patient and emphasize the role and responsibility of all participants in the treatment process, given that performing health care is a risky and responsible profession that requires a high degree of caution and special attention (1, 4–6).

Domestic legislation

According to domestic legislation, doctors and health workers can be criminally liable for the following criminal acts: OFFENCES AGAINST LIFE: Mercy Killing, Illegal Termination of Pregnancy; CRIMINAL OFFENCES AGAINST FREEDOMS AND RIGHTS OF MAN AND CITIZEN: Unauthorized Disclosure of Secret; OFFENCES AGAINST HUMAN HEALTH: Failure to Act Under Health Regulations during Epidemic, Transmitting Contagious Disease, Transmitting HIV Infection, Medical Malpractice, Illegal Conducting of Medical Experiments and Testing of Drugs, Failure to Provide Medical Assistance, Quackery, Malpractice in Preparing and Issuing Medicaments, Grave Offences against Health; CRIMINAL OFFENCES AGAINST THE JUDICIARY: Failure to Report a Criminal Offence or Offender, Perjury—False testimony. The most common criminal acts that have been the subject of medico-legal expertise in domestic judicial practice are medical malpractice (negligent provision of medical assistance) and failure to provide medical assistance (4, 5).

According to Article 251 of the CC, medical malpractice is defined as an action by a doctor or other medical staff during the provision of medical services in which they use inadequate means or unsuitable treatment, fail to observe appropriate hygiene standards, or proceed unconscionably leading to the deterioration of a person's health or medical condition (1, 5, 13). A specific criminal offense can also result from negligence. From the perspective of medico-legal theory and practice, it is important to note that the negative outcome of a medical procedure does not necessarily indicate the doctor's or health worker's undeniable responsibility. Specifically, the unpredictable and unexpected constitutional characteristics of the patient or equipment malfunctions beyond the medical staff's control often lead to health consequences during medical assistance. In such cases, one cannot question the individual's criminal responsibility. On the other hand, individuals bear legal responsibility for harmful consequences that are uncommon and preventable under specific circumstances, like leaving instruments or bandages in body cavities. Additionally, if a doctor or other medical staff member makes a mistake and allows the damage to worsen, it could be considered a premeditated and grave offense against health. The standard of due care and the circumstances in which the critical event occurred determine whether there are elements of malpractice, omission, or negligent action by a doctor or other medical staff. That is the primary goal of medico-legal expertise. The standard of due care implies the attention of a competent expert in providing medical care. Determining the standard of due care involves evaluating how well a doctor or other medical staff adheres to the rules of acceptable clinical practice,

comparing their actions to those of another doctor under similar circumstances, and considering the perpetrator's knowledge and skills in the given context. Many legal systems apply the standard of due care to a conscientious and reasonable doctor of the same specialization under similar conditions, a standard of excellent medical practice that the medical profession has accepted. When providing medical services, the doctor must adhere to and master new treatment methods, with the standard set based on scientific knowledge at the time. In our country, doctors must act with the special attention of a qualified expert, which implies increased attention according to the profession's rules and customs. When a doctor does not act with the care of a qualified expert, it is "ordinary carelessness" (lat. *Culpa Levis*). If he does not act like an average doctor, it is "grave carelessness" (lat. *Culpa Lata*), which entails more significant responsibility (1).

Article 253 of the CC defines the criminal offense of failure to provide medical assistance (4). The offender can only be a doctor, not any other medical staff. This article mandates that a doctor must offer requested medical assistance to anyone in need. At the same time, that person must be in immediate danger of life or at risk of serious bodily injury or severe damage to health. It is disputed in legal practice whether a doctor practicing medicine or any other doctor can be considered an offender. In domestic jurisdictic practice, any doctor can be a potential offender (4, 5, 13). However, when doctors with a prescribed professional qualification work in a different, comparable, or entirely unrelated field, it is crucial to assess if they have fulfilled the requirement of acting "against their medical duty". While some interpretations suggest that the term "doctor" only refers to a medical professional who is currently practicing or has previously practiced medicine and is capable of providing such assistance rather than a recent medical school graduate who has never been professionally involved in medical practice, the judicial practice has demonstrated varying perspectives. Specifically, we can consider any individual with the appropriate professional qualification (doctor of medicine or doctor of dentistry) as a doctor, irrespective of their current or past involvement in medical practice. This opinion is based primarily on the view that during studies and with the acquisition of the title of doctor of medicine or doctor of dentistry, elementary skills for providing medical assistance are acquired, despite the lack of professional practice, especially bearing in mind that a large number of individuals from the broader social community, regardless of profession, are capable of providing at least "first aid". This position is supported by the fact that our criminal legislation stipulates for every individual, regardless of profession, a general duty to assist a person in immediate danger to life, which he is obliged to do within the limits of his capabilities but without danger to himself or others (Article 127, CC: Failure to assist) (4, 5). The criminal offense of failure to provide medical assistance involves the act of inaction, specifically the inability to assist. This refusal need not be explicit, as an intentional failure to provide medical assistance is sufficient. The passive subject of this criminal act, that is, the object of the act, is a person who needs medical help and who is in imminent danger of life, serious bodily injury, or severe health impairment. It implies that a person in immediate danger of death, serious bodily injury, or severe health impairment must require medical assistance to overcome these conditions. Individuals may not need medical assistance if they face immediate danger to their lives due to circumstances other than illness or injury. In such cases, criminal acts do not exist. It follows from the above that the doctor must provide the requested medical assistance at any place and at any time, directly or indirectly, to a person who needs this assistance in such a way that he will examine the patient, make a diagnosis, and provide medical assistance to eliminate harmful consequences. Health institutions must provide emergency medical assistance, particularly those with an organized emergency medicine service. Failure to provide medical assistance is always punishable, while the penalty depends on the outcome (monetary fine or imprisonment for six months to eight years) (13).

Until now, the forensic medical practice has demonstrated that doctors, primarily specialized in surgery and general or internal medicine and typically working in health institutions, frequently face prosecution for health-related crimes when they are not only outside their workplace but also lack essential medical equipment and medicines such as stethoscopes, blood pressure monitors, and drug injection accessories. As a result, instead of providing immediate medical help, they may prioritize transporting the patient to the first healthcare facility as quickly as possible. However, the legislator stipulates that a doctor of medicine, regardless of specialty, must provide medical assistance to a seriously endangered patient when the need arises, regardless of the location. This assistance can take various forms, including staying with the patient, positioning them, securing their airway, stopping bleeding, immobilizing them, initiating manual cardiac massage, and artificial respiration, all without leaving the patient for even a moment. The occurrence of a fatal outcome or severe and permanent health consequences, despite the implemented medical measures, excludes criminal responsibility because the doctor acted according to the ethical and doctrinal principles of the medical profession in emergency conditions. In contrast to criminal liability, civil liability for doctors and medical personnel includes compensation for the patient's damage from medical treatment.

The general regulations of compulsory law, the provisions of the Convention on Human Rights and Biomedicine, and the Law of Patients' Rights guarantee the patient's right to compensation for damages caused by medical intervention. Civil lawsuits realize the right to compensation for

damage when they meet the following criteria: 1) the offender's harmful actions, such as work neglect or actions that deviate from the standard of due care; 2) the illegality of the harmful action, establishing a causal connection between the harmful action and the damage it causes; and 3) the patient's consequences (13–15).

Civil (litigation) court proceedings aim to inflict material and non-material damage on an individual, institution, group of persons, or state institution itself (14, 15). Experts in economics and finance can easily determine and quantify material damage, while medico-legal expertise quantitatively and qualitatively determines the basis and types of non-material damages. Types of non-material damage include difficult-to-measure categories of suffered and future physical pain, primary and secondary fear, mental suffering due to a reduction in general life activity and life joys, and disfigurement (changes in aesthetic appearance). Even in cases where there is no criminal liability, the patient can seek compensation for damages through civil proceedings, as the standards of due diligence for criminal and civil liability differ. Doctors or other medical personnel should observe due care in their professional work, which reflects the main difference between criminal and civil liability (14, 15).

Criminal liability, in particular, is only available for gross or obvious negligence. On the other hand, civil liability requires compensation for damages caused by smaller-scale negligence, also known as ordinary negligence. That is why civil proceedings (lawsuits) for damages caused by medical negligence are far greater than criminal proceedings (13–15).

The medical profession, through the institution of medico-legal expertise, determines what complies with the profession's rules and what does not. Healthcare workers determine the so-called objective criterion based on colleagues in the same profession and the medical procedure's unique circumstances. That means that greater danger and greater risk necessitate superior care, while the urgency of the medical procedure justifies a lower standard of care (5). Undertaking treatment without the patient's consent is illegal, as it goes against medical science and professional achievements. The legal validity of the patient's consent is critical, and the procedures must adhere to its standards. Doctors can only intervene in organs, organ systems, and body parts that they did not get informed consent for before but are necessary because of the patient's condition. For example, they might perform the indicated surgical intervention to stop a life-threatening blood vessel injury for hemostasis or to treat an undiagnosed or intraoperative perforation of the intestines. However, consent does not exclude the illegality of the doctor's actions if the consequences occur due to a medical error. If a procedure fails without the patient's consent, the healthcare worker bears full responsibility for any resulting damage, regardless of whether the procedure adheres to the professional's rules. The patient's entitlement to information about their health condition and their choice to accept or reject the doctor's proposal form the foundation of the Institute of Informed Consent (8).

Considering that the responsibility of the health care worker is one of the most critical assumptions of responsibility, medico-legal expertise plays a crucial role in determining the appropriate behavior of health care workers in providing medical care.

Conclusion

While mistakes are a common occurrence in human nature and across all professions, the medical profession bears a heightened level of responsibility due to the inherent discrepancies in patient trust in medical power, as well as the limitations of medical science, knowledge, and skills. The medical-legal expertise of the healthcare workers plays a crucial role in determining the failure of treatment, given that the judicial authorities receive the necessary information of a medical nature through the institution of expertise. The continuous education of doctors and other medical personnel is crucial for effectively preventing medical errors. Health workers, especially doctors, have the right to make mistakes, but not due to ignorance, negligence, or carelessness.

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SUDSKOMEDICINSKI ASPEKTI EKSPERTIZE LEKARSKE ODGOVORNOSTI

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Sudska medicina je samostalna naučna medicinska disciplina koja proučava i razrešava brojna zdravstvena, pravna i socijalna pitanja u vezi sa narušavanjem zdravlja ili uništenjem života ljudi. Kao takva, ova nauka je neraskidivo povezana sa pravnom naukom kroz instituciju sudskomedicinske ekspertize. Pitanja povezana sa medicinskom etikom, profesionalnom, krivičnom i građanskom odgovornošću lekara i drugog medicinskog osoblja predstavljaju veoma čest predmet sudskomedicinske ekspertize. Priroda medicinskog poziva podrazumeva da zdravstveni radnici obavljaju zdravstvenu delatnost u skladu sa važećom zdravstvenom doktrinom i kodeksom profesionalne etike, što unapred implicira i preuzimanje stručne, etičke, krivične i materijalne odgovornosti za učinjena dela. Jedan deo regulative za propuste u radu sprovodi se u okviru nadležnosti zdravstvenih ustanova u kojima je zdravstveni radnik zaposlen, a drugi u okviru nadležnosti države ili javnih ovlašćenja koja je država prenela na komore zdravstvenih radnika, koje svojim propisima regulišu obaveze i odgovornosti u postupanju zdravstvenih radnika. Ako se sve to posmatra iz najšire perspektive, zapaža se da odgovornost lekara i medicinskog osoblja može proisteći iz povrede humanitarnih principa i univerzalnih ljudskih prava, nepridržavanja utvrđenih i opšteprihvaćenih naučnih medicinskih dostignuća i pravila profesionalne struke u datom trenutku ili ogrešenja o njih (lat. *Vitium Artis*), kao i nepostupanja sa dužnom pažnjom.

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***Ključne reči**: lekarska greška, odgovornost lekara, sudska medicina, sudskomedicinska ekspertiza*

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PERCUTANEOUS NEPHROSTOMY IN OBSTRUCTIVE UROPATHY: COMPLICATIONS AND FEASIBILITY ANALYSIS OF OUTPATIENT SURGERY UNDER LOCAL ANESTHESIA

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This study aimed to examine the efficacy, feasibility, frequency of complications, and outcome of emergency or elective renal unblocking in patients with benign or malignant pathology within the outpatient surgical procedure manner.

A prospective study included 158 patients, of which 94 (59.49%) women and 64 (40.50%) men, who underwent PCN at the Urology Department of General Hospital "Aleksa Savić" in Prokuplje from January 2020 to January 2024. All the patients were admitted in an outpatient manner. The cohort included patients with both benign and malignant obstruction.

The operation success rate was 97.47%. More than 40% of percutaneous nephrostomy (PCN) placements were performed for calculosis. The frequency of issues in our study aligns with results from previous investigations. Regarding the hydronephrosis grade, there was a clear statistical significance in the complication rates among the groups with mild, moderate, and severe hydronephrosis. Every problem was categorized using the five modified C–D (Clavien–Dindo Classification System) grades. Most of the problems were low-grade C–D complications.

Percutaneous nephrostomy primarily gives us time in treatment planning, and in a certain number of patients, it represents the final urine derivation when there is no definitive surgical procedure. In addition to overcoming the learning curve, it is a sovereign method in prompt intervention on developed obstruction. Performing percutaneous nephrostomy in an outpatient manner represents a safe and feasible procedure.

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Key words: *kidney, hydronephrosis, nephrostomy, percutaneous*

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Introduction

Obstructive uropathy is a pathological condition in which urine flow is blocked, resulting in increased pressure within the renal collecting system and possibly permanent kidney damage. The interruption and inability of urine to flow results in pain, infection, sepsis, and loss of renal function in its terminal stage (1). This condition is potentially life-threatening, especially in patients with a single-functioning kidney due to progressive uremia. The very degree of developed hydronephrosis or the possibility of developing primary renal atrophy is an individual patient's response that requires prompt renal decompression (2).

Various modalities allow unblocking the affected organ: retrograde stenting, open drainage, and percutaneous nephrostomy (PCN). Although very widespread as a procedure and a favorite among both urologists and radiologists, there are still no European recommendations and guidelines that would include determined rates of complication (3). Our study included patients who underwent a PCN procedure in a secondary health care facility, in the urology department. All patients included in this study underwent PCN in an outpatient surgery manner. It is inevitable to mention the epidemiological aspect during the COVID-19 pandemic. Due to a drop in elective surgery rates worldwide, PCN represented an opportunity to delay the final intervention without consequences for patients' health effectively (4).

Materials and Methods

The prospective study, included 158 patients, of which 94 (59.49%) women and 64 (40.50%) men who were placed percutaneous

nephrostomy catheter (PCN) unilaterally or bilaterally at the Department of Urology of General Hospital "Aleksa Savić" in Prokuplje from January 2020 to January 2024. All procedures were performed in our center by a urologist, under local anesthesia, and were entirely done under ultrasound guidance. Inclusion criteria: renal blockage in the urinary tract with or without infection, patient living close to the hospital.

The study included patients with benign and malignant pathophysiological mechanisms of obstruction. Patients were held for 2 to 4 hours for observation and continuously monitored for tension, pulse, body temperature and control blood count. Furthermore, blood count, biochemical analysis and ultrasound follow-up within 72 hours postoperatively were also performed. All patients received cefazolin or cefuroxime prophylaxis if there was no positive urine culture. Otherwise, adequate antibiotic was administered.

During the procedure, the posterior calyx of the lower calyx group of the pyelocaliceal system was most commonly used following the avascular line of Brodel for access to avoid vascular injuries. After the incision site was determined, a local anesthetic was administered in the form of 20 ml of 1% lidocaine. After the incision of the skin and fascia under ultrasound vision, a channel was created using the previously fixed guide on the convex probe, following the modified Seldinger technique as described by Pedersen (5).

Postoperative complications were evaluated according to the standardized modified Clavien–Dindo classification system employed for grading complications (6). Patients were stratified by comorbidity status using the Charlson comorbidity index, within investigating the feasibility and complications rate among given groups. A comparison between complications arising from benign and malignant etiology was made by using the Chi-square. A univariate analysis was performed in which the relationship between some independent variables and the occurrence of complications was analyzed. Data were expressed as mean plus standard deviation and a p-value < 0.05 was considered statistically significant. Patients were also categorized according to their BMI groups and investigated through univariate analysis for dependence.

Results

Percutaneous nephrostomy (PCN) was performed in obstructive uropathy due to various benign or malignant conditions in a total of 158 patients. The age structure of the patients was between 25 and 84 years. In men, the mean age was 54.32 years, while in women patients the mean age was 52.13 years. In 97 (61.39%) patients, PCN was placed due to benign, and 61 (38.61%) PCNs were indicated due to obstruction caused by malignant diseases (Table 1).

The success rate was 97.47%, noting that after repeated unsuccessful procedures, that percentage was even higher. Placement failure was noted in 4 (2.53%) patients and was caused by intolerance to the pronation position, difficult anatomy or interposed abdominal organs. In 2 (1.27%) patients, PCN catheter blockage occurred within the first 24 hours, and they required re-placement after failed probing attempts. Over 40% of the indications for placement were calculosis. All the patients included in the study were admitted in an outpatient manner.

The average duration of the procedure in the observed series was 27 minutes with an SD of 7.24. Patients were divided into 8 groups for investigating the learning curve timeline. Within groups, there was statistical significance between the mean operative time of procedure in Group I compared to the means of other given groups ($p < 0.5$). This gives us the proof of a relatively short learning curve of ultrasound guided percutaneous nephrostomy procedure (Figure 1).

The Charlson Comorbidity Index (CCI) score was as follows: 42 patients (26.6%) were classified as Group I with a score of 0; 55 patients (34.8%) were classified as Group II with a score of 1; and 61 patients (38.6%) were classified as Group III with a score of ≥ 2. High CCI score was not significantly related to higher medical complication rates after PCN in our study, enabling feasibility of the procedure in the widest possible pathological states.

In order to achieve data standardization, all complications were classified according to the five grades of modified C–D (Clavien–Dindo Classification system). The majority of complications were low-grade C–D complications out of which 19 patients (12.03%) had fever, pain or transient hematuria (hematuria lasting < 24 h) classified as C–D I. In 2 patients (1.27%), subcapsular hematoma (C–D IIa) was recorded, verified and monitored by ultrasound. Urine leaks and urinoma formation (C–D IIb) were not noted as complications in our series. PCN tube dislodgement/blockage/failure was recorded in 10 patients (6.33%) as C–D III. One patient (0.63%) developed sepsis (C–D IVb) after PCN placement, while 1 patient (0.63%) was referred to the ICU of a tertiary reference center after placement of a nephrostomy catheter (in a single kidney), where he was successfully treated, with previously diagnosed preprocedural septic shock. There were no complications with a fatal outcome or other major complications (C–D V) (Table 2).

Patients included in the study had mild 24 (15.19%), moderate 75 (47.47%) or severe 59 (37.34%) grade of hydronephrosis. Concerning the hydronephrosis grade, the incidence of complications was also observed. Out of the total number of procedures, among mild, moderate and severe hydronephrosis groups, there was clear statistical significance in complication rates ($p = .00017420$; $p < .05$) (Figure 2).

Table 1. Obstruction etiology and gender distribution

	Indication/Cause	N	%	Men N	%	Women N	%
	Calculosis	64	40.51	30	18.99	34	21.52
	UPJ obstruction	10	6.33	4	2.53	6	3.80
Benign	Pyonpehrosis	5	3.16	3	1.90	2	1.27
	Ureteral stenosis	9	5.70	2	1.27	7	4.43
N = 97	Ureteral ligature	9	5.70	2	1.27	7	4.43
	Bladder cancer	9	5.70	7	4.43	2	1.27
	Ureteral malignancy	9	5.70	5	3.16	4	2.53
Malignant	Cervical cancer	24	15.19			24	15.19
	Endometrial cancer	4	2.53			4	2.53
N = 61	Prostate cancer	11	6.96	11	6.96		
	Ovarian cancer	4	2.53			4	2.53
				64		**94**	

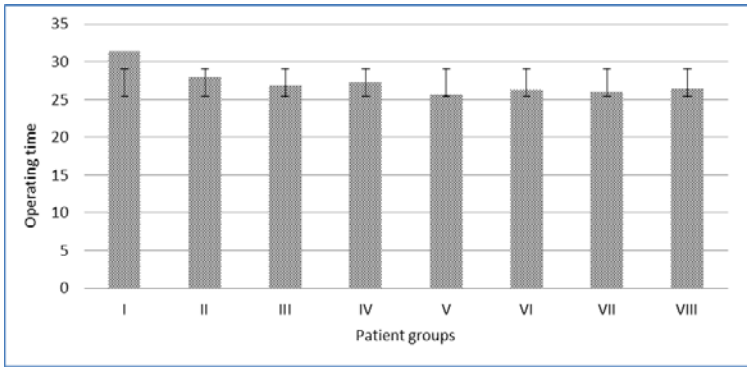

Figure 1. Timeline of procedure duration among groups. Significance in I vs. VII p < .005 (p = .034); with no significance in comparison of operating time between other subsequent groups

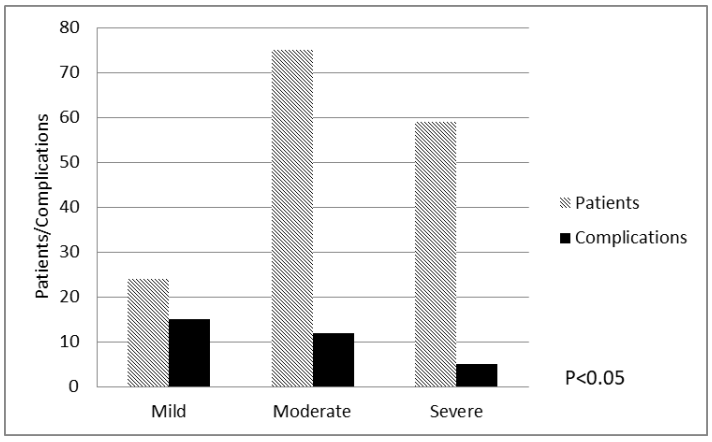

Figure 2. The presence of strong statistical significance concerning hydronephrosis grade and frequency of complications, X^2 (2, N = 158) = 17.31, p = .000174

Table 2. The Clavien–Dindo classification of the resulted complications

Class	Definition	Management	Complication, N (%)
I	Fever, pain, vomiting, transient hematuria(hematuria lasting < 24 h)	Analgesic, antipyretic, antiemetic, conservative	19 (12.03%)
II	Severe hematuria, urinary tract infection, pyelonephritis		0
III	PCN tube dislodgment/blockage/failure	Reposition/change/reinsertio n	10 (6.33%)
IIIa	Subcapsular haemathoma	Prolonged hospital stay (> 72 h)	2 (1.27%)
IIIb	Urinoma / Perirenal abscess		0
IV	Bowel perforation		0
IVa	Hemorrhage not controlled by conservative/minimal invasive procedure		0
IVb	Sepsis, multiorgan dysfunction	ICU care	1 (0.63%)
V	Death		0

The difference in the complication rates between the patients' benign and malignant disease groups was not statistically significant. In the group of patients with benign obstruction, a total of 21 complications occurred in our series, while 11 complications occurred in the group with obstruction based on malignant pathology. The χ^2 test was used to compare the rates of complications that occurred in the observed groups, which showed that there was no statistical significance in the occurrence of complications between the examined groups ($\chi^2 = 0.3033$, $p < .05$).

As mentioned, CCI score was used to compare the "weight" of the comorbidity score, incidence of complications, and feasibility of procedure among weighted groups. Group I included 42 patients (26.6%) with a score of 0, Group II included 55 patients (34.8%) with a score of 1 and Group III included 61 patients (38.6%) with a score of ≥ 2. There was no statistical significance between groups when observing the incidence of complications. Additionally, there was no significance in the feasibility of percutaneous nephrostomy procedure within different comorbidity groups, as indicated by χ^2 (2, N 158) = 0.0546, p = .973082 (Figure 3).

No statistical significance was found when analyzing complications across BMI groups. For the underweight group (BMI < 18.5 kg/m², N = 10, 6.3%), there were 3 complications (1.9%); for the normal weight group (BMI 18.5–24.9 kg/m², N = 74, 46.8%), there were 14 complications (8.86%); for the overweight group (BMI 25–29.9 kg/m², N = 51, 32.3%), there were 10 complications (6.30%); and for the obese group (BMI > 30 kg/m², N = 23, 14.6%), there were 5 complications (3.16%). This was supported by $\chi 2$ (2, N = 158) = 0.4449, p = .930823.

Percutaneous nephrostomy catheter placement was performed under local anesthesia in 142 (89.87%) patients and analgesic sedation in 16 (10.13%) patients. We believe that it is important to note that in patients without problems or contraindications for the PCN procedure under local anesthesia, a better and more precise placement was achieved in our series. This was achieved thanks to better communication with the patient, suggesting rhythm of respiration and reduction of respiration-caused changes in the position of the targeted calyx (respiratory amplitude of the kidney).

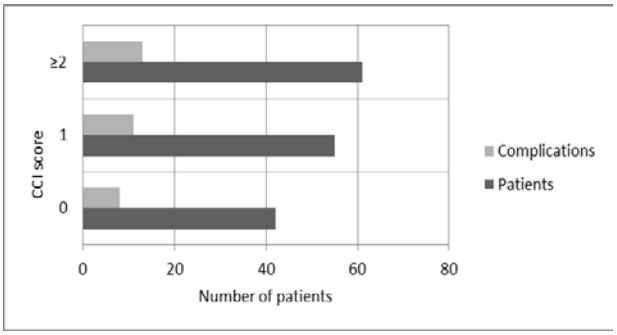

Figure 3. Complications incidence among Charlson Comorbidity Index (CCI) score groups, $\chi 2$ (2, N = 158) = 0.0546, p = .973082

Discussion

In our study, in 4 years, 158 procedures were performed by placing PCN catheters under complete ultrasound guidance as an outpatient surgical procedure. The study is of prospective design. All relevant parameters were evaluated to obtain clear statistical factors on the frequency of complications after this procedure. In order to standardize our cohort we used CCI, Clavien–Dindo classification of complications, BMI observance and "shredded" timeline groups for learning curve observation.

Most papers previously published have shown successful PCN placement without complications in more than 90 percent of cases. However, most of them have not shown the results within the outpatient procedure cohorts. The success rates for nephrostomy catheter placement under exclusive ultrasonic guidance range from 83.1% to 92% (3, 7).

Pedersen was the first to perform a percutaneous nephrostomy completely under ultrasound guidance with a placement success rate of 70%. Today, it is one of the most common interventions performed by urologists in the centers worldwide performing this procedure (5). The AUA guidelines suggest an upper limit of 4% of PCN complications. Guidelines in Europe are still under preparation. Even studies with CT-enhanced PCN procedures are showing relatively similar incidence of complications, although designed for more complex cases (8).

Our study found that none of the patients required a transfusion due to bleeding following PCN. Additionally, there were no reported injuries to intra-abdominal organs such as the spleen, liver, colon, or pleura, which are described in the literature as major complications (9, 10). Modified Clavien–Dindo classification of complications that Kumar used in their study showed similar results to our cohort (11). As noted in the study results, 1 (0.63%) patient developed a septic condition after PCN placement, which brings the rate of major complications to levels below 1% (0.63%) and correlates with data from the literature. The criteria for defining a specific condition during consideration were set based on the Third International Consensus on the definition of sepsis and septic shock (12). Comparatively, in the literature, concerning this definition, the incidence of sepsis as a complication is up to 3.6% (13, 14).

In terms of considering minor complications, it is challenging to classify and standardize some of them concerning primarily technical problems such as slippage of the catheter outside the pyelocalyceal (PC) system due to large respiratory amplitude and renal movement within its physiological limits (15). There were 4 (2.53%) slips in our series, while 2 (1.27%) patients had a catheter blockage that required replacement within 24 hours of initial placement, which correlates with data from the literature (15, 10, 11). Transient hematuria after the procedure is a common condition that is difficult to quantify. However, 19 patients (12.03%) who had hematuria in the urine after PCN placement were classified into minor complications for clearer statistical processing. It should be noted that these patients did not require therapeutic protocol adjustment except for the extension of hospitalization to a maximum of 48 hours. In all patients, haematuria was lost spontaneously or after mild nephrostomy catheter rinsing with saline (< 24 h).

Percutaneous nephrostomy primarily provides time for treatment planning and allows for a multidisciplinary approach to address pathological conditions associated with kidney and ureter blockage, diagnosis and preparation for their definitive surgical solutions. Further, in a certain number of patients, it serves as the final means of urine derivation when no alternative surgical options are available for restoring the natural urine pathway.

Conclusion

Ultrasound-guided percutaneous nephrostomy as an outpatient procedure is a safe and effective procedure in terms of both therapeutic and diagnostic treatment. Studies have highlighted the importance of patient selection criteria to ensure the safety and effectiveness of nephrostomy as one-day surgery. Epidemiological aspect should be emphasized during the pandemic of COVID-19 as PCN is not an aerosol-generating procedure. It enables the functioning and preservation of renal function when the definitive solution should be waited in a limited timeframe.

Performing percutaneous nephrostomy in an outpatient manner represents a safe and feasible procedure.

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PERKUTANA NEFROSTOMIJA U OPSTRUKTIVNOJ UROPATIJI: ANALIZA IZVODLJIVOSTI OPERACIJE I KOMPLIKACIJA U JEDNODNEVNOJ HIRURGIJI I LOKALNOJ ANESTEZIJI

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Opstruktivna uropatija predstavlja patološko stanje u kojem je blokiran prirodni tok urina. Opstruktivna uropatija dovodi do povećanja pritiska unutar kolektornog sistema bubrega i mogućeg trajnog oštećenja funkcije bubrega. Cilj ovog rada bio je da se ispitaju efikasnost i izvodljivost perkutane nefrosmotije, učestalost komplikacija, kao i ishodi hitne ili elektivne deblokade bubrega kao jednodnevne hirurške procedure u lokalnoj anesteziji kod bolesnika sa benignom ili malignom patologijom. Prospektivna studija je do sada obuhvatila 158 bolesnika − 94 žene (59,49%) i 64 (40,50%) muškarca − koji su podvrgnuti proceduri perkutanog plasmana nefrostomskog katetera na Odeljenju urologije u Opštoj bolnici „Aleksa Savić" u Prokuplju između januara 2020. godine i januara 2024. godine. Uspešnost procedure iznosila je 97,47%. Kod više od 40% bolesnika indikacija za plasman nefrostomskog katetera bila je kalkuloza. Incidencija komplikacija u našoj studiji korelira sa incidencijom prikazanoj u literaturi. Kada je reč o gradusu hidronefroze, između blage, izražene i teške hidronefroze postojala je očigledna statistička razlika u učestalosti pojave komplikacija između ispitanih grupa. Sve komplikacije su klasifikovane prema pet gradusa modifikovanog Clavien–Dindo klasifikacionog (C–D) sistema. Većina komplikacija bila je niskog gradusa prema C–D sistemu: 19 bolesnika (12,03%) sa drhtavicom, bolom ili prolaznom hematurijom (klasifikovani kao C–D gradus I). Mada perkutana nefrostomija prvenstveno daje više vremena za planiranje lečenja, kod određenog broja bolesnika predstavlja definitivnu urinarnu derivaciju kada ne postoji mogućnost daljeg operativnog lečenja. Iako postoji proces savladavanja krive učenja, perkutana nefrostomija predstavlja suverenu metodu brze intervencije kod razvijene opstrukcije. Plasman perkutanog nefrostomskog katetera kao jednodnevna hirurška procedura u lokalnoj anesteziji sigurna je i isplativa metoda kod odabranih bolesnika.

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***Ključne reči**: bubreg, hidronefroza, perkutana, nefrostomija*

Case report

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ARTHROSCOPIC TREATMENT OF THE ANTEROLATERAL IMPINGEMENT OF THE ANKLE: CASE REPORT

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In this paper, we present a patient who sustained an ankle injury without a fracture of the malleolus but with damage to the ligaments on the lateral side. The aim of this paper is to highlight the importance and role of the arthroscopic method in the treatment of ankle joint pathology.

The patient was treated conservatively with a plaster cast and physical therapy. Six months after the injury, the patient continued to experience pain, limited dorsiflexion of the foot, and a reduced gait. An MRI of the ankle joint revealed an avulsion of the anterior talofibular ligament (ATFL) with a 6 x 4 mm bone fragment at its end, a capsule lesion, cartilage damage on the anterolateral side of the talus, and synovial hypertrophy of the ankle joint. The arthroscopic method was used to remove the hypertrophic synovium, free chondral bodies from the joint, scar tissue, and the bone fragment from the lateral sinus of the ankle. Consequently, the lateral recess of the ankle joint was decompressed and freed from all factors contributing to painful contact.

The treatment outcome was excellent; pain disappeared, and complete foot function was restored.

Ankle arthroscopy has advantages over the traditional surgical approach in the treatment of anterolateral ankle impingement following injury. It is a minimally invasive technique that preserves soft and bony tissues, allows for the removal of scar tissue and synovial and chondral lesions, and facilitates faster patient recovery.

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Key words: *fibula apical avulsion, ankle arthroscopy, ankle impingement*

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Introduction

Ankle sprains are a common injury, accounting for approximately 25% of all musculoskeletal injuries, with the highest incidence occurring on the lateral side. Around 60−70% of affected individuals develop chronic lateral ankle instability, which is characterized by persistent pain, instability, recurrent injuries, and functional impairment (1−3). The mechanism of a sprain typically involves an acute episode of excessive foot supination and external leg rotation while the kinetic chain is locked.

The lateral ankle ligament complex plays a crucial role in providing stability to the ankle joint. It consists of the anterior talofibular ligament (ATFL), calcaneofibular ligament (CFL), and posterior talofibular ligament (PTFL). In 85% of cases, ankle sprains occur with the foot in a varus position, and in 62% of these cases, the ATFL is affected—either through partial rupture or avulsion from the apex of the fibula (4). Chronic ankle instability can lead to the development of anterolateral impingement syndrome, characterized by painful contact between bone and soft tissues in the anterolateral recess of the ankle joint. The anterolateral recess is a pyramidal space formed by the tibia on the medial side, the fibula on the lateral side, the anteroinferior tibiofibular ligament (AITFL) above (which is part of the tibiofibular syndesmosis), the calcaneofibular ligament (CFL) below, and the ATFL and capsule in front (5).

Anterolateral impingement syndrome presents with localized pain during internal and external rotation, along with restricted dorsiflexion of the foot. Several factors contribute to impingement, including hemarthrosis, chronic reactive synovitis, thickening of the anterior-inferior tibiofibular ligament (AITFL) (6), the presence of an accessory ligament beneath the

AITFL (7), avulsion injuries from the fibular apex or anterolateral tibia (8), ATFL scarring (9), osteochondral lesions of the anterolateral talus (10), and adhesive capsulitis of the ankle (11). These factors contribute to chronic ankle instability (Chronic Ankle Instability – CAI) and the progression of impingement syndrome. Repetitive microtraumas and soft tissue bruising lead to inflammation, hypertrophy, and scarring, resulting in painful soft tissue friction and impingement. Additionally, hypertrophy of the lower ATFL or its avulsion from the lateral malleolus often occurs when a small bone fragment is pulled along with it (9, 12, 13).

Our research question was: What is the outcome of arthroscopic treatment in a patient with a rare consequence of anterior tibiofibular ligament injury? Our working hypothesis was that arthroscopy would provide excellent results in treating the consequences of ankle joint distortion with damage to the anterior tibiofibular ligament. The aim of this paper is to present the arthroscopic treatment of anterolateral ankle impingement.

Case report

We present the case of a patient who sustained a right ankle injury due to slipping and falling. Clinical examination and radiographic findings ruled out a malleolar fracture. The patient was initially treated conservatively with a plaster cast for two weeks. After cast removal, he continued to experience pain in the lateral malleolus region and in the projection of the lateral sinus of the ankle. Despite undergoing physical therapy, persistent pain, swelling, and restricted dorsiflexion impaired gait and activity levels. Six months post-injury, pain and restricted movement persisted.

Ultrasound and MRI examinations of the ankle joint confirmed an ATFL rupture at the apex of the lateral malleolus, along with the presence of a small bone fragment, capsular thickening, soft tissue changes in the anterolateral recess, a small fluid accumulation, and chondral lesions on the lateral side of the talus (Figure 1). The patient developed anterolateral impingement and chronic lateral ankle instability (Scheme 1).

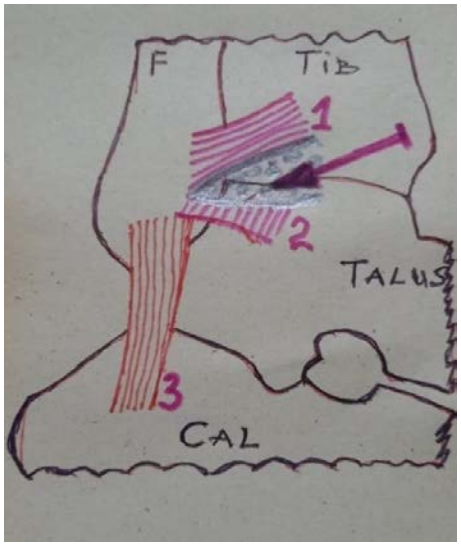
To confirm the diagnosis, we used the anterior drawer test and the external rotation stress test, both of which were positive, indicating lateral ankle instability (14). These tests involve dorsiflexion of the foot, during which the anterolateral talus exerts pressure on the anterolateral recess. If pathological tissue is present, it obstructs dorsiflexion, leading to soft tissue compression and significant pain on the lateral side of the ankle (15).

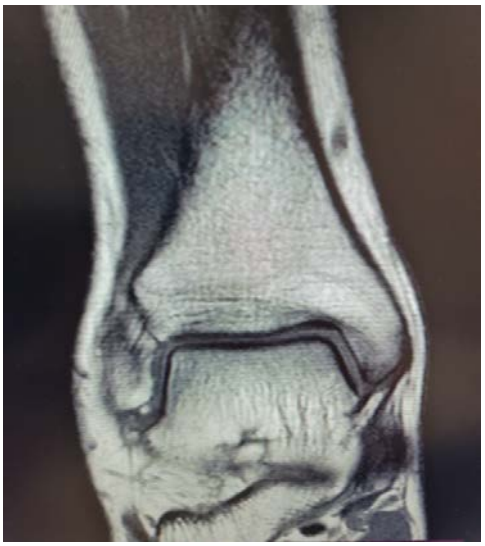
To assess pain severity, we used the Visual Analog Scale (VAS), which ranges from 0 to 10 points (16). A score of 0 indicates no pain, while a score of 10 represents severe pain. Pain levels were categorized into three groups: 0–3 points (mild pain, does not interfere with sleep), 4–6 points (moderate pain, allows sleep), and 7–10 points (severe pain, disrupts sleep). Chondral lesions of the talus were classified according to the Berndt and Harty classification (17). A first-degree lesion involves compression of a small area, while a second-degree lesion presents as a partial rupture of the osteochondral fragment. A third-degree lesion is characterized by a complete rupture of the osteochondral fragment without displacement, and a fourth-degree lesion involves separation and displacement of the osteochondral fragment. To assess intra-articular fibrosis, we used the Utsugi et al. (18) classification, where Grade B0 indicates no fibrosis, Grade B1 represents a moderate extent of fibrosis, and Grade B2 signifies extensive fibrosis with impingement. Following treatment, functional outcomes were evaluated using the Olerud–Molander scoring system (19).

The procedure began with the injection of 20 ml of physiological solution into the ankle joint to expand the joint space and dilate the capsule. An anterolateral approach was made 1 cm below and 1 cm in front of the apex of the lateral malleolus, extending along the anterior edge of the fibula (16). This entry point was selected to avoid damage to the tibialis anterior tendon and the lateral branch of the superficial peroneal nerve. Upon entering the joint space, we observed hypertrophic synovium, third-degree cartilage damage on the outer upper side of the talus (according to the Berndt and Harty classification), a moderate volume of intra-articular fibrosis (type B1), and a relaxed ATFL, indicating avulsion (Figure 2). In the anterolateral recess, soft tissue hypertrophy was noted. Below the apex of the lateral malleolus, a 6 x 4 mm bone fragment was identified, which was fixed to the ATFL and confirmed as an avulsion of the malleolus. A 3.5 mm shaver was used to remove hypertrophic synovium, fibrous bands, free bodies, and cartilage fragments from the anterolateral talus. No auxiliary ligament was found beneath the AITFL, ruling out the presence of the Bassett ligament, which occurs in 21% of cases (7, 20), (Figure 3, Scheme 2). The bone fragment, along with a small amount of soft tissue and fibrous scar tissue, was removed, thereby decompressing the anterolateral recess and the surrounding lateral malleolus area (Figure 4). Following the procedure, a plaster cast was applied with the foot in plantar flexion and valgus positioning for two weeks. Antibiotics were administered for two days. Weight-bearing on the operated leg was restricted for two weeks, after which the cast was removed and gradual weight-bearing was allowed within the patient's pain tolerance. Physical therapy was then initiated.

According to the Visual Analogue Scale (VAS), the patient reported moderate pain before surgery but was able to sleep. Postoperatively, the pain resolved completely. The Olerud–Molander scoring system showed an improvement from 68

points preoperatively to 96 points postoperatively. After eight weeks, the patient's ankle range of motion improved, with painless varus positioning and dorsiflexion. By four months, complete recovery was achieved, with full, pain-free movement of the ankle.





Scheme 1. Lateral ligaments of the ankle: 1. Anterior inferior tibiofibular ligament (AITFL). 2. Anterioror and posterioror talofibular ligament (ATFL, PTFL). 3. Calcaneofibular ligament (CFL). The place of the most common impingement of the talus and fibula (arrow).

Figure 1. MR findings of the ankle joint. Below the top of the lateral malleolus, a bone fragment is observed that is fixed to the ATFL and represents an avulsion of the malleolus.

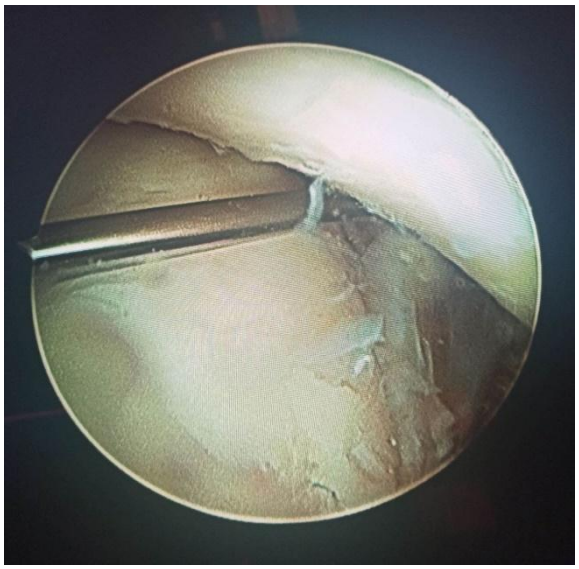


Figure 2. Talus cartilage lesion and synovial hypertrophy.

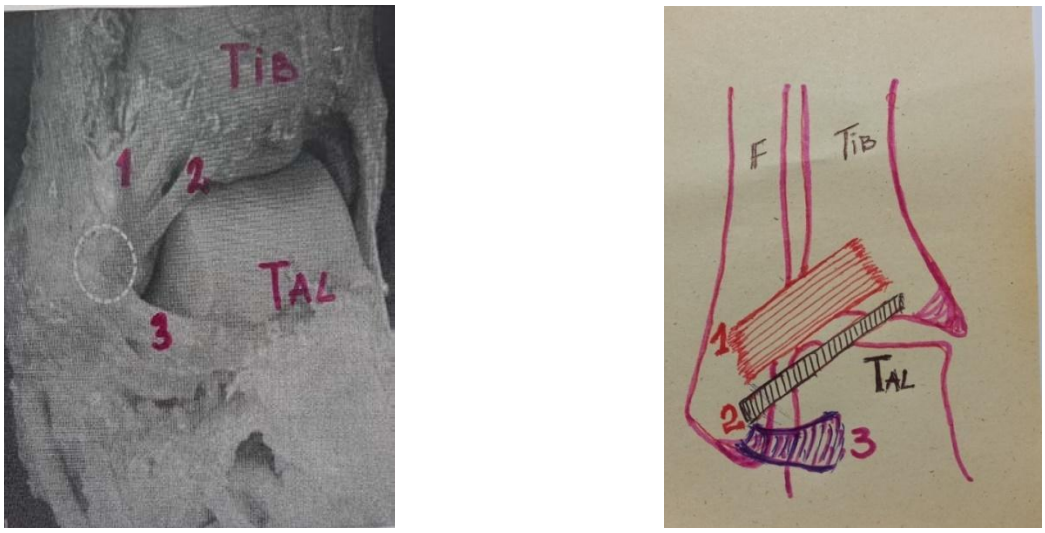


Figure 3 and Scheme 2. Anatomical and schematic representation of the ankle joint. 1. Anterior inferior tibiofibular ligament (AITFL). 2. Inferior fascicle of the anterior inferior tibiofibular ligament – Basett's ligament. 3. Anterior talofibular ligament (ATFL).

Figure 4. Bone fragment detached from the apex of the fibula with scar tissue.

Discussion

XGPN is well known as the "great imitator" This study demonstrates that a more severe form of ankle sprain can lead to damage to the anterior talofibular ligament (ATFL) and the cartilage in the lateral column of the ankle joint.

Anterolateral impingement syndrome of the ankle is caused by obstruction of the anterolateral recess. It is characterized by localized pain during internal or external rotation and restricted dorsiflexion of the foot. Several factors contribute to this syndrome, but it most commonly occurs following an ankle sprain, which results in significant hemarthrosis and reactive synovitis in response to the injury (5, 9). Feng et al. (16), in a series of 37 patients, identified the presence of an avulsion fracture at the apex of the lateral malleolus as the cause of impingement in 2 patients (5.4%). The recommended treatment was resection of the small bone fragment along with the surrounding soft scar tissue. Similarly, in our patient, we identified a small bone fragment resulting from ATFL avulsion at the apex of the lateral malleolus, which we removed along with the surrounding soft tissue, thereby relieving the obstruction in the anterolateral recess.

For acute ATFL avulsions, many authors recommend anchoring the bone fragment to the apex of the lateral malleolus and tightening the ligament (21, 22). However, in chronic injuries, this approach is not indicated due to ligament shortening and fibrotic scar tissue formation. In such cases, debridement of the chondral surfaces, synovium, and scar tissue is advised (13, 23). Monden et al. (8) reported similar findings in their

study of 111 patients, where fragment excision was performed in 95 patients (85.6%), while fragment osteosynthesis was carried out in 16 patients (14.4%) due to the acute nature of their injuries. We applied the same approach in treating our patient.

The advantages of ankle arthroscopy for impingement syndrome include a minimally invasive approach that avoids arthrotomy, the ability to remove pathological tissue (hypertrophic synovium, thickened capsule, and scar tissue) with minimal damage to vital structures, direct visualization of the anterior inferior tibiofibular ligament (AITFL) and associated accessory ligaments, as well as thorough debridement of the anterolateral recess to remove hypertrophic tissue or bone fragments from the apex of the lateral malleolus (24). However, ankle arthroscopy carries certain risks, including iatrogenic cartilage damage and injury to the superficial branch of the peroneal nerve or the tibialis anterior tendon. The incidence of such complications is reported to be up to 4% (25). In our case, we encountered no complications. This case study highlights the successful treatment of ATFL rupture and chondral lesions of the ankle joint using arthroscopy. A limitation of this study is that it presents only a single case and lacks a comparative analysis with cases treated through open surgical methods.

Conclusion

This study demonstrates that ankle arthroscopy offers significant advantages in the treatment of anterolateral impingement following injury. As a minimally invasive procedure, it preserves soft tissue integrity, maintains vascularization, and facilitates a faster postoperative recovery.

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ARTROSKOPSKO LEČENJE ANTEROLATERALNOG NAGNJEČENJA SKOČNOG ZGLOBA: PRIKAZ SLUČAJA

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U radu se prikazuje slučaj pacijenta kod kojeg je došlo do povrede skočnog zgloba bez preloma maleolusa, ali sa oštećenjem ligamenata lateralne strane. Cilj ovog rada bio je da se ukaže na značaj i ulogu artroskopske metode u lečenju skočnog zgloba.

Za lečenje pacijenta korišćene su konzervativne metode: gipsana longeta i fizikalna terapija. Šest meseci nakon povrede pacijent je imao bolove, ograničenu dorzalnu fleksiju stopala i umanjenu sposobnost kretanja (hoda). Urađena je magnetna rezonanca skočnog zgloba i utvrđena avulzija prednjeg talofibularnog ligamenta (ATFL), na čijem su kraju registrovani koštani fragment veličine 6 mm x 4 mm, lezija kapsule, oštećenje hrskavice na prednjoj lateralnoj strani talusa i hipertrofija sinovije skočnog zgloba. Artroskopskom metodom uklonili smo hipertrofisanu sinoviju, hondralna slobodna tela iz zgloba, ožiljačno tkivo i koštani fragment iz lateralnog sinusa skočnog zgloba; tako je lateralni recesus skočnog zgloba oslobođen i rasterećen svih faktora koji su izazivali bolni kontakt.

Rezultat lečenja bio je odličan – bolovi su nestali, a stopalo je povratilo kompletnu funkciju.

Artroskopija skočnog zgloba ima prednosti u odnosu na klasičan hiruški pristup u lečenju anterolateralnog nagnječenja skočnog zgloba nakon povrede budući da pošteđuje meko i koštano tkivo, omogućava uklanjanje ožiljačnog tkiva i sinovijalnih i hondralih lezija i čini oporavak pacijenta bržim.

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***Ključne reči**: avulzija apeksa fibule, artroskopija skočnog zgloba, nagnječenje skočnog zgloba*

Case report

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CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF TAKAYASHU'S ARTERITIS: PATIENT REPORT

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Takayashu's arteritis is a chronic, immune-mediated vasculitis of the large blood vessels, which usually occurs in patients younger than 50 years and primarily affects the aorta and its main branches. The majority of affected are women. A patient with Takayashu's arteritis who first visited the doctor due to fatigue, palpitations and rapid heart rate is presented. On clinical examination, over both carotid arteries, audible murmurs, the pulse of the right radial artery is very weak, and the pulse of the left radial artery is not palpable. Laboratory analyzes revealed increased sedimentation of erythrocytes and the level of C-reactive protein. The diagnosis of the disease was confirmed by Doppler ultrasound of blood vessels, computed tomography angiography (CTA) and positron emission tomography (18 F-FDG PET/CT). The patient fulfilled five out of six criteria for the clinical diagnosis of Takayashu's arteritis of the American College of Rheumatology and belonged, according to the angiographic and clinical classification of Takayashu's arteritis, to Type I. She was treated with corticosteroids, immunosuppressants and percutaneous transluminal angioplasty.

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Key words: *Takayashu's arteritis, Macaroni sign, Doppler of blood vessels, Multislice computed tomography, positron emission tomography / computed tomography*

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Introduction

Takayashu's arteritis is a chronic, immune-mediated vasculitis of the large blood vessels, which usually occurs in patients younger than 50 years and primarily affects the aorta and its main branches, the carotid, subclavian, renal, coronary, digestive, and iliac arteries (1). It is also known as pulseless disease, aortic arch syndrome, thromboaortopathy and thromboarteriopathy.

The disease is widespread throughout the world but is thought to be much more common in Asian populations. The total annual incidence of Takayashu's arteritis is 0.3 to 3.4, and the prevalence is 0.9 to 40 per million inhabitants. The majority of affected are women with a female-to-male ratio ranging from 5:1 to 9:1 in favor of women (1).

The etiology of Takayashu's arteritis has not been clearly defined so far, but it is believed that genetic predisposition, the autoimmune nature of the disease and environmental factors play an important role in its genesis (2).

Both humoral and cellular immune mechanisms are involved in the pathogenesis of Takayashu's arteritis. Constant activation of immune cells and continuous release of pro-inflammatory cytokines in the adventitia and arterial media leads to chronic vascular inflammation, thickening of the adventitia, intimo-medial hyperplasia due to cell infiltrates, fibrosis of the media and intima, which can lead to artery stenosis or occlusions, occasional thrombosis or aneurysm formation (3).

Pathohistological examination of the wall of the affected arteries shows medial-adventitial giant cell panarteritis. In the acute phase, inflammatory infiltrates in the adventitia predominate, which in the chronic phase are replaced by fibrous lesions and arterial calcifications (4).

It has been confirmed that the inflammatory infiltrates consist of CD4, CD8, gamma delta T lymphocytes, natural killer cells (NK cells), macrophages and neutrophils, as well as the production of Tumor necrosis factor-alpha (TNF-α), which is important in the formation of granulomas,

takes place primarily in macrophages, T cells and NK cells. Pathohistological findings of aortic tissue samples show that gamma delta T and NK cells are involved in endothelial cell apoptosis by producing perforin (5).

Clinically, Takayashu's arteritis is characterized by an acute phase with general symptoms, fever, higher temperature, night sweats, loss of appetite and body weight, fatigue and weakness, muscle and joint pain followed, months or years later, in a chronic phase with symptoms and signs caused by stenosis or occlusion of blood vessels, manifested by rapid fatigue, lack of effort, heart palpitations and rapid heartbeat, hard breathing and feeling of pressure in the chest, reduced or absent pulse, difference in blood pressure between the arms, dizziness, fainting, headache, increased blood pressure and visual impairment. In most patients, there is an overlap of both phases and their corresponding symptoms (3). The diagnosis of Takayashu's arteritis is based on a group of clinical, biological, radiological and sometimes histological elements (4).

In the diagnosis and follow-up of patients with Takayashu's arteritis, the most significant application is the use of Doppler echosonography of blood vessels, computed tomography with contrast angiography (CTA), nuclear magnetic resonance angiography (NMR) and positron emission tomography with the use of a radiolabel - fluorodeoxyglucose (18FDG PET-CT) (6).

The progression of Takayashu's arteritis is variable and about 50% of sufferers have recurrence or development of vascular complications within 10 years of the diagnosis of the disease (4).

In the therapy of Takayashu's arteritis, corticosteroids are used as the basic and most effective drugs, immunosuppressants in patients who have a disease with high activity and when the dose of corticosteroids should be reduced and biological drugs. (5). In symptomatic stenotic or occlusive lesions, surgical revascularization or percutaneous transluminal angioplasty (PTA) with stenting is often necessary (7).

Takayashu's arteritis is associated with increased mortality. Previous research has shown that survival for 10 years is 97%, 15 years 85%, and 20 years 75% (4).

The aim of the research was to show the clinical characteristics, applied diagnostic and therapeutic procedures in a patient with Takayashu's arteritis, to compare them with the findings of patients with Takayashu's arteritis in other studies and to show the latest knowledge about this disease.

Presentation of the patient

37-year-old patient, at the end of September 2021, comes to the doctor for the first time when she states that she occasionally feels unable to breathe to the full extent of her lungs and that she has a feeling that her heart is racing and skipping. A little later, in mid-October 2021, at two specialist examinations of a rheumatologist, she states that since July 2021 she has had extreme fatigue, tingling and discomfort in her legs, acceleration of heart rate and heart palpitations. She states that for the past two years she has occasionally had a feeling of palpitations, and since July 2021. the complaints have become more frequent. Since September 2021. she noticed that she could not measure her blood pressure, which was normally around 110/70 mmHg. In November 2021. the patient reported rapid fatigue and loss of strength in her left hand. Since January 2022. she has had a stabbing sensation in her chest when exposed to cold air, a tingling sensation, and an unconfortable pain in her legs.

Personal and family history: The patient denies previous illnesses. There were no similar or other diseases significant for heredity in the family.

Physical examination showed that the findings on the heart and lungs were normal. Audible murmurs above both carotid arteries. The pulse of the right radial artery is very weak, and the pulse of the left radial artery is not palpable. Weakened pulses on the left tibial artery and the left popliteal artery. The pulses of both femoral arteries are properly palpated. During the month of November, during the examination, the pulses on both radial arteries and the pulses on both brachialis arteries are not palpable. Unmeasurable blood pressure bilaterally.

In laboratory analyzes performed at the end of September 2021, positive, non-specific indicators of inflammation were found: increased sedimentation of erythrocytes 38 mm/1h and increased level of C reactive protein (CRP) 19.7 mg/L.

The patient immediately underwent diagnostic examinations. First, color Doppler echosonography of the blood vessels of the neck was performed, which showed the presence of significant stenosis of the left 75−90% and the right 70−85% of the common carotid artery (ACC). Both ACCs have almost uniformly thickened walls in their proximal segments ("macaroni sign"), which leads to 70% stenoses (Figure 1). Significant stenosis of the subclavian arteries was found on both sides. The ultrasound findings indicated the existence of Takayashu's arteritis in the patient, so further diagnostics were continued.

After the ultrasound examination, a computerized tomography (CT) angiography of the head and neck was performed with the finding: The right ACC was affected throughout its course by a concentric tubular lesion with a reduced lumen of up to 60%. The right subclavian artery is of the lusoria type, it is narrowed by a concentric lesion about 30% to the vertebral artery, and after it, tubular, in a length of about 1.5 cm with a reduced lumen over 90%. The left ACC is

proximaly in the longer segment of the concentrically tubular reduced lumen with the greatest stenosis over 65%. The left internal carotid artery (ACI) is after the bulbus, eccentrically narrowed by a mixed plaque up to 50%. The left subclavian artery is, right after the separation of the vertebral artery, reduced lumen over 90% in a length greater than 2.5 cm.

Positron emission tomography of the whole body with anatomical localization (18 F-FDG PET/CT) was performed then with the finding: Increased accumulation of FDG is shown in the wall of both common carotid arteries, more intensively on the left. Moderately increased FDG accumulation is observed in the initial parts of both subclavia. FDG accumulation was discretely increased at the level of the wall of the aortic arch and the initial part of the descending aorta. The finding indicated an FDG-active underlying disease (Figure 2).

During October and November 2021 and January 2022, the patient underwent three echocardiographic examinations and all three showed normal findings on the heart.

Two EKGs performed in October 2021 showed normal findings with sinus rhythm, without ST and T segment changes. An EKG performed in November registered the existence of right bundle branch block.

Due to significant narrowing of the blood vessels, a vascular surgeon was consulted. Vascular conciliation set the indication for percutaneous transluminal angioplasty (PTA). The patient underwent balloon dilatation and stent implantation in the right subclavian artery.

Before the complete diagnosis, the patient occasionally used non-steroidal anti-inflammatory drugs, and after the diagnosis and the 18 F-FDG PET/CT performed and the findings that showed FDG active disease, therapy with corticosteroids and immunosuppressants was started.

In April 2022, a control CT scan of the blood vessels of the neck was performed with the following findings: left ACC circumferentially narrowed in the proximal and medial segments by 40%, and the left subclavian artery postvertebrally narrowed by 90%; right ACC and right subclavian artery are without significant narrowing. Control CT angiography showed, after five months of treatment with corticosteroids and immunosuppressants, significant improvements, so the therapy was continued.

In September 2022, a control PET CT with FDG was performed, which showed that, unlike the previous PET CT examination in November 2021, the common carotid arteries and subclavian arteries did not show increased accumulation of FDG, i.e. that the previously described zones of increased glucose metabolism in the blood vessel walls are not showing in the moment of the exam (Figure 3).

The criteria of the American College of Rheumatology (1) were used for the clinical diagnosis of Takayashu arteritis, the criteria of the International Takayashu's Conference from 1994 were used for the angiographic classification, and the classification given by Ishikawa was used for the clinical classification of Takayashu's arteritis (8, 9).

According to the criteria for establishing the diagnosis of Takayashu's arteritis of the American College of Rheumatology, the patient meets 5 out of 6 criteria, and according to the angiographic and clinical classification, she belongs to Type I.

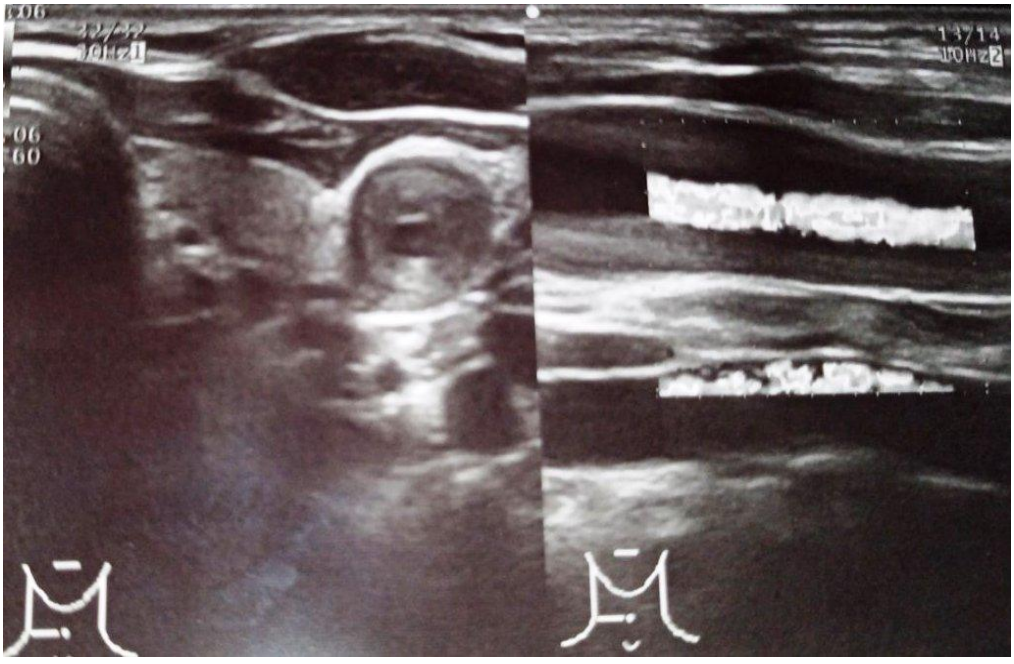

Figure 1. Ultrasonography of the left common carotid artery on transverse and longitudinal section – ,,Macarone sign''

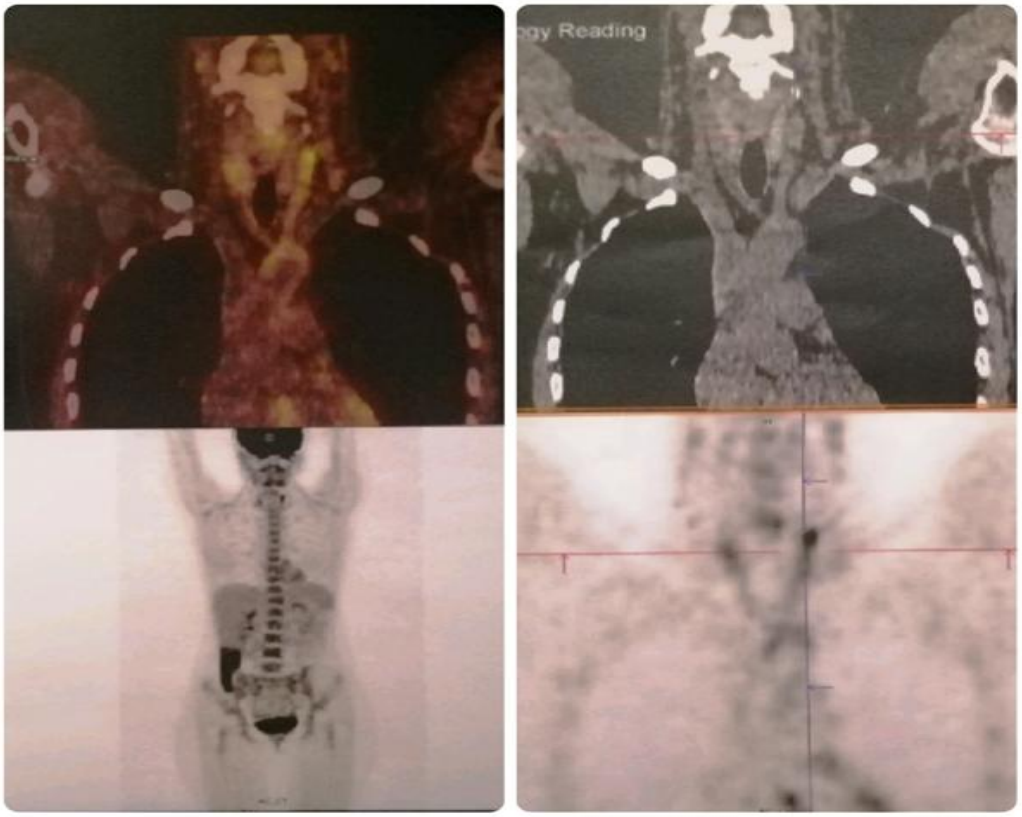

Figure 2. PET/CT with fluorodeoxyglucose – first examination

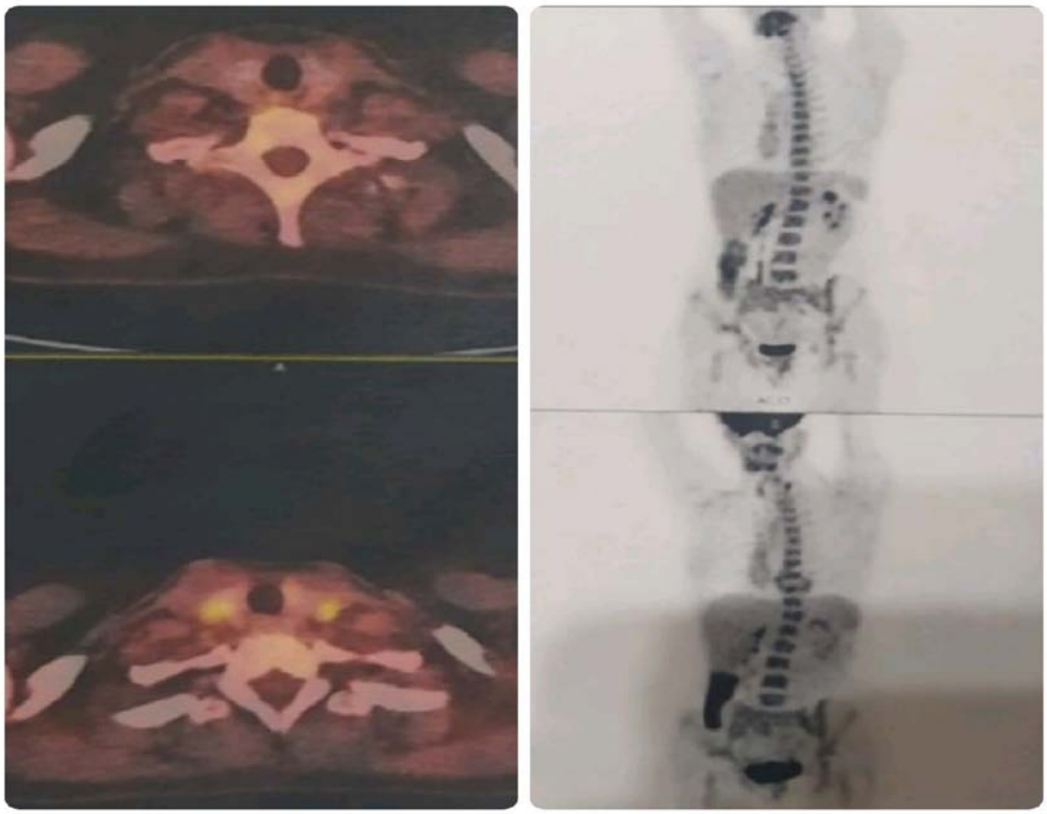

Figure 3. PET/CT with fluorodeoxyglucose – control examination after 10 months from the first examination

Discussion

Nowadays, it is accepted that the onset of Takayashu's arteritis is based on immuno-pathogenetic mechanisms with the primary role of autoimmunity and inflammation, and that both humoral and cellular immunity play a role in this (1). The initial agent to initiate the immune response is unknown, but it is capable of inducing an immune response directed at the walls of large arteries, where severe vascular damage can occur (1).

Takayashu's arteritis was suspected in our patient after an ultrasound examination of the carotid and subclavian arteries with findings of significant lesions on these arteries. Ultrasound examination showed the existence of a characteristic thickening of the peripheral arterial wall of both common carotid arteries, as a "macaroni", a diffusely thickened intimo-medial complex that arose as a result of chronic and persistent vascular inflammation that led to thickening of the adventitia and intimomedial hyperplasia due to cellular infiltrates (2). The "Macaroni sign" is pathognomonic for Takayashu's arteritis and studies have shown that it is present in 80.0% to 100% of patients (10, 11).

The presence of the "macaroni sign" on the ultrasound examination of the carotid arteries, not only significantly indicates Takayashu's arteritis, but also confirms the usefulness of ultrasound in its diagnosis. This is supported by studies that have shown that ultrasonography is more sensitive and superior in detecting this characteristic thickening of the intima-media complex in patients with Takayashu's arteritis, compared to contrast angiography, which showed carotid lesions in about 56.0% of patients and which is usually used to establish a definitive diagnosis of this disease. It is believed that angiography can show narrowing of the lumen and the degree of narrowing, but ultrasound is a better way to assess the vessel wall (2). However, there are opinions that Doppler sonography can detect stenosis of the affected arteries, but that it is non-specific for Takayashu's arteritis (12, 13).

According to angiographic and clinical classification, the patient belonged to Type I, which indicates relatively favorable vascular lesions and rare serious complications. Earlier studies showed that the frequency of type I in our population of patients with Takayashu's arteritis was the highest and was 50.0% (14).

It has been shown that the prevalence of type I is more common in women and type V in men (1), which correlates with the findings of some studies that women have more frequent lesions affecting the aortic arch and its branches, while in men, the abdominal aorta is much more often involved.

This difference in frequency may also be the result of selection of patients in different stages of Takayashu's arteritis development. Because Takayashu's arteritis is a chronic inflammatory disease, patients more often have type I in the early stage of the disease, while type V can be seen in the late stage (15).

The patient had significant bilateral ACC and subclavian stenoses, with the lesions of the left ACC and left subclavian being more significant, which is in accordance to earlier findings that showed that the subclavian arteries, the left more than the right, were most often affected, followed by the ACC, also the left more than the right (16).

The frequency of carotid artery lesions, in different studies, ranges from 25.6% to 79.1% and subclavian from 20.9% to 79.8% (17).

The high prevalence of affection of the left branches of the aortic arch is in correlation with the hypothesis (9) that in Takayashu arteritis the arterial lesions begin in the left subclavian and then spread to other locations (18).

Stenosis of the left subclavian was also the most common in our population and was found in 88% of patients.

Our patient fulfill the first criteria of the American College for the diagnosis of Takayashu's arteritis because she was less than 40 years old when her disease was diagnosed. According to numerous studies, the average age of patients at diagnosis of Takayashu's arteritis ranged from 20.5 to 45.4 years. In our population, the average age at diagnosis of Takayashu's arteritis is 43.9 years. Recent studies conducted in different populations indicate that the proportion of patients older than 40 years, at the beginning of the disease, varies from 9% to 32% (19, 20).

It is accepted that the diagnosis of Takayashu's arteritis can be established, in persons younger than 50 years, if there are characteristic radiological and ultrasound lesions of large-caliber arteries without arguments for another vascular cause (4).

The much higher frequency of Takayashu's arteritis in women and younger age indicates that one of the reasons for this may be hyperestrogenism as one of the presumed causative factors of this vasculitis, and this is supported by the findings that most young women with Takayashu's arteritis have increased urinary excretion of estrogen in comparison with healthy persons of the same age (21).

There are difficulties in the early diagnosis of Takayashu's arteritis due to the frequent absence of disease activity and clinical symptoms, in the phase of remission, which explains the delay in diagnosing the disease from several months to 4 years (1).

Our patient had a negligible time delay in establishing the diagnosis thanks to an early ultrasound examination of the blood vessels when significant stenoses of the carotid and subclavian arteries with the "macaroni sign" were observed.

Symptoms of Takayashu's arteritis are often vague and nonspecific, and may be absent. The patient had no pronounced general symptoms at the time of presentation, which is not unusual because many studies find that general symptoms were absent in 34% to 57% of patients. From the clinical manifestations of the disease, the patient

had murmurs over the carotid arteries and weakened pulse, i.e. loss of pulse, over the radial arteries. Research has shown that the frequency of murmurs over the carotid arteries is observed in 62.5% to 70% of the patients, and the weakened pulse over the radial arteries from 34.8% 64% to 88% (22, 23).

The patient had, at the beginning of the presentation, high sedimentation rate and a high level of CRP. Previous studies have shown that the inflammatory syndrome is present in the early stage of Takayashu's arteritis in 71% to 85% of sufferers. Erythrocyte sedimentation rate in the acute phase of Takayashu's disease increased in 53.7% to 89.7%, and high CRP level in 79.1% (24, 25).

Due to the lack of a specific serum marker for Takayashu arteritis (22), the inflammatory syndrome remains a significant but imperfect reflection of the activity of the underlying disease, as active disease is possible in the absence of the inflammatory syndrome in approximately 30% of patients (4). Elevated erythrocyte sedimentation rate is a strong indicator of an underlying inflammatory process such as Takayashu's vasculitis. However, erythrocyte sedimentation rates within the normal range should not rule out the existence of Takayashu's arteritis (18) because vascular damage can progress even in the absence of systemic inflammatory changes.

The treatment of our patient was started with the simultaneous administration of corticosteroids and immunosuppressants, and the goals of the treatment were to control active inflammation, minimize arterial damage and the development of vascular complications, which was achieved with the treatment, because control CT-angiography showed that regression of lesions occurred in some vessels, while further progression was stopped in others and control PET/CT confirmed that there is no longer FDG active disease (26).

Corticosteroid therapy is effective when the disease is diagnosed early, and remission can be achieved in 25% to 50% of cases with the use of corticosteroids alone. The use of immunosuppresants as a first-line treatment in order to reduce the use of corticosteroids has shown good results. The addition of immunosuppressants to corticosteroids allows remission in 50% to 80% of corticosteroid-resistant cases (4).

The patient had symptomatic stenotic lesions, which required percutaneous angioplasty with stent placement (7).

Conclusion

Ultrasonography is an effective and non-invasive method for early detection of Takayashu's arteritis, and the presence of the "macaroni sign" on an ultrasound examination of the carotid arteries significantly indicates Takayashu's arteritis.

Positron emission tomography angiography is significant and effective in determining and identifying disease activity in the vascular wall. Combined therapy with corticosteroids and immunosuppressive drugs is successful in preventing further progression of the disease.

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Prikaz slučaja

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KLINIČKE I ANGIOGRAFSKE KARAKTERISTIKE TAKAYASUOVOG ARTERITISA: PRIKAZ BOLESNIKA

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Takayasuov arteritis je hroničan, imunoposredovan vaskulitis velikih krvnih sudova, koji se obično javlja kod bolesnika mlađih od 50 godina i prvenstveno zahvata aortu i njene glavne grane. Među obolelima preovladavaju žene. Prikazana je bolesnica sa Takayasuovim arteritisom koja se prvi put javila lekaru zbog umora, palpitacija i ubrzanog rada srca. Kliničkim pregledom ustanovljeni su, iznad obeju karotidnih arterija, čujni šumovi i veoma oslabljen puls desne arterije radialis, a puls leve radijalne arterije nije se mogao izmeriti palpacijom. Laboratorijskim analizama utvrđeni su povišena sedimentacija eritrocita i povišen nivo C-reaktivnog proteina. Dijagnoza bolesti potvrđena je ultrazvučnim doplerom krvnih sudova, kompjuterizovanom tomografijom i angiografijom (engl. *computed tomography angiography* – CTA) i pozitronskom emisionom tomografijom (engl. *fluorine-18 fluorodeoxyglucose positron emission tomography* – 18 F-FDG PET/CT). Bolesnica je ispunjavala pet od šest kriterijuma Američkog koledža za reumatologiju za postavljanje kliničke dijagnoze Takayasuovog arteritisa i, prema angiografskoj i kliničkoj klasifikaciji Takayasuovog arteritisa, pripadala Tipu I. Bolesnica je lečena kortikosteroidima, imunosupresivima i perkutanom transluminalnom angioplastikom.

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Ključne reči: Takayasuov arteritis, znak makarona, dopler krvnih sudova, višeslojna kompjuterizovana tomografija, pozitronska emisiona tomografija / kompjuterizovana tomografija

Case report **UDC: 616-089.5:[616.24-005+616.13-004.6**
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THE SIGNIFICANCE OF AXILLARY BLOCK IN UPPER ARM AMPUTATION IN A PATIENT WITH SERIOUS COMORBIDITIES: A CASE REPORT

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Surgical management is sometimes the only viable treatment option for patients with peripheral arterial occlusive disease. However, performing surgery under general endotracheal anesthesia in patients with hemodynamic and respiratory instability poses a significant challenge. In such cases, neuraxial blocks may provide a safer alternative.

An 80-year-old male patient was urgently admitted to the Department of Internal Medicine at the Military Hospital Niš due to difficulty breathing and a livid discoloration of the left hand and forearm. Carpal pulses were absent, and the patient had experienced loss of movement and sensation in the hand for several days. Clinical examination and Multislice computed tomographc angiography of the pulmonary and major arteries of the left arm confirmed a diagnosis of pulmonary embolism and occlusion of the subclavian and brachial arteries. After evaluating the patient's condition, the anesthesiologist opted for a neuraxial block instead of general endotracheal anesthesia.

Avoiding general endotracheal anesthesia and utilizing neuraxial blocks could minimize the possibility of adverse events in high-risk patients.

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Key words: *neuraxial anesthesia, pulmonary embolism, peripheral arterial occlusive disease*

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Introduction

Peripheral arterial occlusive disease is a condition that impairs the normal function of the arterial system, leading to reduced blood flow to the extremities. Risk factors include hypertension, dyslipidemia, smoking, diabetes, physical inactivity, and genetic predisposition (1). Peripheral arterial disease is also considered a significant contributor to overall cardiovascular risk. The most common symptom is intermittent claudication, characterized by calf pain that worsens with walking and subsides with rest. In advanced cases, pain persists even at rest, especially in the supine position (2, 3). Upper limb ischemia of the is not as frequent as that affecting the lower limbs. From a clinical point of view, the anatomical region of the shoulder and elbow is much more resistant to ischemia due to its well developed collateral circulation; ischemic symptoms are thus more frequently observed in the forearm region. Ischemia-related amputation is far less frequently performed in the upper than in the lower limbs. In 2005, out of 1.6 million people with limb amputation, it was estimated that 573,000 had upper limb amputation (4). Traumas accounted for the most part of major upper limb amputations, while vascular diseases accounted for only 12% of these operations (5).

Axillary block is a peripheral nerve block performed under ultrasound guidance, often with the assistance of a peripheral nerve stimulator. The injection of local anesthetic into the axillary region blocks the brachial plexus, providing effective anesthesia for upper limb surgery (6–8).

This method is relatively easy to perform and carries a low risk of complications.

We report a case of irreversible ischemia of the left arm in a patient with pulmonary thromboembolism and multiple comorbidities, in whom upper arm amputation was a vital necessity.

Case report

A 80-years old male patient was transported by an ambulance to the Department for Internal Diseases of the Military Hospital in Niš needing immediate medical attention due to difficulty breathing. After admission, a clinical examination was performed and his blood samples were taken for laboratory analyses. The patient had dementia and was unable to communicate effectively, so his medical history was obtained hetero-anamnestically, from his wife. He was hypertensive, diabetic, and had a post-stroke status. He had difficulty breathing (Cheyne-Stokes type respiration). Hemodynamic parameters at admission were BP 80/50 mmHg, HF 137/min, O_2 saturation 83%. Laboratory parameters at admission were as follows: RBC 5.0 10^12/L, HGB 147 g/L, PLT 199 10^9/L, WBC 13.4 10^9/L, CRP 39 mg/L, glycemia 21.1 mmol/L, urea 14.8 mmol/L, creatinin 171 μmol/L, total proteins 66.8 g/L, albumin 35.3 g/L, AST 40 U/L, ALT 45 U/L, gamma-GT 24 U/L, alpha-amilase 91 U/L, LDH 552 U/L, CK 276 U/L, sodium 145 mmol/L, potassium 4.7 mmol/L, calcium 2.04 mmol/L, chlorids 114 mmol/L, phosphorus 2.17 mmol/L, D-DIMER 34533 ηg/mL. The vascular surgeon prescribed the following conservative therapy: Sol. 0.9% NaCl 250 ml + amp. Meropenem 500mg/8h i.v, Sol. Metronidazole 500mg/8h i.v, sir. Enoxaparine 80mg/12h s.c, amp. Pantoprazole 40mg/12h, amp. Furosemide 40 mg/12h, a vasoactive coctail (amp. Pentoxifylline 300mg+amp. Lidocaine No 60 mg+amp. Metamizole 2.5 g+amp. Ascorbic acid 500mg+amp. Thiamine 100 mg.

A neurologist was consulted and prescribed an endocranial MSCT. The results indicated no acute worsening of the existing neurological condition.

Clinical examination revealed a livid discoloration of the left hand and forearm. Left-sided carpal pulses were absent, and the hand had no motor or sensory function. Heteroanamnestically, it was reported that this condition had been present for several days. Multislice computed tomographc angiography of the pulmonary and major arteries of the left arm confirmed a diagnosis of pulmonary embolism and occlusion of the subclavian and brachial arteries. Due to serious comorbidities and the unavailability of vascular surgeons at the Military Hospital in Niš, the patient was referred to the Emergency Centre of the University Clinical Centre Niš.

Following admission and detailed clinical evaluation, emergency upper arm amputation was indicated due to irreversible ischemia. The patient was in critical condition upon arrival at the Vascular Surgery Clinic. After brief preoperative preparation, the patient was transferred to the surgical block for the planned operative treatment. After reviewing the patient's medical records and conducting a medical examination, the anesthesiologist determined that the procedure should be performed under an axillary block, as general anesthesia posed a significantly high risk due to the patient's hemodynamic instability.

After positioning the patient in supination with his arm abducted at 90°, the skin was disinfected and a tube was placed transversally to the anteromedial part of the upper arm, in the direction of *m. pectoralis major* attachment to the humerus. At the 1−3 cm depth, ultrasound visualized axillary artery, two veins (usually), hyperechogenic structures: *n. medianus* (laterally and superficially to the artery), *n. ulnaris* (superficially and medially to the artery) and *n. radialis* (posteriorly and laterally or medially to the artery) and three muscles*: m. biceps brachii*, *m. coracobrachialis* and *m. triceps brachii*, as well as *n. musculocutaneous*, extending between the tendons of *m. biceps brachii* and *m. coracobrachialis* (9, 10). Following the identification of the nerves and vascular structures, a local anesthetic (0.5% levobupivacaine, 20 ml) was administered perivascularly at a 45° angle using a 22G, 50 mm needle (Figure 1).

After administering the axillary block to the left arm, an upper arm amputation was performed (Figure 2). The patient's immediate postoperative course remained stable.

After surgery, the patient was transferred to the intensive care unit at the Anesthesia and Intensive Therapy Clinic. Upon admission, the patient was conscious but unable to communicate. He was breathing spontaneously with oxygen support via an O_2 mask at a flow rate of 8 L/min, maintaining blood oxygen saturation of 97–98% with this oxygen supply. His hemodynamic parameters at admission were as follows: blood pressure (BP) 148/80 mmHg and heart rate (HR) 80/min. The patient arrived in the intensive care unit with a urinary catheter in place, and his initial diuresis after admission was 1,400 mL. The immediate post-anesthesia and postoperative course were uneventful. The patient's hemodynamic and respiratory parameters remained stable, with no signs of fever. His total diuresis reached 3,600 mL by the following morning.

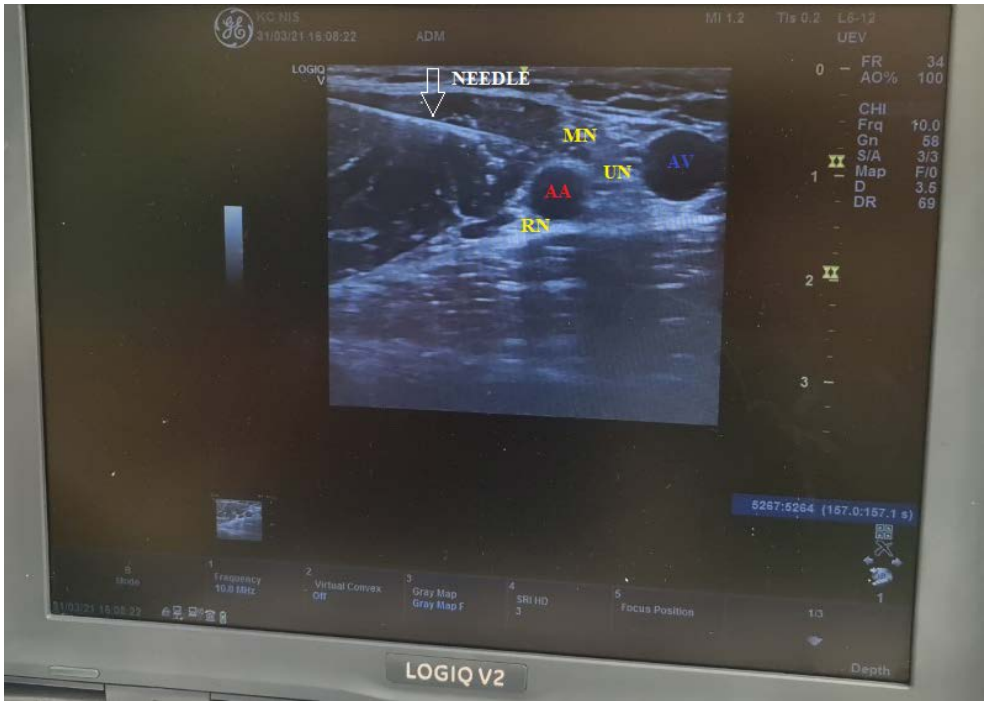

Figure 1. Ultrasound-guided axillary block – University Clinical Centre Niš;*AA – axillary artery, AV – axillary vein, RN – radial nerve, UN – ulnar nerve, MN – medial nerve

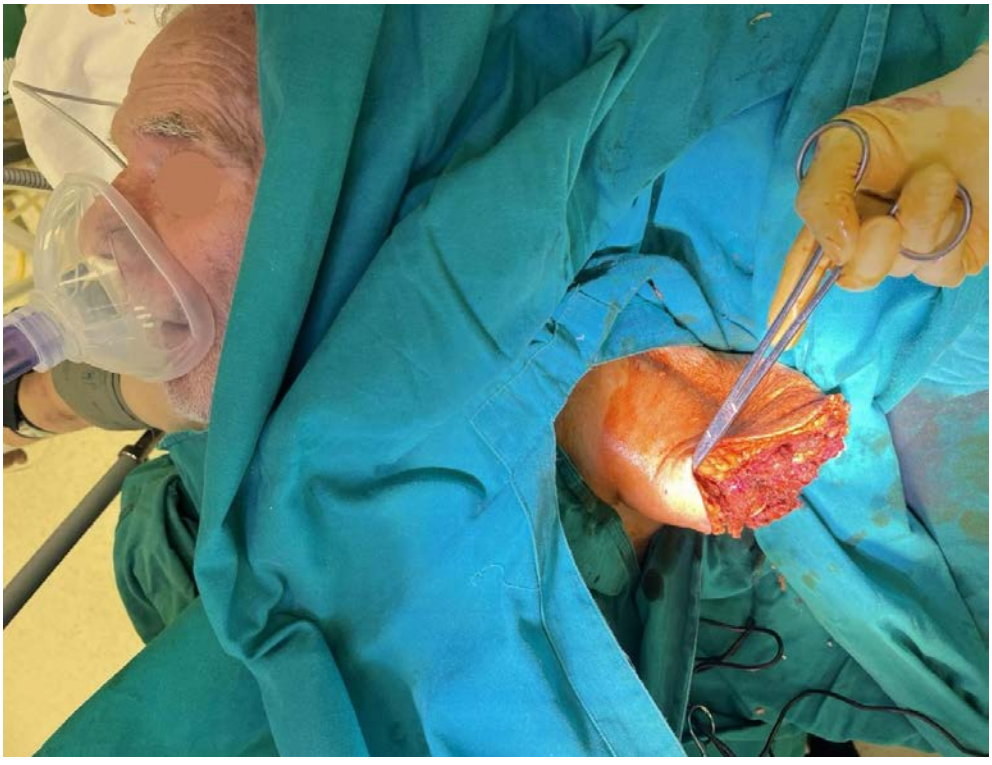

Figure 2. Upper arm amputation performed in an axillary block

On the second postoperative day, the patient remained conscious but was still unable to establish verbal communication. He was breathing spontaneously with oxygen supplementation via a mask at a flow rate of 7 L/min, maintaining an O_2 saturation of 99%.

The patient's hemodynamic parameters were as follows: BP 130/70 mmHg, HF 73/min; laboratory parameters: RBC 4.58 10^12/L, HGB 133 g/L, HCT 0.397 L/L, PLT 213 10^9/L, WBC 13.8 10^9/L, CRP 175.6 mg/L, glycemia 15.8 mmol/L, urea 30.5 mmol/L, creatinin 308.0 μmol/L, total bilirubin 8.7 μmol/L, direct bilirubin 2.0 μmol/L, total proteins 55 g/L, albumin 26 g/L, AST 54 U/L, ALT 56 U/L, alkaline phosphatase 58 U/L, gamma-GT 23 U/L, alpha-amilase 47 U/L, LDH 646 U/L, sodium 153 mmol/L, potassium 4.3 mmol/L, chlorids 116 mmol/L, calcium 2.11 mmol/L, magnesium 1.06 mmol/L.

After evaluation by the vascular surgeon and anesthesiologist, the patient was transferred to the intensive care unit of the Department of Surgery at the Military Hospital in Niš for further monitoring and treatment.

Discussion

Regional anesthesia and peripheral nerve blocks offer numerous advantages, including minimal patient preparation. Since intravenous anesthetics and opioids are avoided, better cardiorespiratory stability can be achieved compared to general anesthesia, along with a reduced incidence of postoperative nausea and emesis (11−13). All these factors contribute to early patient rehabilitation, a shorter hospital stay, increased patient satisfaction, and a reduction in overall treatment costs (14–16). The impact of regional versus general anesthesia on postoperative morbidity and mortality in older patients remains a topic of debate in the medical literature. However, numerous studies have examined this issue. For example, Neuman et al. demonstrated that regional anesthesia is associated with lower inpatient mortality and fewer pulmonary complications compared to general anesthesia (17). Rashid et al. emphasized in their study that anesthesia should be tailored to individual patient needs and preferences (18).

The choice of anesthesia should be based on the patient's overall medical condition and the type of surgery, carefully determined through communication between the surgeon, anesthesiologist, and patient (19). The debate over the advantages of peripheral nerve blocks versus general anesthesia in upper limb surgeries remains ongoing. In cases like this, where the patient has critical hemodynamic and respiratory parameters alongside multiple comorbidities, the anesthetic approach should be limited to methods that minimize hemodynamic and respiratory impact. This approach avoids additional complications associated with mechanical ventilation, intravenous anesthetics, opioids, and neuromuscular relaxants.

Conclusion

Upper arm amputation can be performed using a peripheral nerve axillary block, avoiding general anesthesia, mechanical ventilation, intravenous anesthetics, opioids, and neuromuscular relaxants, thereby reducing the risk of further compromising the patient's respiratory and hemodynamic status.

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ZNAČAJ UPOTREBE AKSILARNOG BLOKA KOD BOLESNIKA SA AMPUTIRANOM NADLAKTICOM I BROJNIM KOMORBIDITETIMA: PRIKAZ SLUČAJA

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Operativni tretman osoba sa okluzivnom bolešću perifernih arterija ponekad predstavlja jedini terapijski pristup. S obzirom na to da izvođenje hirurške intervencije u opštoj endotrahealnoj anesteziji kod hemodinamski i respiratorno nestabilnog bolesnika ponekad predstavlja pravi izazov, primena neuraksijalnih blokova može biti pravi izbor.

Osamdesetogodišnji bolesnik je prevezen kao hitan slučaj na Odeljenje za kardiovaskularne bolesti Vojne bolnice u Nišu zbog otežanog disanja, blede leve šake i podlaktice. Izostajale su karpalne pulsacije, a u šaci bolesnika poslednjih nekoliko dana nije bilo motorike i senzibiliteta. Posle kliničkog pregleda i laboratorijskih analiza urađena je višeslojna kompjuterizovana tomografska angiografija plućnih i magistralnih arterija leve ruke, prilikom koje je postavljena dijagnoza plućne embolije i okluzije a. *subclavia* i a. *brachialis*. Nakon uvida u medicinsku dokumentaciju i kliničkog pregleda, anesteziolog se opredelio za neuraksijalnu anesteziju.

Izbegavanje opšte endotrahealne anestezije i primena neuraksijalnih blokova mogli bi minimalizovati mogućnost pojave neželjenih efekata kod bolesnika sa hemodinamskom i respiratornom nestabilnosti.

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***Ključne reči**: neuraksijalna anestezija, plućna embolija, okluzivna bolest perifernih arterija*

Review article **UDC: 616.724-001.6**
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TEMPOROMANDIBULAR DISC DISPLACEMENT: REVIEW ARTICLE

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The articular disc, a resilient structure situated between the surfaces of the temporomandibular joint (TMJ), plays a crucial role in joint function. Composed of dense fibrous tissue and cartilaginous cells, its primary function is to increase the contact surface area under load and ensure even force distribution. Disc dislocation, most commonly anterior or anteromedial, can be either reducible or irreducible. Clinical presentation varies depending on the type of dislocation and the degree of TMJ tissue inflammation. Diagnosis is based on clinical assessment and, when necessary, magnetic resonance imaging (MRI), often prompted by pain. Treatment approaches depend on the type of dislocation; reducible cases may not require intervention, as retrodiscal tissue adaptation can compensate for the disorder. Pain-related dislocations may be managed conservatively with analgesics, muscle relaxants, or reversible occlusal therapy (splints), depending on severity. Acute anterior dislocations without reduction typically require manual reduction followed by stabilization splint use. In chronic cases, a stabilization splint may be used initially to promote retrodiscal tissue adaptation, with surgery considered only if conservative measures fail. Treatment decisions are guided by pain severity, with carefully tailored interventions aimed at alleviating symptoms, restoring joint function, and improving the patient's quality of life.

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Key words: *articular disc, temporomandibular joint, disc displacement, splint*

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Introduction

Discus articularis, also known as the meniscus, is a vascularized, oval-shaped, fibrocartilaginous structure with a biconcave form. Located between the articular surfaces of the temporomandibular joint (TMJ), it is composed of tough, dense fibrous tissue and cartilaginous cells, providing both flexibility and adaptability. Its primary function is to increase the contact area between joint surfaces under load, ensuring the even distribution of forces (1).

Material and Methods

In 1954, Rees defined four zones of the disc (observed in the sagittal direction) (2):

- anterior thickening zone
- intermediate zone
- posterior thickening zone
- bilaminar zone.

The anterior and posterior thickenings form a circular ring that stabilizes the disc on the condyle and prevents its dislocation during mandibular movements. The intermediate zone is thinner, allowing for flexibility and shaping. The disc's shape and thickness result from functional adaptation, meaning it continuously adjusts during mandibular movements due to the incongruence of the articular surfaces. The bilaminar zone consists of two layers: the upper and lower. The upper layer is composed of loose elastic fibrous tissue elastic fibrous tissue that is well-vascularized and attaches the disc to the capsule and the posterior wall of the glenoid fossa. The lower layer is made of solid, dense, inelastic fibrous tissue, securing the disc to the condyle. Medially and laterally, the disc is fused with the capsule and anchored to the condylar poles. Fibers of the superior bundle of the lateral pterygoid muscle (LPM, *musculus pterygoideus lateralis*) directly enter the medial end of the disc. Contraction of the superior head of the LPM moves the disc forward (protraction) and inward, limiting backward movement (retraction) of the disc. The lateral pterygoid muscle is active in nearly all movements of the lower jaw, with its role in initiating mouth opening being particularly significant (3).

The disc divides the articular space into upper and lower compartments (superior and inferior synovial cavities), which do not normally

communicate. It plays a crucial role in absorbing excessive or abrupt forces, distributing the load over a larger surface area, and compensating for the incongruence of the joint surfaces (1, 2, 4).

Histologically, the disc is composed of dense fibers of type I collagen, water, proteoglycans, cells, and elastic fibers. Degeneration of discal collagen and the loss of cartilage on articular surfaces play a key role in the development of disc disease. Therefore, identifying structural abnormalities, such as degeneration, is essential for an accurate diagnosis (5).

Load Distribution on Temporo-mandibular Joint Structures

The craniomandibular joint functions as a bilateral stabilizing structure for the masticatory muscles during all movements of the masticatory system. Due to its unique characteristics, it distributes loads differently from other joints, allowing a wide range of motion without the risk of excessive strain. Unlike other joints, where maximum load coincides with the largest contact surface, the mandibular condyles do not rest deepest within the articular pits during peak loading. Instead, they are positioned on the posterior slopes of the articular eminences. This arrangement ensures that load transmission occurs through these slopes rather than the bony roof of the articular fossa, which is covered by a thin layer of fibrous tissue and is not structurally adapted to bear significant loads (4).

The small area of contact between the joint surfaces during loading poses a risk to the integrity of the joint structures. However, this risk is mitigated by the presence of the disc and the high-elastic fibrous cartilage covering the articular surfaces. Unlike hyaline cartilage in other joints, which resists compressive forces, fibrous cartilage deforms under load. Due to its high elasticity, the disc tissue compresses during loading, enabling the condyle to 'sink' into alignment with the disc and slide smoothly along the articular eminence. In this manner, the disc compensates for the incongruence of the temporomandibular joint surfaces with its structure (4).

An internal disorder is defined as a localized mechanical dysfunction that disrupts normal joint movement. Internal temporomandibular joint disorders involve abnormalities in the disc's position relative to the mandibular condyle or the articular eminence (6).

In a healthy joint, the disc is secured to the poles of the condyle by ligaments, permitting only translational movement between the condyle-disc complex and the articular eminence. The only physiological movement between the condyle and the disc is rotational, wherein the disc rotates around its ligamentous attachments to the condyle, which restrict excessive motion. The degree of disc rotation per condyle under normal physiological conditions is influenced by the disc's shape, interarticular pressure, and the coordinated function of the upper head of the lateral pterygoid muscle (LPM) and the superior portion of the bilaminar zone of the disc (4).

During physiological posterior rotation of the disc as the mouth opens, the condyle-disc complex moves forward. Subsequently, the upper layer of the bilaminar zone becomes taut and retracts, facilitating the posterior rotation of the disc. This structure is the only one capable of pulling the disc posteriorly, exerting force solely during the disc's back-and-forth movement in mouth opening. When the mouth closes, the upper layer of the bilaminar zone is no longer under tension. Additionally, as the mouth opens, intra-articular pressure increases, ensuring that the condyle remains positioned beneath the intermediate zone and preventing it from shifting into the region of the anterior thickening of the disc (4).

During physiological anterior rotation of the disc, contraction of the superior bundle of the lateral pterygoid muscle (LPM), which is activated during mouth closure, propels the disc forward. Consequently, the disc rotates anteriorly while the entire condyle-disc complex moves backward and upward, enabling translational motion (4).

The controlled rotation of the disc by the condyle, within moderate parameters and facilitated by the described mechanisms in a healthy joint, ensures continuous intimate contact between the disc and condyle during all mandibular movements and positions. Smooth and uninterrupted motion is further enabled by the lubricated, low-friction surfaces of the condyle, disc, and articular eminence (4).

The normal condyle-disc relationship is also maintained due to the disc's distinct biconcave shape. The thin intermediate zone and the annular thickening play a crucial role in stabilizing the disc on the condyle (4).

Disc dislocation can occur in multiple directions. Larheim systematized disc positions based on closed-mouth MRI recordings, classifying them into three main categories:

1. Normal superior disc position: The disc is correctly positioned at both sagittal and coronal cross-sections of the MRI.

2. Partial disc dislocation: The disc is partially displaced, with or without medial or lateral dislocation, while maintaining a normal position in certain sagittal sections.

3. Complete disc dislocation: The disc is dislocated at all cross-sections, with or without lateral or medial dislocation.

A modification of this categorization was proposed by Tasaki:

a. Normal-superior disc position ("at 12 o'clock").

b. Pathological position of the disc: includes anterior, internal, external, and posterior dislocations (7).

The most common type of disc dislocation is anterior or anteromedial displacement. Disc dislocations represent a spectrum of progressive

pathological conditions. Typically, anterior disc dislocation with reduction occurs first, which may eventually progress to anterior disc dislocation without reduction. However, in some patients, anterior dislocation with reduction can persist for decades. Several factors contribute to the progression and development of disc disorders, including gaps in the dental arch (due to the loss of lateral teeth), systemic ligamentous laxity, and parafunctional habits. These factors can significantly influence the course of the disorder (4).

Anterior Reciprocal Disc Displacement (Anterior Disc Dislocation with Reduction)

In Tasaki's classification, the normal position of the disc in the sagittal plane is the superior position, commonly referred to as the "12 o'clock position," where the posterior portion of the disc is aligned directly above the mandibular condyle (8).

In anterior displacement with reduction, the disc does not maintain its normal position relative to the condyle and articular eminence when the mouth is closed. Instead, it is displaced forward or forward and medially. However, upon mouth closure, the disc repositions itself to a more or less normal position on the condyle (4).

When the shape of the disc changes and the ligaments protrude, translational movement between the condyle and the disc becomes possible. The extent of this movement depends on alterations in disc shape, the degree of ligament elongation, and chronic hyperactivity of the upper bundle of the lateral pterygoid muscle (LPM). Since discal ligaments lack elasticity, they remain stretched once elongated. When the mouth is closed, the upper beam of the bilaminar zone does not affect disc position. However, in this state, the upper bundle of the LPM can shift the disc anteriorly. The disc maintains this position while the mouth is closed and returns to rest on the condyle's head upon opening. The displacement of the disc is limited by ligament length and the thickness of its posterior edge. Prolonged displacement can thin the posterior edge, allowing the condyle to extend beneath it or even into the retrodiscal tissue (4). As this represents the initial stage of disc disorder development, characterized as the mildest, subjective symptoms are equally mild (4) (Figure 1).

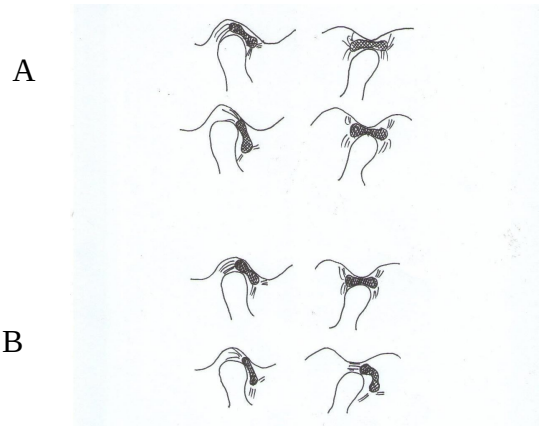


Figure 1. A) Normal position of the disc when the mouth is closed (left) and the normal position when the mouth is opened (right). B) Anterior dislocation of the disc with the mouth closed (left), followed by reduction of the disc, returning it to the normal position upon mouth opening (right).

Clinical Presentation of Anterior Disc Dislocation with Reduction

A single "click" during mouth opening and/or closing (reciprocal click) occurs when the condyle passes over the thickened posterior edge of the disc to position itself beneath the thinned intermediate zone. This click can happen at any point in the translational cycle. The term "reciprocal click" refers to a softer click upon mouth closure, indicating the disc's return to its anterior position.

• Mandibular deviation toward the affected side occurs early in mouth opening due to temporary blockage of condylar translation by disc dislocation. As the disc repositions relative to the condyle, the midline of the mandible normalizes until full mouth opening. This deviation is pathognomonic for anterior disc dislocation with reduction.

• Mandibular deflection refers to a persistent midline deviation throughout the entire mouth-opening movement. It is a key indicator of acute or chronic anterior disc dislocation without reduction (permanent disc dislocation).

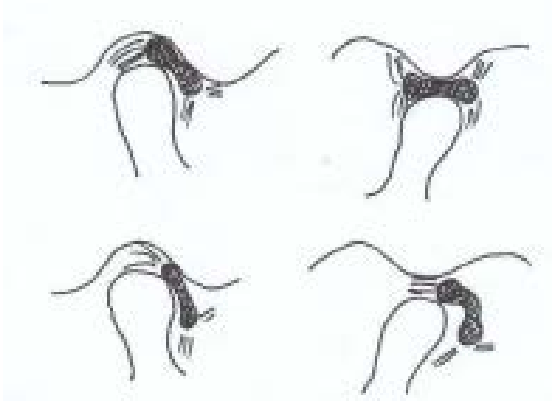
• The normal mouth opening range is 40–50 mm, with the potential for even greater maximum opening. When trismus occurs, it is often due to muscle spasm from pain rather than mechanical obstruction by the disc.

• Pain is not always present in anterior disc dislocation with reduction. When it does occur, it is typically due to sprained discal ligaments or condylar pressure on the retrodiscal tissue (4).

Permanent Anterior Disc Dislocation (Disc Dislocation without Reduction)

This condition is characterized by anterior or anteromedial dislocation of the disc in the closed-mouth position, with the disc failing to return to its normal alignment upon mouth opening. It arises from the gradual, progressive degeneration of joint structures and is often preceded by symptoms of anterior disc dislocation with reduction. In this case, condylar translation along the articular surface is restricted or impaired because the displaced and deformed disc acts as a physical barrier, preventing the condyle from passing beneath it. The disc undergoes morphological changes, shifting from a biconcave to a biconvex shape. Additionally, loosening of the anterior discal attachment leads to the loss of contact between the condyle, disc, and articular eminence. These structural deformations and the altered disc position significantly limit the translational movement of the condyle within the affected joint (4) (Figure 2).

A



B

Figure 2. A) Normal position of the disc when the mouth is closed (left) and the normal position when the mouth is opened (right). B) Anterior dislocation of the disc in the closed mouth (left), with the disc returning to an anterior position upon mouth opening (right).

Clinical Presentation of Anterior Disc Dislocation without Reduction

• Mouth opening is limited to 25–30 mm and may sometimes present as a complete blockage ('closed lock'). Some patients report sudden onset of blockage without any prior trauma to the area.

• Clicking Sounds: Some patients report joint clicking, sometimes accompanied by blockages during prolonged chewing or episodes of bruxism. Occasional blockages may indicate irreversible elongation of the bilaminar zone of the disc, leading to a loss of elasticity and function.

• Mandibular deviation towards the affected side during mouth opening (mandibular deflection).

• Restricted mandibular movements:

-Limited protrusion may occur in some patients with mandibular deflection.

-Lateral movement of the mandible toward the healthy side remains unaffected, as the dislocated disc obstructs all translational movements of the condyle. Unrestricted lateral movement toward the affected joint serves as an important differential diagnostic indicator, distinguishing this condition from anterior irreversible disc dislocation caused by trauma.

• Pain: Results from concurrent inflammation of the of the joint capsule, retrodiscal connective tissue, and discal ligaments. Some patients find relief by applying pressure to the affected joint, which alleviates the pain.

• Impaired activity of the temporal and masseter muscles on the affected side: Muscle spasms exacerbate pain and further restrict mouth opening.

• Crepitus During Mandibular Movement: Absent in the acute stage when joint function is

significantly impaired but may develop in chronic cases due to degenerative changes in the joint surfaces (4).

Magnetic Resonance Imaging

In 1946, Purcell and Bloch established the principles of nuclear magnetic resonance spectroscopy, which later paved the way for the development of magnetic resonance imaging (MRI). In 1973, Lauterbur produced the first images using proton MR signals on phantoms. The first application of MRI to the temporomandibular joint (TMJ) was reported by Helms in 1984, though image quality at the time was limited by low resolution and thicker cross-sections. In 1985, Katzberg, Harms, and Roberts highlighted the advantages of MRI in detecting disc pathology. TMJ MRI provides imaging in the parasagittal and coronal planes without requiring reconstruction. While axial imaging has limited diagnostic significance, it helps determine the positioning of sagittal and coronal cross-sections. Standard imaging of the condyle-disc complex is performed with the mouth in habitual occlusion (closed position) and at maximal opening. The most critical parameters assessed in MRI scans using the T1 sequence include the continuity of articular surfaces, the bony architecture of the articular eminence and condyles, and the position and shape of the disc. The T2 sequence is used to detect inflammatory exudate within the TMJ (9, 10).

Contraindications for MRI are categorized as absolute and relative. Absolute contraindications include patients with implanted aneurysm clips or pacemakers. Other absolute contraindications include the presence of ferromagnetic objects in critical areas (such as the eyes), metal heart valves, claustrophobia, uncooperative patients, individuals in the first trimester of pregnancy, and those unable to lie down for the examination. Dental fillings, implants, fixed orthodontic appliances, and metal dentures do not contraindicate MRI imaging; however, they may cause artifacts that compromise image quality (11). Additionally, MRI findings provide valuable data for anthropology, paleontology, and forensic medicine (12).

Disc Dislocation Therapy

Therapy for Anterior Disc Dislocation with Reduction

Treatment for this disorder is not necessary in every case. Some dislocations can persist for years without progression, due to the adaptation of temporomandibular joint structures. In many cases, the retrodiscal tissue elongates over time, transforming into a modified extension of the posterior edge of the disc, allowing it to function as a load-bearing structure for the condyle (13, 14). In cases where patients do not experience pain or significant impairment of joint function, such as limited mouth opening, and the surrounding muscles are not tender upon palpation, treatment is not necessary. Nevertheless, regular monitoring is recommended to identify any potential progression of the disorder over time (4). If patients report sensitivity upon palpation of the joint, even in the absence of pain, it suggests that the joint tissue has not yet adapted to the new condition. In such cases, patients should be educated about the condition, the factors influencing its progression, and potential treatment options. This is especially important for individuals engaging in parafunctional activities, as they may benefit from home-based interventions (2). Adaptation of the joint tissue is challenging and nearly impossible without adequate support from a stable bite in the lateral segments of the jaw. Therefore, referring patients for appropriate prosthetic treatment is essential (4).

If the dislocation is accompanied by pain, the treatment options follow a range of selectable approaches:

- Conservative methods (analgesics, myorelaxants)
- Reversible occlusal therapy (splint) - the choice of reversible occlusal therapy depends on the degree of dysfunction
- Permanent occlusal therapy.

These measures aim to:

- Relieve and eliminate pain, often through repositioning therapy or a repositioning splint. These interventions temporarily stabilize the mandible in a forward (propulsive, anterior) position, allowing the disc to realign with the condyle. This reduces pressure on the retrodiscal tissue, alleviating pain and joint clicking.
- Re-establish the most normal condyle-disc relationship possible by using a repositioning splint. This approach encourages adaptation and regeneration of the retrodiscal tissue, leading to the formation of a pseudodisc (fibrous tissue). This tissue is more resistant to pressure, helping reduce pain even if the disc remains permanently dislocated forward.

Repositioning therapy is generally effective in alleviating pain and clicking. However, studies show that in about 50% of clinically successful cases (where pain is absent), the disc never returns to its normal position (14). A major drawback is the potential need for extensive, irreversible occlusal reconstruction to maintain the mandible's new therapeutic position. In some cases, the degree of mandibular protrusion required to prevent disc dislocation is too significant for long-term occlusal therapy. As a result, repositioning therapy is an effective yet temporary solution that quickly relieves pain and joint sounds. Despite its limitations, it remains a valuable conservative approach for managing recurrent anterior disc dislocation (4).

Li suggests first using a stabilizing splint for a set period. If it does not produce the desired results, it should be converted into a repositioning splint (15).

The stabilizing splint is a flat, smooth plate made of transparent acrylic, primarily covering the

maxillary dental arch (although, for patients unable to tolerate an upper splint, a splint may be constructed for the lower dental arch). Commonly known as the Michigan splint, this device aims to provide optimal functional occlusion. By establishing a stable musculoskeletal relationship in the central position and increasing vertical occlusal dimension, it allows for maximum engagement of all antagonist muscles. It also provides canine guidance on the working side. Other types of stabilizing splints include the Tanner splint, Schoettl occlusal plate, and Gausch programmable functional plate, among others. However, the Michigan splint is the most commonly used in the treatment of these conditions (4). In more severe cases, where reversible occlusal therapy fails to yield satisfactory outcomes, surgical intervention may be necessary (4).

Anterior Disc Dislocation Therapy without Reduction

Acute Irreversible Disc Dislocation

During the acute phase, treatment focuses on repositioning the dislocated disc, either by the clinician or the patient. The clinician achieves this by pulling the mandible downward while pressing on the occlusal surfaces of the lower lateral teeth with their thumbs. This maneuver separates the condyle from the articular eminence, creating space for the disc to realign. Successful repositioning requires a healthy upper layer of the bilaminar zone, which helps pull the disc back into place (4).

If the repositioning is successful (restoring the normal range of mouth opening and movement to the contralateral side), it is necessary to immediately introduce an anterior repositioning splint that the patient will wear continuously for 10 days (day and night, even during meals), in order to prevent redislocation of the disc. If the disc remains in place after 10 days, the patient should continue wearing the repositioning splint day and night, with a smaller splint made for daytime use. If stability persists after two months, the patient can transition to a stabilizing splint (4).

If repositioning is unsuccessful, it is recommended to use only a stabilizing splint, assuming the patient will adapt to the new disc position by forming a pseudodisc. Surgical treatment is not recommended due to its invasiveness, and repositioning therapy is discouraged, as it may cause unnecessary tension on the retrodiscal tissue (15).

However, if there is persistent pain in the joint area, it suggests inadequate adaptation of the retrodiscal tissue. In such cases, surgical treatment options should be considered (4).

Chronic Irreversible Disc Dislocation

Given that manual disc repositioning does not yield favorable outcomes in these cases, treatment options should be carefully evaluated. The initial approach involves the introduction of a stabilizing splint to facilitate adaptation of the retrodiscal tissue. Alternatively, surgical treatment may be considered. The selection of treatment depends on the severity of pain associated with the dislocation (4).

Conclusion

The most common condition in TMJJ that require examination is anterior disc displacement. Therefore, frequent indication for TMJ imaging with MRI is to evaluate the position and structure of the disc in patients with temporomandibular joint pain. Understanding the parameters and standard dimensions of the TMJ is essential in dentistry, particularly in prosthetics, orthodontics, and maxillofacial surgery.

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DISLOKACIJE *DISCUSA ARTICULARISA* TEMPOROMANDIBULARNOG ZGLOBA: OPŠTI PREGLED

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Discus articularis je žilava, ovalna, fibrokartilaginozna, bikonkavna pločica, interponirana između zglobnih površina temporomandibularnog zgloba (TMZ). Ova pločica je sastavljena od tvrdog, gustog, fibroznog tkiva i hrskavičavih ćelija, a njena uloga je da poveća površinu kontakta između zglobnih površina u momentu opterećenja i da omogući pravilnu distribuciju opterećenja. Dislokacija diska može se kretati u više pravaca, a najčešće anteriorno ili anteromedijalno. Anteriorna dislokacija diska može biti sa redukcijom (povratna) ili bez redukcije (nepovratna). Klinička slika prednje dislokacije diska zavisi od tipa dislokacije i stepena inflamacije tkiva temporomandibularnog zgloba. Dijagnoza dislokacije diska postavlja se na osnovu kliničkog nalaza i, ako je potrebno, na osnovu snimaka sa magnetne rezonance. Najčešći razlog snimanja temporomandibularnog zgloba magnetnom rezonancom jeste prisustvo bola. Terapija dislokacije diska zavisi od vrste dislokacije. U slučaju povratne dislokacije terapija nije uvek neophodna pošto postoji mogućnost adaptacije retrodiskalnog tkiva, što rezultira kompenzacijom nastalog poremećaja. Ukoliko je dislokacija praćena bolom, mogu se primeniti konzervativne mere (analgetici, miorelaksansi) ili reverzibilna okluzalna terapija (upotreba splintova). Vrsta indikovanog splinta zavisi od stepena ozbiljnosti dislokacije. U slučaju akutne anteriorne dislokacije bez redukcije pribegava se repoziciji i upotrebi stabilizacionog splinta. Ako je reč o hroničnoj anteriornoj dislokaciji bez redukcije, prvo rešenje je uvođenje stabilizacionog splinta i omogućavanje adaptacije retrodiskalnog tkiva, a alternativa hirurška terapija. Odluka o tretmanu zavisi od intenziteta bola koji prati dislokaciju.

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***Ključne reči**: discus articularis, temporomandibularni zglob, dislokacija diska, splint*

Case report

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ACUTE APPENDICITIS IN POSTPARTUM PERIOD: A DIAGNOSTIC CHALLENGE

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Acute appendicitis in pregnancy and the puerperium is the most common non-obstetric condition requiring urgent surgery. Unlike appendicitis during pregnancy, reports of appendicitis occurring during delivery and the early puerperium are rare. The most common puerperal infections include puerperal endometritis, urinary tract infections, adnexal torsion, tubo-ovarian abscess, ovarian vein thrombosis, sepsis, pelvic thrombophlebitis, pyelonephritis, pneumonia, and cholecystitis. Diagnosing acute appendicitis in pregnancy and the puerperium is challenging due to atypical or diminished symptoms caused by abdominal wall distension, displacement of abdominal organs, and reduced tissue response to inflammation. The primary symptoms of appendicitis during pregnancy include vomiting, anorexia, nausea, fever, and pain in the lower right abdomen or flank. Appendicitis can lead to refractory postpartum sepsis and should be considered in postpartum patients with sepsis of unknown origin, necessitating a multidisciplinary approach involving both obstetricians and surgeons.

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Key words: *appendicitis, pregnancy, puerperium*

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Introduction

Acute appendicitis in pregnancy and the puerperium is the most common non-obstetric condition requiring urgent surgery (1). Appendix perforation is more frequent during pregnancy, with an incidence of 55%, compared to 4–19% in the general population, where it is most commonly observed in children and the elderly, regardless of gender (1, 2). Appendicitis is less common in the early puerperium than during pregnancy. The most common puerperal infections include puerperal endometritis, urinary tract infections, adnexal torsion, tubo-ovarian abscess, ovarian vein thrombosis, sepsis, pelvic thrombophlebitis, pyelonephritis, pneumonia, and cholecystitis (3). Appendicitis during pregnancy may follow a fulminant course for several reasons. Increased pelvic vascularization and appendix displacement can accelerate strangulation, while enhanced local lymphatic drainage and reduced omental mobility—due to the enlarged uterus—may facilitate the systemic spread of inflammation. In some cases, signs and symptoms of appendicitis may be absent, as anatomical changes can mask the classical clinical presentation, reducing the likelihood of an accurate diagnosis (4). Diagnosing acute appendicitis during pregnancy is challenging due to diminished signs and symptoms caused by abdominal wall distension, displacement of abdominal organs, reduced tissue response to inflammation, and appendix displacement. Nausea, vomiting, and abdominal pain are common in normal pregnancy, particularly during the first trimester (5). The primary symptoms of appendicitis in pregnancy include vomiting, anorexia, nausea, fever, tachycardia, and pain in the lower right quadrant or flank (6, 7). Appendicitis during pregnancy increases the risk of miscarriage, preterm birth, small-for-gestational-age newborns, and neonatal mortality within the first seven days after birth (8). Laparoscopic appendectomy is the preferred treatment (7).

Case report

The first patient was a 30-year-old woman in her first pregnancy, admitted to the Obstetrics Department of the General Hospital in Pirot at 40 weeks of gestation due to lower abdominal pain and lower limb edema, more pronounced in the

right leg. Her pregnancy had been uneventful until admission. She underwent clinical, ultrasound, and cardiotocographic examinations. Blood test results were normal, while a urine sample revealed proteinuria (0.15 g/L), 10–15 erythrocytes, 50–60 leukocytes, numerous squamous epithelial cells, and a high bacterial presence. A urine culture was requested, and treatment with Cefuroxime 1.5 g every 8 hours was initiated. Labor was stimulated with Syntocinon during the expulsion phase and completed vaginally. At the end of the fourth stage of delivery, the patient reported dizziness, weakness, and headache. She was hypotensive (60/40 mmHg) with a thready pulse. She received 1L of crystalloids through two intravenous lines. Bimanual and ultrasound examinations were normal. There was no apparent bleeding, and the uterus was contracted, with the fundus at the umbilical level. Her condition initially improved, but thirty minutes later, she again reported dizziness and headache. An urgent blood count was performed, revealing the following: Erythrocytes 2.92 x 10^{12}/uL, haemoglobin 86g/l, hematocrite 25.25%, leucocytes 27.9 x 10^{9}/uL, platelets 247 x 10^{12}/uL, protein 51g/l, albumin 28g/l. The patient was stabilized, with a blood pressure of 115/70 mmHg and a pulse of 90 bpm. Two units of blood and 50 mL of 20% albumin were ordered. Specialists in internal medicine, neurology, and infectious diseases were consulted. A repeat blood sample was obtained, a urinary catheter was placed, and diuresis was monitored. Procalcitonin was 0.54 ng/ml, D-dimer 6000 ng/ml, leucocytes 23.14 x 10^{9}/uL, eritrocytes 3. .05 x 10^{12}/uL, haemoglobin 85g/l, hematocrit 28.3%, platelets 227x 10^{12}/uL. An infectious disease specialist was consulted due to persistently elevated procalcitonin levels (0.53 ng/ml). The abdominal surgeon found no significant clinical findings on the abdomen, and a Doppler ultrasound of the lower limbs was also normal. Urine cultures from both samples were sterile. On the third day, procalcitonin levels remained largely unchanged (0.49 ng/ml), leading to the addition of Ciprofloxacin (500 mg twice daily). The general urine examination was now normal. On the fourth postpartum day, the patient reported a sudden onset of abdominal pain in the lower right quadrant. She was nauseous without vomiting and had a fever of 37.5°C. An internal medicine specialist and a general surgeon were consulted. An ultrasound of the abdomen and ileocecal region revealed a blind-ended tubular structure measuring 11 mm in diameter and 5.5 cm in length, with subserosal edema—findings consistent with acute appendicitis. Additionally, enlarged mesenteric lymph nodes measuring 11×16 mm were observed. Follow-up laboratory tests showed leukocytosis with 21.3 × 10^{9}/uL leukocytes, neutrophilia of 87.2%, and a procalcitonin level of 0.26 ng/ml. The patient was transferred to the general surgery department, and surgery was performed on the same day. Intraoperatively, an altered appendix was observed, along with mesenteric lymphadenopathy and a small amount of ascitic fluid in the Douglas recess. An antegrade appendectomy was performed, followed by hemostasis and suturing. The excised tissue was sent for pathological examination. Two antibiotics, analgesics, thromboprophylaxis, and rehydration therapy were administered. The postoperative course was uneventful. Follow-up laboratory tests, gynecological evaluation, and ultrasound examinations were all normal. The patient was discharged in good general condition. Pathohistological examination confirmed purulent phlegmonous-gangrenous appendicitis.

The second case involves a 21-year-old primiparous woman who was admitted for a post term pregnancy. An urgent cesarean section was performed due to imminent fetal asphyxia and posterior occipital presentation. She was discharged in good condition. Fourteen days after delivery, she reported upper abdominal pain that gradually spread to the entire abdomen. She experienced nausea, anorexia, fever of 38.5°C, and diarrhea. Initially, she was examined by a surgeon and a gynecologist and was discharged home. However, eight days later, she presented to the emergency department of General Hospital Pirot, appearing pale and adynamic, with an axillary temperature of 37.7°C and a rectal temperature of 38.5°C. Blood pressure was 120/70 mmHg, heart rate of 100/min. All clinical signs of appendicitis were negative. Following blood tests were performed: Leu- 16, 06 x 10^{9}uL, Er-3,39 x 10^{12}, Hgb-98 g/l, HCT-29,3%, Tr-368x 10^{9}/L, PCT-0,07 ng/ml, D-dimer 6783,33 ng/ml, CRP 215,9 mg/L. Abdominal ultrasound revealed interintestinal ascites in the right iliac region and the Douglas pouch, along with meteorism. Computed tomography of the abdomen and pelvis showed an irregular hypodense structure in the lower right quadrant, encompassing the cecum and terminal ileum en bloc, with a possible intraluminal hemorrhage. Fluid accumulation was noted around the structure. Additionally, a large number of enlarged lymph nodes were observed in the right retroperitoneum and along the branches of the superior mesenteric artery. Ascites was also present in Morison's pouch and the right paracolic gutter. Surgery was performed the same day. An en bloc abscess, approximately the size of two male fists, was found in the right inguinal fossa, containing the ileum, terminal ileum, and cecum. After careful dissection, around 200 mL of pus was drained from the abscess cavity and sent for microbiological analysis. The small intestines were irrigated, and the cecal base was examined, revealing only the tip of the appendix and a coprolite—the appendix itself was absent. The base of the appendix was sutured, and drainage was placed in the Douglas pouch and the retrocecal space. The patient received antibiotics, antisecretory drugs, analgesics, and crystalloids. She was discharged on the seventh postoperative day in stable condition and was feeling well at her scheduled follow-up appointment.

Discussion

There is insufficient evidence to suggest that pregnancy increases the incidence of appendicitis. The incidence of appendicitis during pregnancy ranges from 1 in 1,200 to 1 in 1,500 pregnancies, with the highest occurrence typically in the second trimester (9). Early puerperal appendicitis is less common, with regional variations and a decreasing trend in incidence (3). In contrast to appendicitis during pregnancy, there is very limited data on appendicitis around the time of delivery and in the early puerperium. A large cohort study conducted in England in 2015 showed that the incidence of appendicitis in the postpartum period is similar to that of the general population, with an incidence rate ratio (IRR) of 1.01 (95% CI, 0.81–1.26) in women aged 15 to 34. However, the incidence is slightly higher in women over 34 years old, with an IRR of 1.84 (95% CI, 1.18–2.86) (10). According to the most widely accepted theory, appendicitis is caused by a mechanical obstruction of the appendix lumen, which may result from stagnant feces, lymphoid hyperplasia, or a parasitic infection of the appendix wall (11). Diagnosing appendicitis during pregnancy is challenging, particularly in the second half of pregnancy, during labor, and in the first few days postpartum (4). This is due to the anatomical and physiological changes that occur during pregnancy and the puerperium, which must be considered when interpreting anamnestic data and clinical examination results. During pregnancy, the uterus enlarges twentyfold, stretching ligaments and muscles, and exerting pressure on abdominal structures and the layers of the abdominal wall, which reduces its tone, even several weeks postpartum (12). Typical features of acute surgical conditions, such as abdominal tenderness and stiffness, are often absent or diminished in the early postpartum period. Additionally, the high levels of circulating estradiol, progesterone, estriol, and glucocorticoids during this time diminish the tissue's response to inflammation, masking early signs of infection and its localization (13). Constant abdominal pain is the most common symptom, with pain in the lower right quadrant being the most reliable indicator, present in 84% of patients (14). The main symptoms of appendicitis during pregnancy include vomiting, anorexia, nausea, fever, tachycardia, and pain in the lower right quadrant and flank (9). Nausea is particularly noteworthy, as early pregnancy nausea and vomiting are typically self-limiting and confined to the first trimester. The appendix typically returns to its original position at McBurney's point ten days after delivery (7). Classical migration of pain strongly suggests appendicitis and is present in 50% of patients (4). While some of the classical signs of appendicitis, such as Rowsing's, Alder's sign, obturator sign and psoas sign may not be highly sensitive, they are considered specific (15). The mid-axillary temperature for proven appendicitis ranges between 37.2°C and 37.8°C (present in 50% of cases), but can rise to as high as 39°C in cases of perforation and diffuse peritonitis (16). An increased heart rate has a similar positive predictive value, though it is not a sensitive sign (9). Average leucocyte count after delivery is 13.39 x 10^9 uL, with significant differences regarding the modality of delivery (vaginal birth, vaginal assisted delivery or cesarean section) (17). White blood cell count of over 16 × 10^9 uL should raise suspicion. C-reactive protein (CRP) levels are elevated during pregnancy, although the mechanism behind this increase is unknown. The levels remain elevated until after delivery, peaking on the second day postpartum (18). We monitored procalcitonin levels. A cohort study conducted in Geneva in 2009 concluded that a procalcitonin level of 0.25 μg/l should be used as a threshold during the third trimester and delivery (19). As a non-invasive test, abdominal ultrasound is the diagnostic tool of choice. It provides high precision during the first and second trimesters, although its accuracy decreases in the third trimester. A non-compressible, dead-ended tubular structure in the lower right quadrant with a diameter greater than 6 mm is considered diagnostic (20). Sensitivity ranges from 75% to 100%, but specificity is only between 40% and 50% (14). Perforated appendicitis is a known cause of preterm delivery and may have contributed to the onset of labor in our case, despite the patient not reporting any abdominal pain. There is anecdotal evidence supporting conservative antibiotic treatment for perforated appendicitis during pregnancy. It is possible that the symptoms of appendicitis were masked due to the use of antibiotics.

Conclusion

Appendicitis can lead to refractory sepsis in the postpartum period and should be considered when no obvious cause of sepsis is found. Due to physiological changes during pregnancy and early puerperium, diagnosing appendicitis is challenging and should be considered whenever abdominal pain occurs. Delayed or missed diagnosis and treatment can result in serious complications for the mother, highlighting the importance of a collaborative approach between surgeons and obstetricians.

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Prikaz bolesnika

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AKUTNI APEDNICITIS U POSTPARTALNOM PERIODU: DIJAGNOSTIČKI IZAZOV

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Apendicitis u trudnoći i puerperijumu najčešći je uzrok neginekološkog oboljenja koje zahteva hitnu hiruršku intervenciju. Za razliku od apendicitisa u trudnoći, mali broj radova bavi se apendicitisom koji nastaje u toku porođaja i u ranom puerperijumu. Najčešće infekcije u puerperijumu su puerperalni endometritis, infekcije urinarnog trakta, adneksalna torzija, tubo-ovarijumski apscesi, tromboza ovarijumskih vena, sepsa, pelvični tromboflebitis, pijelonefritis, pneumonija i holecistitis. Do poteškoća prilikom dijagnostikovanja akutnog apendicitisa u trudnoći i puerperijumu dolazi zbog oslabljenih simptoma i znakova usled distenzije trbušnog zida, dislokacije intraabdominalnih organa i smanjenog odgovora tkiva na upalu. Glavni simptomi apendicitisa u trudnoći uključuju povraćanje, anoreksiju, mučninu, povišenu telesnu temperaturu, tahikardiju i bol u donjem desnom kvadrantu ili boku. Budući da apendicitis može biti uzrok neprepoznate refraktorne sepse u postpartalnom periodu, kod pacijentkinja posle porođaja, osim na sepsu, treba obratiti pažnju na upalu slepog creva. Stoga, neophodan je timski rad ginekologa i hirurga.

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***Ključne reči**: apendicitis, trudnoća, puerperijum*

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