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ENDOMETRIAL CARCINOMA IN ASYMPTOMATIC POSTMENOPAUSAL WOMEN WITH A THICKENED ENDOMETRIUM

KARCINOM ENDOMETRIJUMA KOD ŽENA U POSTMENOPAUZI, BEZ SIMPTOMA, SA ZADEBLJALIM ENDOMETRIJUMOM

Ljiljana MLADENOVIĆ SEGEDI[1, 2], Miloš PANTELIĆ[1, 2] and Dragan STAJIĆ[1, 2]

Summary

Introduction. The most common clinical manifestation of endometrial cancer is postmenopausal bleeding, as well as irregular uterine bleeding. Far less often, endometrial cancer may also be present in postmenopausal women without bleeding. The aim of our study was to examine the incidence of endometrial cancer in asymptomatic postmenopausal women with a thickened endometrium. **Material and Methods.** The research included 251 asymptomatic postmenopausal women with endometrial thickness over 4 mm established by ultrasound. Exploratory curettage was performed in all the patients, followed by histopathological examination of the obtained material. **Results**. The average age of the respondents was 65.38 ± 26.69 years. The average thickness of the endometrium was 15.68 ± 5.06 mm. Of all the patients, 70.13% presented with benign endometrial disease; endometrial polyps were found in 58.18% and simplex hyperplasia of the endometrium without atypia in 11.95%. Endometrial cancer was found in 1.59% of patients, ovarian cancer metastasis in 0.4%, and endometrial hyperplasia with atypia in 1.59% of patients. All cases of endometrial cancer were diagnosed in patients with endometrial thickness over 11 mm. **Conclusion.** The approach to asymptomatic women with endometrial hyperplasia should be individual. Exploratory curettage/hysteroscopy should be recommended to patients with endometrial thickness over 11 mm in order to detect and evaluate for endometrial cancer. Asymptomatic women with endometrial thickness of 4 - 10 mm should be further examined, especially in case of associated risk factors or other ultrasound parameters that indicate more serious endometrial pathology.

Key words: Endometrial Neoplasms; Postmenopause; Endometrial Hyperplasia; Ultrasonography; Risk Factors

Sažetak

Uvod. Najčešća klinička manifestacija karcinoma endometrijuma je krvarenje u postmenopauzi kao i iregularno krvarenje iz materice. Daleko ređe, karcinom endometrijuma može biti prisutan i kod žena u postmenopauzi koje ne krvare. Cilj našeg rada bio je da ispitamo učestalost karcinoma endometrijuma kod žena u postmenopauzi, bez simptoma, sa zadebljalim endometrijumom. **Materijal i metode.** Istraživanje je obuhvatilo 251 ženu bez simptoma, u postmenopauzi, sa ultrazvučno izmerenom debljinom endometrijuma većom od 4 mm. Svim ispitanicama je urađena eksplorativna kiretaža i načinjen patohistološki pregled dobijenog materijala. **Rezultati**. Prosečna starost ispitanica iznosila je 65,38 ±26,69 godina. Prosečna debljina endometrijuma iznosila je 15,68 ±5,06 mm. Benigno oboljenje endometrijuma imalo je 70,13% ispitanica: 58,18% polip endometrijuma, odnosno simpleks hiperplaziju endometrijuma bez atipije 11,95%. Kod 1,59% ispitanica utvrđeno je postojanje karcinoma endometrijuma, kod 0,4% ispitanica utvrdili smo prisustvo metastaze karcinoma jajnika, a kod 1,59% ispitanica utvrdili smo postojanje endometrijalne hiperplazije sa atipijom. Svi slučajevi karcinoma endometrijuma dijagnostikovani su kod pacijentkinja sa debljinom endometrijuma većom od 11 mm. **Zaključak.** Pristup ženama bez siptoma, sa hiperplazijom endometrijuma, treba da bude individualan. Pacijentkinjama sa debljinom endometrijuma većom od 11 mm treba preporučiti eksplorativnu kiretažu/histeroskopiju u cilju evaluacije na karcinom endometrijuma. Žene bez simptoma, sa debljinom endometrijuma 4–10 mm, uputiti na dalju dijagnostiku u slučaju prisustva faktora rizika kao i prisustva drugih ultrazvučnih parametara koji ukazuju na težu patologiju endometrijuma.

Ključne reči: neoplazme endometrijuma; postmenopauza; hiperplazija endometrijuma; ultrazvuk; faktori rizika

Introduction

Endometrial cancer is the most common malignant tumor of the female genital organs in developed countries [1]. In the last three decades, the incidence of endometrial cancer has increased by approximately 1% per year, which is primarily related to the increase in the proportion of obese and

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Abbreviations
US – ultrasound
ET – endometrial thickness
CIN – cervical intraepithelial neoplasia

elderly women [2, 3]. Also, in about 5% of cases, the occurrence of endometrial cancer is genetically determined by the mutation of one of the four mismatch repair genes [4]. Women with hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome) have a cumulative incidence of endometrial cancer of 20 - 60% by the age of 70 [4–6].

The most common clinical manifestation of endometrial cancer in postmenopausal women is uterine bleeding [7, 8]. However, endometrial cancer may also be found in postmenopausal women without bleeding, but with a thickened endometrium (endometrial hyperplasia) confirmed by a routine gynecological ultrasound examination [7]. The incidence of endometrial thickening in postmenopausal women is from 3% to 17%, while the incidence of postmenopausal endometrial cancer in asymptomatic women is up to 3% [9, 10].

The high rate of cure in the initial stages of the disease with about 80 - 85% five-year survival has created a false belief that endometrial cancer is a low-risk disease. Nonetheless, advanced stages of the disease, as well as some histological types of endometrial cancer, are associated with a poor prognosis [3]. Despite of this, modern guidelines for endometrial cancer do not recommend screening, or routine ultrasound (US) examination or endometrial biopsy in asymptomatic postmenopausal women, because they do not improve the outcome of endometrial cancer [11–15]. Screening for endometrial cancer is recommended only for women at risk for Lynch syndrome [15, 16].

The aim of this research was to examine the prevalence of endometrial cancer in asymptomatic postmenopausal women with a thickened endometrium in our sample and to try to answer the question if it is necessary to perform exploratory curettage/hysteroscopy in every patient with a thickened endometrium.

Material and Methods

The research was a retrospective study conducted at the Clinic of Gynecology and Obstetrics, Clinical Center of Vojvodina and it was approved by the Ethics Committee of the Clinical Center of Vojvodina. The research included 251 asymptomatic postmenopausal women who underwent fractional exploratory curettage due to a thickened endometrium in the period from January 1, 2020 to December 31, 2020. Exploratory curettage was performed under general intravenous anesthesia in the one-day hospital of the Department of General and Emergency Gynecology.

We defined postmenopausal women as those who have not had their period for more than a year. All women underwent a transvaginal US examination. As a criterion for a thickened endometrium, we used endometrial thickness (ET) ≥ 4 mm established by transvaginal ultrasound.

Histopathological analysis of the obtained material was done at the Center for Pathology and Histology, Faculty of Medicine, University of Novi Sad, and the final diagnosis was established. The patients waited 2 - 3 weeks for the histopathological findings. After data collection, a descriptive and univariate analysis was carried out. Data analysis was performed using the SPSS version 22 software.

Results

Out of a total of 342 postmenopausal patients who underwent fractional exploratory curettage in 2020, 251 patients were asymptomatic and included in further research. Due to postmenopausal bleeding, 91 patients were excluded from the study. The average age of the respondents was 65.38 ± 26.69 years. The average ET in the examined patients was 15.68 ± 5.06 mm.

The largest number of the respondents (70.13%) had a benign endometrial disease: endometrial polyps were found in 58.18% and simplex hyperplasia of the endometrium without atypia in 11.95%. Endometrial cancer was found in 1.59% of subjects, breast cancer metastases were found in 0.4%, and endometrial hyperplasia with atypia was found in 1.59% of patients **(Table 1)**.

All cases of endometrial cancer were diagnosed in patients with ET > 11 mm. Breast cancer metastasis was diagnosed in one patient with ET < 11 mm. Atypical endometrial hyperplasia was diagnosed in 2 patients (1.61%) with ET < 11 mm and in 2 patients (1.57%) with ET > 11 mm. The largest number of patients in both groups had endometrial polyps (56.7%, 59.68%) or endometrial hyperplasia without atypia (13.39%, 10.14%). Insufficient material was obtained in 22.83% of patients with ET > 11 mm and in 27.42% with ET < 11 mm **(Table 2)**.

Table 1. Histopathological findings of exploratory curettage
Tabela 1. *Patohistološki nalazi eksplorativne kiretaže*

	No./*Br.*	%
Endometrial cancer/*Karcinom endometrijuma*	4	1.59
Endometrial polyp/*Polip endometrijuma*	146	58.18
Simplex endometrial hyperplasia without atypia/*Simpleks hiperplazija bez atipije*	30	11.95
Simplex endometrial hyperplasia with atypia/*Simpleks hiperplazija sa atipijom*	4	1.59
Cervical cancer/*Karcinom grlića*	1	0.4
Cervical intraepithelial neoplasia 3/*Cervikalna intraepitelna neoplazija 3*	2	0.79
Breast cancer metastasis/*Metastaza karcinoma dojke*	1	0.4
Insufficient material/*Oskudan materijal*	63	25.1

Table 2. Histopathological diagnoses in relation to endometrial thickness
Tabela 2. *Patohistološke dijagnoze kod pacijentkinja prema debljini endometrijuma*

Endometrial thickness/*Debljina endometrijuma*	11 mm		< 11 mm		Total/*Ukupno*
	No./*Br.*	%	No./*Br.*	%	
Endometrial cancer/*Endometrijalni karcinom*	4	3.15	0	0	4
Endometrial polyp/*Endometrijalni polip*	72	56.7	72	59.68	146
Simplex endometrial hyperplasia without atypia/*Simpleks hiperplazija bez atipije*	17	13.39	13	10.48	30
Simplex endometrial hyperplasia with atypia/*Simpleks hiperplazija sa atipijom*	2	1.57	2	1.61	4
Cervical cancer/*Karcinom grlića*	1	0.79	0	0	1
Cervical intraepithelial neoplasia 3/*Cervikalna intraepitelna neoplazija 3*	2	1.57	0	0	2
Breast cancer metastasis/*Metastaza karcinoma dojke*	0	0	1	0.81	1
Insufficient material/*Oskudan materijal*	29	22.83	34	27.42	63
Total/*Ukupno*	127	50.60	124	49.40	251

Discussion

An increasing number of postmenopausal women without any gynecological symptoms have preventive gynecological examinations as well as transvaginal US examinations, even when it is not indicated, in order to detect ovarian tumors, uterine tumors or tumors of other organs of the small pelvis.

In case of accidental finding of thickened endometrium, the gynecologist immediately refers the patient to a tertiary health institution, for further examination, endometrial biopsy, i.e. exploratory curettage or hysteroscopy.

However, the accidental finding of a thickened endometrium in postmenopausal asymptomatic women is a diagnostic dilemma for gynecologists, because there are still no clear guidelines and consensus among gynecologists regarding the threshold value of ET when the patient should be referred for further diagnostics [5, 17]. Without clear guidelines, the incidental finding of a thickened endometrium is based on the clinician's decision, taking into account the patient's wishes and risk factors [17].

In case of postmenopausal women with bleeding, the guidelines are clear. A transvaginal US examination should be performed, and if the endometrium is > 4 mm, they should be referred for further diagnostics, since the probability of endometrial cancer increases with each increase in the thickness of the endometrium by 1 mm. If the thickness of the endometrium is between 8 - 11 mm, the probability increases by 1.17, whereas if the thickness is over 11 mm, the probability that it is endometrial cancer is 4.7 times higher [18]. If the thickness of the endometrium is < 4 mm, the risk of endometrial cancer is small, less than 1% (0.3%), and regular examination should be recommended, but if the woman has recurrent bleeding or continues to bleed, further invasive diagnostics should be performed [7, 19].

The ET > 4 or 5 mm, which is used as a cut off value in cases of postmenopausal bleeding, cannot be applied to asymptomatic postmenopausal women, due to poor positive predictive value. With this approach, asymptomatic women with a low risk of endometrial cancer are subjected to invasive diagnostics, which is associated with the risks of complications of the intervention itself, increase in stress and anxiety, without affecting the reduction of morbidity and mortality due to endometrial cancer [5, 11, 20].

In our research, endometrial cancer was diagnosed in 4 patients (1.59%), where all patients had an ET over 11 mm. Four patients (1.59%) were diagnosed with atypical endometrial hyperplasia, while 2 patients had ET under 11 mm and the other two over 11 mm. The largest number of patients had benign endometrial disease, namely endometrial polyps (58.18%) and endometrial hyperplasia without atypia (11.95%). Insufficient material was obtained from 25.1% of the respondents. Our results are consistent with those of other authors.

In their study of 148 asymptomatic postmenopausal patients with endometrial hyperplasia, Gambacciani et al. found one case of adenocarcinoma by hysteroscopic biopsy (0.7%) in a woman with ET was 16 mm. They found that transvaginal US, as a screening method for endometrial pathology in asymptomatic postmenopausal women, has 93.2% false positive results. They concluded that US measurement of ET in this population of women should not be recommended in order to detect endometrial cancer [21]. In their study of 81 asymptomatic postmenopausal women with thickened endometrium, Ghoubara et al. found endometrial carcinoma or atypical endometrial hyperplasia in only 4 women (4.9%), all of whom had ET ≥ 10 mm [22]. A study of Ozelci et al. included 148 asymptomatic postmenopausal women who underwent hysteroscopic biopsy of the endometrium, and endometrial cancer was found in only 0.7% (one) of the cases [23]. A study by Allam et al. in Egypt, in a similar population, determined the presence of atypical endometrial hyperplasia in 6.8% and endometrial cancer in 4.1% [24].

These wide variations may result from differences in study design, patients' demographics, the number of patients included in the study, as well as differences in ethnicity and profiles.

In 2018, Alcazar et al. published the first meta-analysis that compared the risk of endometrial cancer

in asymptomatic postmenopausal women with ET ≥ 11 mm versus < 11 mm. It was observed that the risk of endometrial cancer in women with ET ≥ 11 mm was almost three times higher than those with ET 5 - 10 mm [25].

A study by Smith et al. included 10.000 asymptomatic postmenopausal women and found that the risk of endometrial cancer in women with ET ≥ 11 mm was 6.7% with 100% sensitivity and 80% specificity for the detection of endometrial cancer, and this risk was similar to the risk of endometrial cancer in women with postmenopausal bleeding and ET ≥ 5 mm, which is 7.3%. They suggest that endometrial biopsy in asymptomatic postmenopausal women should be performed if the ET is ≥ 11 mm [26].

However, there are studies that failed to determine the threshold thickness of the endometrium in asymptomatic postmenopausal women, which would be used in clinical practice to rationalize further diagnostics, indicating that every woman should be offered further diagnostics [7, 9].

Today, numerous authors agree that when setting indications for further diagnostics in asymptomatic postmenopausal women, in addition to measuring the thickness of the endometrium, other risk factors should also be taken into account, such as: obesity - body mass index > 25, high blood pressure, diabetes mellitus type 2, nulliparity, infertility, polycystic ovary syndrome, early menarche/late menopause, use of exogenous estrogen or estrogen-secreting tumors, and use of Tamoxifen [14, 20, 26–28].

In a retrospective study Aggarwal et al. studied asymptomatic postmenopausal women and ET of 10 mm was used as a cut off value. Endometrial cancer was detected in 1.2% of subjects and atypical hyperplasia in 2.4%. In subjects with ET < 10 mm, histopathological analysis showed no malignancy. Endometrial cancer was diagnosed in patients with ET ≥ 10 mm, and all of these cases had at least one risk factor for endometrial cancer. The authors recommended using ET ≥ 10 mm as a threshold value for endometrial biopsy or hysteroscopy in asymptomatic postmenopausal women. In asymptomatic women with ET of 4 - 10 mm, the decision on further examinations should be made individually, from case to case, taking into account risk factors as well as US characteristics of the endometrium [20].

Also, current recommendations regarding asymptomatic postmenopausal women with ET < 11 mm, apart from ET other US characteristics should be examined: uniformity and homogeneity of the endometrium, presence of cystic changes within the endometrium, echogenicity of the endometrium in relation to the myometrium, whether there is a clear border between the endometrium and myometrium and what that border is like (regular, irregular, interrupted or undefined), color and power Doppler parameters: no color, minimal color to prominent color. Blood vessels and increased vascularity must also be observed and described: the number of dominant blood vessels, whether they are branched, and nature of the flow through the blood vessels (dispersed or circular) [15, 20, 29–33].

Every asymptomatic postmenopausal woman with ET of 4 - 10 mm, risk factors, and US parameters indicating more severe endometrial pathology, should be offered further diagnostics [20]. Each woman should be explained the potential benefits of further diagnostics as well as the risks and possible limitations of further testing for endometrial cancer in order to make a clear decision on further treatment. Women with increased risk of endometrial cancer should be informed about the risks and symptoms of endometrial cancer and encouraged to report any unexpected vaginal bleeding [15].

Conclusion

The approach to asymptomatic women with endometrial hyperplasia should be individual. Patients with endometrial thickness > 11 mm should be advised to undergo exploratory curettage/hysteroscopy in order to evaluate for endometrial cancer. Asymptomatic women with endometrial thickness of 4 - 10 mm should be referred for further diagnostics individually, in case of associated risk factors, as well as other ultrasound parameters which indicate more severe pathology of the endometrium.

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PREOPERATIVE DETERMINATION OF TUMOR THICKNESS IN ORAL SQUAMOUS CELL CARCINOMA BY COMPUTED TOMOGRAPHY

PREOPERATIVNO ODREĐIVANJE DEBLJINE TUMORA ORALNOG SKVAMOCELULARNOG KARCINOMA KOMPJUTERIZOVANOM TOMOGRAFIJOM

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Summary

Introduction. Evaluation of the prognostic factors and the survival rate in oral squamous cell carcinoma is extremely important, because patients in the same tumor-node-metastasis stage may have a different survival rate. Numerous studies have been conducted on various clinical and pathological prognostic factors in order to develop a prognostic model for the survival rate of patients with oral cancer. **Material and Methods.** The study was designed as a prospective study including 65 consecutive patients (n = 65) of both sexes who underwent surgical treatment of oral cancer. The diagnosis of oral cancer was based on the medical history, physical examination, and biopsy. The clinical tumor-node-metastasis staging was determined based on clinical examination. The radiological tumor-node-metastasis staging was done by computed tomography of the head, neck, and chest. The tumor thickness was determined by computed tomography and histopathological analysis of surgical specimens. **Results.** The histopathological analysis showed a mean tumor thickness of 13.446 mm, while the mean computed tomography tumor thickness was 15.2707 mm. The correlation between computed tomography tumor thickness and histopathological tumor thickness was moderately significant (Spearman's rho=.581, p =0.000). **Conclusion.** This study supports the use of computed tomography in the determination of tumor thickness in patients with oral squamous cell carcinoma. We want to emphasize the importance of preoperative, detailed imaging evaluation of patients in order to avoid multiple surgical procedures, significant morbidity, and unnecessary costs.

Key words: Carcinoma, Squamous Cell; Tomography, X-Ray Computed; Preoperative Period; Mouth Neoplasms; Prognosis; Survival Rate

Sažetak

Uvod. Poznavanje prognostičkih faktora stope preživljavanja kod oralnog skvamoznog karcinoma je od izuzetnog značaja jer pacijenti u istom tumor-čvor-metastaza stadijumu bolesti mogu imati različitu stopu preživljavanja. Sprovedene su brojne studije o različitim kliničkim i patološkim prognostičkim faktorima u cilju razvoja prognostičkog modela stope preživljavanja pacijenata sa oralnim karcinomom. **Materijal i metode.** Studija je osmišljena kao prospektivna i obuhvatila je 65 uzastopnih pacijenata (n = 65) oba pola koji su imali hirurški tretman za oralni karcinom. Dijagnoza karcinoma usne šupljine postavljena je na osnovu anamneze, fizičkog pregleda i biopsije. Klinički tumor-čvor-metastaza stadijum utvrđen je na osnovu kliničkog pregleda. Radiološki tumor-čvor-metastaza stadijum uključivao je pregled kompjuterskom tomografijom glave, vrata i grudnog koša pacijenta. Debljina tumora je određena kompjuterizovanom tomografijom i patohistološkim merenjem na postoperativnom uzorku tumora. **Rezultati.** Prosečna debljina tumora na patohistološkom preparatu bila je 13,446 mm, dok je prosečna debljina tumora kod pregleda kompjuterskom tomografijom bila 15,2707 mm. Korelacija između debljine izmerene kompjuterskom tomografijom i postoperativne debljine bila je umereno značajna (*Spearman rho* = 581, P =0,000). **Zaključak.** Ova studija podržava ulogu kompjuterske tomografije u određivanju debljine tumora kod pacijenata sa oralnim skvamocelularnim karcinomom. Želimo da istaknemo važnost preoperativne, detaljne slikovne evaluacije pacijenta kako bi se izbegli višestruki hirurški zahvati, značajan morbiditet i nepotrebni troškovi.

Ključne reči: skvamocelularni karcinom; CT; preoperativni period; oralne neoplazme; prognoza; stopa preživljavanja

Introduction

Oral squamous cell carcinoma (OSCC) is the 8th most common malignancy in the world. More than 177,000 people die annually from oral cancer [1]. Evaluation of the prognostic factors and the survival rate in OSCC is extremely important, because patients in the same tumor-node-metastasis (TNM) stage may have a different survival rate. Numerous studies have been conducted on various clinical and pathological prognostic factors in order to develop a prognostic model of the survival rate of patients with oral cancer [2]. The presence of nodal cervical metastasis is certainly the most significant prognostic factor; however, the presence of occult cervical metastasis represents a therapeutic problem for OSCC since it is present in 18 - 53% of patients with T1-2 N0 OSCC, therefore, the prediction of the nodal change is of great importance [3].

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Abbreviations

TNM – tumor-node-metastasis
OSCC – oral squamous cell carcinoma
SCC – squamous cell carcinoma
CT – computed tomography
TT – tumor thickness
HP – histopathological
NMR – nuclear magnetic resonance
MRI – magnetic resonance imaging

Current diagnostic methods are insufficiently sensitive in detecting occult nodal metastasis, which is why many patients with T1-2 N0 OSCC undergo elective neck dissection which can represent an overtreatment in patients without nodal cervical metastasis [4]. Tumor thickness (TT), compared with melanoma treatment, is increasingly used as a predictor of cervical nodal metastasis in OSCC [5]. It is measured by default on postoperative pathological specimens, but preoperative determination of TT would be very useful to avoid two-step surgery or overtreatment. Different diagnostic techniques were used for preoperative determination of TT and conflicting results were obtained [4, 5].

The aim of this study was to evaluate the use of computed tomography (CT) in preoperative determination of TT in OSCC.

Material and Methods

The study was designed as a prospective study including 65 consecutive patients (n = 65) of both sexes who underwent surgical treatment of oral cancer at the Clinic of Maxillofacial and Oral Surgery of the Clinical Center of Vojvodina, from January 2013 to December 2015. All the patients signed an informed consent for all the examinations and treatment conducted during the study. The diagnosis of oral cancer was based on the medical history, physical examination, and biopsy. According to the localization of the tumor in the oral cavity, patients were divided into five groups: tumors on the tongue, on the floor of the mouth, on the hard palate, on the gingiva, and on the buccal mucosa. The TNM cancer staging was based on clinical examination. The radiological TNM cancer staging was done by CT of the head, neck, and chest, which provided reliable data about the tumor size. The patients with lung metastasis were excluded from the study. After obtaining clinical findings and CT results, the patients' treatment was planned based on their TNM status. The TT was measured on the coronal CT scans **(Figure 1a)**. The surgically resected tumor specimens were fixed on the surface of polystyrene and marked according to the localization in the mouth and according to the regions of the neck of the neck samples. After measuring tumor diameters, they were fixed with formalin and embedded in paraffin. The tissue sections were stained with hematoxylin and eosin. Postoperative pathological examination was performed by the same experienced pathologist. The TT was determined by CT examination and by the pathologist performing the postoperative histopathological (HP) analysis **(Figure 1b)**.

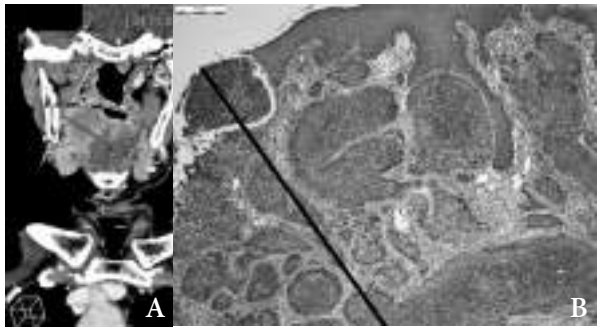


Figure 1. Determination of TT in OSCC by CT (A) and HP measurements (B)
Slika 1. *Određivanje debljine tumora oralnog skvamocelularnog karcinoma korišćenjem kompjuterizovane tomografije (A) i patohistološkim merenjem (B)*

The statistical analysis of the collected data was performed by using appropriate methods. Variables were summarized by descriptive statistics. Mean, median, standard deviation, minimum and maximum values were computed for numerical variables, while categorical variables were summarized by percentages. Normality of variables was tested by the Shapiro Wilk test. Bland-Altman plot was used to validate the agreement between two variables. To access linear relationship between variables, correlation analysis and linear regression were performed. All tests were conducted with a statistical significance level of $p < 0.05$. The IBM SPSS 20 software was used for quantitative data analysis.

Results

In total, 65 patients were included in the study. The median age was 59.65 years (range 38 - 84). There were 12 females (18%) and 53 (82%) males. Alcohol consumption was reported by 69% of patients. Regarding smoking habits, 17% of patients were non-smokers, and 83% were smokers. The pathologically positive nodal disease was reported in 41.2%. Clinical stages I, II, III, and IVa and IVb were reported in 9%, 26%, 23%, 22%, and 20%, respectively. The mean follow-up duration was 36.2 months (± standard error 4.7). Overall, 25.1% of patients died from any cause in this cohort. In 32 patients the primary tumor localized on the tongue, 22 on the floor of the mouth, in 4 on the hard palate, in 4 on the gingiva, and in 3 on the buccal mucosa.

Tumor thickness - pathological and radiological correlation

The mean postoperative final pathological TT was 1.345 cm while the mean CT TT was 1.527 cm. Relevant descriptive measures are provided in **Table 1.**

The relationship between CT thickness and HP thickness was positive, moderately correlated and statistically significant **(Table 2, Graph 1)**.

Next, a regression model was built with CT TT as predictor of HP TT **(Table 3)**. The model is adequate and it confirms that CT TT can predict HP TT. Results show that explanation of models is 30%. According to the results, higher CT TT increases HP TT.

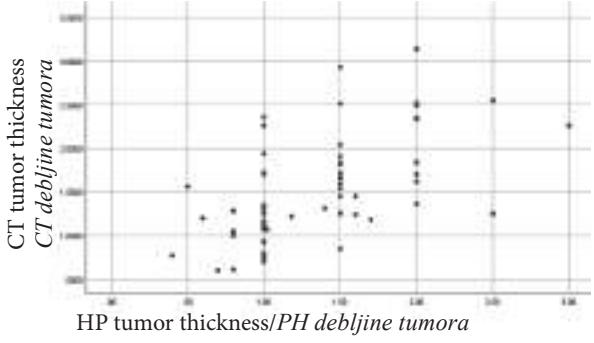
Table 1. Parameters obtained by computed tomography (CT) and histopathology (HP)
Tabela 1. *Parametri određeni kompjuterizovanom tomografijom (CT) i na osnovu patohistoloških merenja (PH)*

	No. *Br.*	Minimum *Minimum*	Maximum *Maksimum*	Mean *Srednja*	Std. Deviation *Std. devijacija*
CT tumor size A (cm)/*CT dimenzija A (cm)*	65	1.5000	8.0000	3.543077	1.0414787
CT tumor size B (cm)/*CT dimenzija B (cm)*	65	1.0000	4.0000	2.095385	.6462466
CT tumor thickness (cm)/*CT debljina tumora (cm)*	65	.6000	3.1400	1.527077	.5834534
Valid N (listwise)/*Validan broj (sa svim podacima)*	65				
	No. *Br.*	Minimum *Minimum*	Maximum *Maksimum*	Mean *Srednja*	Std. Deviation *Std. devijacija*
HP tumor size A/*patohistoloških dimenzija tumora A (cm)*	65	1.0	8.0	3.192	1.4185
HP tumor size B/*patohistoloških dimenzija tumora B (cm)*	65	.2000	7.0000	2.226154	1.0023842
HP tumor thickness/*patohistoloških debljina tumora (cm)*	65	.40	3.00	1.3446	.50704
Valid N (listwise)/*Validan broj (sa svim podacima)*	65				

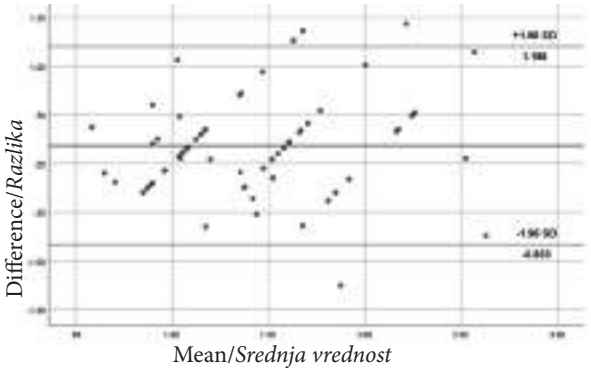
Table 2. Correlation of parameters obtained by computed tomography (CT) and histopathology (HP)
Tabela 2. *Korelacija parametara određenih kompjuterizovanom tomografijom (CT) i na osnovu patohistoloških merenja (PH)*

			CT tumor thickness (cm) *CT debljina tumora (cm)*	HP tumor thickness (cm) *PH debljina tumora (cm)*
Spearman's rho *Spearmanov rho*	CT tumor thickness (cm) *CT debljina tumora (cm)*	Correlation coefficient *Koeficijent korelacije*	1.000	.581**
		p (two-tailed test) *p (dvosmerni test)*	.	.000
		No./*Br.*	65	65
	HP tumor thickness (cm) *PH debljina tumora (cm)*	Correlation Coefficient *Koeficijent korelacije*	.581**	1.000
		p (two-tailed test) *p (dvosmerni test)*	.000	.
		No./*Br.*	65	65

Legend: **Correlation is significant at the 0.01 level (two-tailed)/*Legenda*: ** *Korelacija je značajna na nivou 0,01 (dvosmerni test)*



Graph 1. Correlation between CT tumor thickness and HP tumor thickness
Grafikon 1. *Korelacija između debljine tumora određene kompjuterizovanom tomografijom i patohistološkim merenjem*



Graph 2. Bland-Altman plot of differences between CT and HP tumor thickness
Grafikon 2. *Blad Altmanov grafikon razlika debljine tumora određene kompjuterizovanom tomografijom i patohistološkim merenjem*

The Bland-Altman, i.e. mean-difference or limits of agreement, plot to compare CT TT and HP TT is shown in **Graph 2**.

Discussion

In order to achieve better classification of patients with OSCC and develop a system for prediction of occult cervical metastases, different qualitative and quantitative parameters that describe the tumor itself are used, and one of them is TT. For surgeons, preoperative determination of TT is very important, so that they can plan surgical therapy and avoid two-step surgery. To date, preoperative establishment of TT has never become a standard procedure. Several methods have

Table 3. Regression model
Tabela 3. *Regresioni model*

R = 0.556; R^2 = 0.309; MS = 5.083; F = 28.164; df = 54; p = 0.001					
Model/*Model*	Unstandardized coefficients *Nestandardizovani koeficijent*		Standardized coefficients *Standardizovani koeficijent*	t	p/*p*
	B/*B*	Std. error/*Std. greška*	Beta/*Beta*		
1 Constant/*Konstanta*	0.607	0.149		4.084	.000
CT tumor thickness/*debljina tumora određena kompjuterizovanom tomografijom (cm)*	0.483	0.091	0.556	5.307	.000

Dependent variable: HP tumor thickness (cm)/*Zavisna varijabla: patohistološka debljina tumora*

been investigated: intraoral ultrasonography, nuclear magnetic resonance (NMR), and CT imaging.

Intraoral ultrasonography is used for predicting preoperative TT. Kodama et al. measured TT intraoperatively using intraoral ultrasound in 13 patients with biopsy-proven OSCC of the tongue [6]. They also marked the parts which were 1cm from the greatest thickness of tumor invasion with needles in order to determine the precise surgical margins. The Pearson's correlation test was used to compare ultrasound and HP measured TT, and a high degree of correlation was found, namely 91.4 - 98.2%. Intraoperative ultrasound of the tongue has been proven to be very reliable for determination of tissue characteristics and depth of tumor invasion in patients with squamous cell carcinoma (SCC) of the tongue [6].

Shintani et al. described the correlation between preoperatively determined TT by intraoral ultrasound and the pathological postoperative TT in oral tongue carcinoma [7]. The limitations of this method are tenderness, trismus, and anatomical localization which may make it difficult to place the ultrasound probe. In tumors thicker than 20 mm, there was a discrepancy between HP and ultrasound-determined TT both due to the limitation of ultrasound transducers and due to tissue shrinkage during fixation and HP preparation [8, 9].

In addition to intraoral ultrasound, other techniques that may be used for measuring preoperative TT in oral cancer were investigated. One of them is NMR. This technique was also used to measure the thickness of OSCC tumors as a superior technique compared to ultrasound measurement. Lam et al. showed the importance of NMR in determining TT in their study. The study included 18 patients with OSCC located on the tongue that underwent preoperative NMR. The TT obtained on images at T1 and T2 time was compared with TT determined by HP after glossectomy [10]. At both times, the tumor had complementary characteristics with the images obtained by NMR examination. Using the Pearson's correlation test, they found a statistically significant correlation between these two parameters; there was a significant correlation between the value obtained by measuring at T1 time and HP TT (R = 0.938) and concluded that NMR examination of patients with SCC of the tongue could be performed preoperatively to determine TT, and they also recommended this technique for planning surgery in patients with OSCC. Preda et al. examined the correlation between TT measured during NMR examination and HP measured TT in 33 patients with OSCC located on the mobile part of the tongue [11]. They also observed a statistical association between TT and the occurrence of ipsilateral or contralateral nodal cervical metastases. They found a high correlation between TT measured by NMR and TT measured by HP measurement, as well as an association between TT and the occurrence of nodal cervical metastases: they recommended that tumor depth of ≥ 5 mm indicated ipsilateral neck dissection and tongue tumors of ≥ 20 mm indicated bilateral neck dissection [11]. Most of the studies reported in the literature covering the measurement of OSCC TT by NMR examination focus on SCC of the mobile part of the tongue. The NMR is a technique that is superior to CT examination, since it provides excellent soft-tissue resolution, excellent visualization of all structures in the oral cavity, and shows tumor invasion of bones very early, even before CT scan, and the patient is not exposed to radiation as in CT examination. The NMR examination shows more detailed data on the degree of tumor extension as well as on the cervical nodal status in head and neck tumors. Data on a strong correlation between HP TT and TT measured by NMR can be found in the literature [12, 13]. Alsaffar et al. in particular, reported that there was a strong correlation between these two parameters in tumors with a greater thickness. In their study, which included 53 patients with OSCC of the tongue, a strong correlation between radiologically and HP measured TT was found in tumors with thickness ≥ 5 mm, while in tumors less than 5 mm thick, the radiological correlation between clinical and HP TT was weak [14]. The problem about NMR technique is that it is less accessible to healthcare facilities in comparison to ultrasonography or CT, it is more expensive, lasts longer, it is uncomfortable for patients, and cannot be used in case of claustrophobic patients [12, 13]. Therefore, it can be concluded that this technique of measuring OSCC TT cannot yet be enforced as the standard in planning OSCC treatment.

The CT is now believed to be the standard in staging OSCC and this radiological method is now available in almost all health care institutions. Nowadays,

CT is a widely used method for the diagnosis and planning of treatment of patients with OSCC. It is a non-invasive, accessible method that visualizes soft tissues, bones, and blood vessels as well. Also, CT is fast, cost-effective and, unlike magnetic resonance imaging (MRI), patients with implanted medical metal implants can undergo this examination. It lasts shorter than MRI and it is therefore more comfortable for patients. The disadvantage of CT examination is the high dose of radiation, as well as the possibility of allergic reaction to the contrast agent, which may occur in some patients. The CT examination should be avoided in case of severe diabetics or patients with renal impairment, because the contrast agent may impair the renal function. During the CT examination of patients with OSCC, the surgeon obtains information on the size of the tumor, the degree of tumor invasion, the relationship between the tumor and the vascular components, the condition of bones of the upper and lower jaw, and nodal cervical status. In addition to ultrasound and NMR, the literature also mentions the use of CT in determining preoperative TT in patients with oral planocellular carcinoma. The most accurate measurement of TT from its surface to its deepest point can be performed on coronal images and is expressed in mm.

Our data set is comparable to the group of patients analyzed by Madama et al. They included 116 patients treated for OSCC, of whom 50 were women and 66 men. In their study, 27.2% of patients were smokers, while 35.1% were ex-smokers. Of the total number, 41.2% of patients had nodal cervical metastases and in our study 46.15% of patients had nodal cervical metastases. The average TT measured by CT in their study was 12.88 mm, while in our study it was 15.27 mm. The average TT measured by HP measurement in the Madama's study was 11.60 mm, while in our study it was 13.45 mm (1.345 cm). Madama's study showed a statistically highly significant correlation between preoperatively and postoperatively measured TT (Spearman $r = 0.755$, $p < 0.001$) [15].

The estimation of TT by using different imaging methods has not been discussed sufficiently. Authors who have studied this issue have presented different results. The study about utilization of NMR in determination of TT in different oral carcinoma localizations was performed by Park et al. Their study showed a strong correlation between TT measured by NMR and postoperatively on HP specimens of the tongue, tongue base, and tonsil cancers (Pearson's correlation coefficient was 0.949, 0.941, and 0.578) [16]. This study is also significant because it proved the existence of correlation between TT measured by NMR and existence of cervical lymph node metastasis with cut-off values of 9.5 mm and 14.5 mm, respectively [16]. On the other hand, they found that the histological mean TT was less than TT determined by NMR. They explained this result by tissue shrinkage after resection and processing, which was previously reported in the literature [15, 16].

However, Lwin et al. reported contradictory views on this issue. In their study, NMR was used for determination of TT preoperativly, and they concluded that TT measured by NMR could not precisely determine the indication for neck dissection in OSCC. What is interesting is that they reported a total of 11 tumors, from 2 to 24 mm in size, which were clinically evident but immeasurable by NMR [17].

Conclusion

The results of this study support the use of computed tomography in the assessment of tumor thickness in patients with oral squamous cell carcinoma. It is important to emphasize the importance of preoperative detailed imaging evaluation of patients in order to avoid multiple surgical procedures, significant morbidity, and unnecessary costs.

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FEVER AND SEPSIS – DANGEROUS CONTROVERSIES

GROZNICA I SEPSA – OPASNE KONTROVERZE

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Summary

Introduction. Sepsis is the body's response to infection, leading to tissue and organ damage. Although fever was considered to be an important sign of sepsis, it has been shown that half of the critically ill patients with sepsis do not have fever at the time of diagnosis. Absence of high body temperature may be a serious disruption of the thermoregulatory response to infection and therefore a reflection of the disease severity. The aim of this study was to determine the percentage of patients with sepsis without fever, and to compare the clinical presentation and outcome of the disease in febrile and afebrile patients. **Material and Methods.** A retrospective study included 597 patients with sepsis who were divided into two groups: the first included patients with elevated body temperature (≥ 37.7 °C) and the second included patients who were afebrile (< 37.7 °C). Demographic data, clinical, laboratory and microbiological data, gas analysis parameters, length of hospitalization, and data on the disease outcome were collected and analyzed for all patients. **Results**. The results show that 41.9% of patients with sepsis did not have fever in the first 24 hours of hospitalization. In the group of afebrile patients, the average age was higher (67.38 ± 14.63 vs. 61.38 ± 18.96 years; $p < 0.001$) and comorbidities were more common. Patients with elevated body temperature had a significantly lower degree of organ dysfunction measured by the Sequential Organ Failure Assessment score compared to afebrile patients. There were 29.2% of patients with lethal outcome in the group of afebrile patients compared to 18.4% of deceased febrile patients. **Conclusion**. We conclude that the absence of fever does not rule out the diagnosis of sepsis, but on the contrary, it is associated with greater organ dysfunction and higher mortality, while the elderly are a particularly vulnerable group.

Key words: Fever; Sepsis; Body Temperature; Prognosis; Organ Dysfunction Scores; Risk Factors

Sažetak

Uvod. Sepsa predstavlja odgovor organizma na infekciju, dovodeći do oštećenja tkiva i organa. Iako se smatralo da je febrilnost vrlo važan znak sepse, dokazano je da polovina kritično bolesnih pacijenata sa sepsom nema povišenu telesnu temperaturu u momentu postavljnja dijagnoze sepse. Neuspeh povećanja telesne temperature može predstavljati ozbiljan poremećaj termoregulacionog odgovora na infekciju i samim tim odraz ozbiljnosti bolesti. Ciljevi ovog israživanja su utvrđivanje procenta obolelih od sepse bez povišene telesne temperature i poređenje kliničke slike i ishoda bolesti u odnosu na bolesnike sa povišenom telesnom temperaturom. **Materijal i metode.** Retrospektivnom studijom je obuhvaćeno 597 pacijenata obolelih od sepse, a pacijenti su podeljeni u dve grupe, od kojih je prva obuhvatala pacijente sa povišenom telesnom temperaturom (≥ 37,7° C), a druga grupa pacijente koji su afebrilni (< 37,7° C). Za sve pacijente prikupljeni su i analizirani demografski podaci, podaci o kliničkim i laboratorijskim vrednostima, parametri gasnih analiza kao i podaci o uzročniku bolesti, dužina hospitalizacije i podaci o ishodu bolesti. **Rezultati.** Rezultati pokazuju da čak 41,9% pacijenata obolelih od sepse nije imalo povišenu temperaturu u prvih 24 h hospitalizacije. U grupi afebrilnih bolesnika veća je prosečna starost i češći su komorbditeti. Oboleli sa povišenom telesnom temperaturom imali su značajno manji stepen organske disfunkcije meren Skorom za sekvencijalnu procenu otkazivanja organa u odnosu na afebrilne bolesnike. U grupi afebrilnih bolesnika preminulo je njih 29,2%, naspram18,4% preminulih febrilnih pacijenata. **Zaključak**. Odsustvo febrilnosti ne isključuje dijagnozu sepse, već nasuprot tome, povezuje se sa većom organskom disfunkcijom i većim mortalitetom, pri čemu posebno izloženu kategoriju čine stariji bolesnici.

Ključne reči: groznica; sepsa; telesna temperatura; prognoza; SOFA skor; faktori rizika

Introduction

Sepsis is defined as a life-threatening dysfunction of organs caused by the inappropriate response of the body to infection [1 - 3]. The definition of sepsis has changed, from the first definition in 1992, which implied the fulfillment of at least two criteria of systemic inflammatory response syndrome (SIRS), to the definition which is used today (SEPSIS-3) that implies dysfunction of organs caused by infection. As a measure of organ dysfunction, the increase of sequential organ failure assessment (SOFA) score by two or more points has been proposed [4, 5]. If it is not recognized in time and adequately treated, it can lead to septic shock, organ failure, and death [6]. Even though it represents one of the leading symptoms of sepsis, elevated body temperature does not occur in all patients [6–8]. The febrile response, in

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Abbreviations
SIRS – systemic inflammatory response syndrome
SOFA – sequential organ failure assessment

which the elevated body temperature is just a component, presents a complex physiological reaction that includes creation of immune reactants and the activation of numerous physiological, endocrinological, and immune components [1]. Since the definition of the disease changed in the last 40 years, the place and role of fever as a diagnostic parameter of sepsis has also changed, thus elevated body temperature was one of the four SIRS criteria for diagnosing sepsis [4, 10–13]. Although fever was considered to be an important sign of sepsis, it has been proven that half of the critically ill patients with sepsis do not have an elevated body temperature at the time of the diagnosis [14–16]. The results of recently conducted researches point to the fact that the absence of fever may represent a serious disorder of the thermoregulatory response to infection, therefore a reflection of the severity of the disease, suggesting the patient's immune status could be assessed based on the body temperature [14, 17, 18]. All of this has influenced the decision not to mention fever as a diagnostic parameter in the new criteria for diagnosing sepsis [11].

The aim of this research was to determine the distribution of afebrile patients with sepsis, to compare the severity of the clinical presentation of sepsis between febrile and afebrile patients, and to examine the prognostic significance of the body temperature in evaluating the outcome of sepsis.

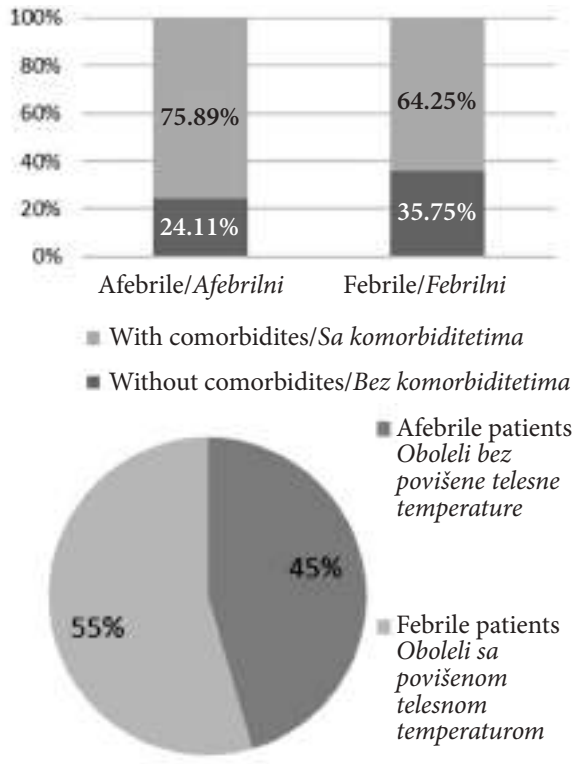
Material and Methods

The retrospective study included 597 patients diagnosed with sepsis and treated at the Clinic of Infectious Diseases of the Clinical Center of Vojvodina, during the period from January 2010 to December 2019. The data were collected from medical histories and entered into a specially created database. The study was approved by the Medical Ethics Committee of the Clinical Center of Vojvodina (number 00-47/2020). The inclusion criteria were: diagnosis of sepsis according to the SEPSIS-3 criteria [10] (the increase of the SOFA score by > 2 points, as a consequence of the infection) and the age of 18 years and over. All data were collected and analyzed from the medical records. Also, the data of clinical and laboratory test results of routinely measured parameters were recorded in the first 24 hours of hospitalization. The aforementioned laboratory tests were performed by using standard procedures at the Center for Laboratory Diagnostics of the Clinical Center of Vojvodina and the microbiology laboratory of the Institute of Public Health of Vojvodina.

Patients who met the inclusion criteria were divided into two groups: the first group included patients with elevated body temperature in the first 24 hours of hospitalization (≥ 37.7 °C) and the second group included patients who were afebrile in the first 24 hours of hospitalization (< 37.7 °C). This is in accordance with modern textbooks of infectious diseases and internal medicine stating that the normal body temperature is up to 37.2 °C in the morning, and up to 37.7 °C in the evening [1, 2]. Considering the fact that there is a circadian rhythm of body temperature, which is lowest at 6 a.m. and the highest during the afternoon hours, between 4 and 5 p.m. [1], as well as the fact that antipyretics were used to lower the elevated temperature, the highest recorded value in the first 24 hours of hospitalization was taken as the representative value of the body temperature. Statistical data processing was done using SPSS v. 23.0 program.

Results

The ratio between febrile and afebrile patients with sepsis and the prevalence of comorbidities among the mentioned groups is shown in **Graph 1**. Gender distribution, comorbidities, and fatal outcome among afebrile and febrile sepsis patients are shown in **Table 1**. The average age in febrile patients was 61.38 ± 18.96 years, while the average age in afebrile patients was 67.38 ± 14.63 years. Correlation analysis confirms the connection between body temperature and age. Namely, age statistically signifi-



Graph 1. The ratio between the febrile and afebrile patients with sepsis and the prevalence of comorbidities among the groups
Grafikon 1. *Odnos između febrilnih i afebrilnih pacijenata sa dijagnozom sepse i prevalencija komorbiditeta između grupa*

Table 1. Gender distribution, comorbidities, and fatal outcome among the afebrile and febrile patients with sepsis
Tabela 1*. Pol, komorbiditeti i smrtni ishod između febrilnih i afebrilnih pacijenata obolelih od sepse*

Comorbidity *Komorbiditeti*		Afebrile/*Afebrilni*		Febrile/*Febrilni*		Total/*Ukupno*		p/*p*
		No./*Br.*	%	No./*Br.*	%	No./*Br.*	%	
Hypertension *Hipertenzija*	Yes/*Da*	128	50.4	126	49.6	254	42.5	<0.001
	No/*Ne*	122	35.6	221	64.4	343	57.5	
Diabetes mellitus *Dijabetes melitus*	Yes/*Da*	78	50.0	78	50.0	156	26.1	0.017
	No/*Ne*	172	39.0	269	61.0	441	73.9	
Malignancy *Malignitet*	Yes/*Da*	24	40.7	35	59.3	59	9.9	0.835
	No/*Ne*	226	42.1	311	57.9	537	901	
Chronic renal insufficiency *Hronična bubrežna insuficijencija*	Yes/*Da*	49	79.1	13	20.9	62	10.4	0.009
	No/*Ne*	201	37.6	334	62.4	535	89.6	
Hematologic disease *Hematološko oboljenje*	Yes/*Da*	10	41.7	14	58.3	24	4.0	0.394
	No/*Ne*	240	41.9	333	58.1	573	96.0	
Liver cirrhosis *Ciroza jetre*	Yes/*Da*	4	36.4	7	63.6	11	2.2	0.636
	No/*Ne*	246	42.0	340	58.0	586	87.8	
Male/*Muškarci*		132	52.8	193	55.6	325	54.4	0.424
Female/*Žene*		118	47.2	154	44.4	272	45.6	
Total male + female/*Ukupno muškarci+žene*		250	100	347	100	597	100	
Fatal outcome/*Smrtni ishod*		73	29.2	64	18.4	137	22.9	0.002
Favorable outcome/*Povoljan ishod*		177	70.8	283	81.6	460	77.1	
Fatal outcome (younger than 65 years) *Smrtni ishod (mlađi od 65 godina)*		15	17.4	14	8.6	29	11.7	0.040
Favorable outcome (younger than 65 years) *Povoljan ishod (mlađi od 65 godina)*		71	82.6	148	91.4	460	88.3	

Table 2. Values of mean arterial pressure, heart rate, respiratory rate, Glasgow coma score and laboratory parameters of inflammation in the observed groups of patients
Tabela 2*. Vrednosti srednjeg arterijskog pritiska, srčane frekvencije, respiratorne frekvencije, Glasgow koma skora i laboratorijskih parametara između posmatranih grupa pacijenata*

Parameter/*Parametar*	Group/*Grupa*	Median/*Medijana*	IQR*	p/*p*
MAP* [mmHg]	Afebrile/*Afebrilni*	85	73 - 100	0.862
	Febrile/*Febrilni*	85	73 - 97	
RR*	Afebrile/*Afebrilni*	16	14 - 18	0.268
	Febrile/*Febrilni*	17	14 - 19	
HR*	Afebrile/*Afebrilni*	89	80 - 100	0.013
	Febrile/*Febrilni*	90	80 - 105	
GCS*	Afebrile/*Afebrilni*	15	14 - 15	0.210
	Febrile/*Febrilni*	15	14 - 15	
WBCs* [$10^9 10^9$/l]	Afebrile/*Afebrilni*	12.94	8.47 - 19.04	0.318
	Febrile/*Febrilni*	12.40	8.43 - 17.40	
NEUT* (aps.br) [$10^9 10^9$/l]	Afebrile/*Afebrilni*	11.15	6.87 - 16.84	0.464
	Febrile/*Febrilni*	10.40	7.03 - 15.14	
LYMPH* (aps.br) [$10^9 10^9$/l]	Afebrile/*Afebrilni*	0.90	0.52 - 1.34	0.941
	Febrile/*Febrilni*	0.91	0.51 - 1.32	
CRP* [mg/l]	Afebrile/*Afebrilni*	203.70	122 - 293.20	0.970
	Febrile/*Febrilni*	208.50	135.92 - 279.95	
PCT* [ng/ml]	Afebrile/*Afebrilni*	12.43	3.12 - 38.18	0.113
	Febrile/*Febrilni*	8.07	1.95 - 36.17	
Fibrinogen [mmol/l]	Afebrile/*Afebrilni*	5.79	4.35 - 6.90	0.006
	Febrile/*Febrilni*	6.08	5 - 7.60	

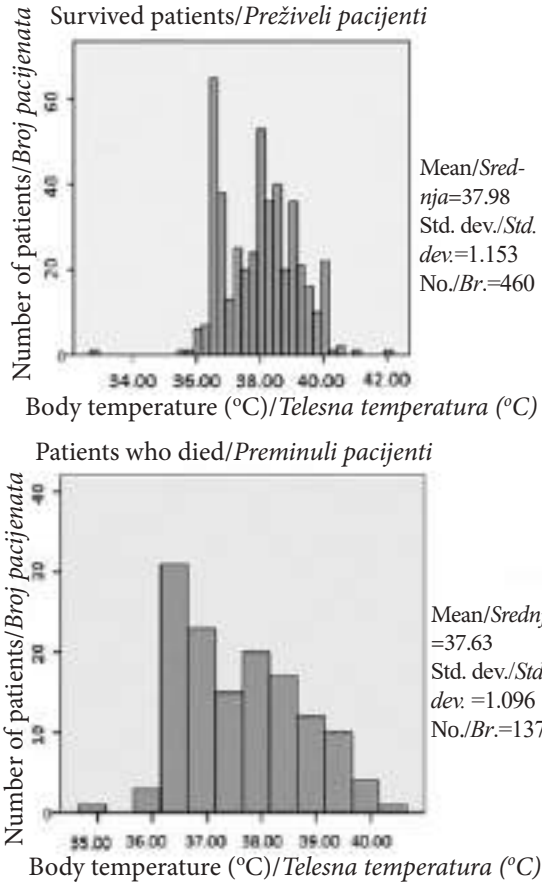
Legend: *MAP - mean arterial pressure; *HR - heart rate; *RR - respiratory rate; *GCS - Glasgow coma score; WBCs - white blood cells; *NEUT - neutrophils; *LYMPH - lymphocytes; *CRP - C-reactive protein; *PCT - procalcitonin; *IQR - interquartile range
*Legenda: *MAP - srednji arterijski pritisak; *HR - srčana frekvencija; *RR - respiratorna frekvencija; *GCS - Glasgov koma skor; WBCs - leukociti; *NEUT - neutrofili; *LYMPH - limfociti; *CRP - C-reaktivni protein; *PCT – procalcitonin; IQR - interkvartilni raspon*

Table 3. Degree of organ dysfunction in the studied groups of patients
Tabela 3. *Stepen organske disfunkcije između dve ispitivane grupe pacijenata*

	Group/Grupa	No./*Br.*	Arithmetic mean/*Aritmetička sredina*	Standard deviation/*Standardna devijacija*	p/*p*
SOFA	Afebrile/*Afebrilni*	250	4.36	2.69	< 0.001
	Febrile/*Febrilni*	347	3.62	2.17	
qSOFA	Afebrile/*Afebrilni*	250	0.88	0.82	0.620
	Febrile/*Febrilni*	347	0.85	0.86	
SIRS	Afebrile/*Afebrilni*	250	1.292	0.86	< 0.001
	Febrile/*Febrilni*	347	2.052	0.91	

Legenda: SOFA – Skor za sekvencijalnu procenu otkazivanja organa, SIRS – Sindrom sistemskog inflamatornog odgovora

cantly negatively correlated with body temperature in septic patients (Spearman's correlation coefficient is - 0.145, p < 0.001). Values of mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), Glasgow coma score (GCS), and laboratory parameters of inflammation in the observed groups of patients are shown in **Table 2**. The laboratory parameters of inflammation did not differ between the observed groups of patients. Patients with elevated body temperature had higher HR values **(Table 2)**. Compared to afebrile patients, patients with elevated body temperature had a significantly lower degree of organ dysfunction measured by the SOFA score. Also, these patients had higher SIRS values, which was expected given that fever is one of the SIRS criteria **(Table 3)**. The mean temperature value in patients who died was 37.6 ± 1.09, while in the group of survivors it was statistically significantly higher at 38.0 ± 1.15 ºC (p = 0.002) **(Graph 2)**.



Graph 2. Distribution of the highest measured body temperatures in the first 24 hours of hospitalization in patients who survived and patients who died
Grafikon 2. *Distribucija najviše izmerene telesne temperature u prva 24h hospitalizacije kod pacijenata koji su preživeli i kod pacijenata koji su preminuli*

Discussion

Our study shows that two of five patients diagnosed with sepsis did not have a body temperature above 37.7 °C. One of the reasons for excluding this parameter from the definitions of sepsis, as well as the clinically significant scores used for diagnosis (SOFA and quick SOFA), is probably the high percentage of sepsis cases with normal body temperature [11, 12]. Results similar to ours were reported by Bhavani et al. where 61.87% of patients did not develop high temperature; while in the study by Drewry et al. 52.17% of patients did not develop elevated body temperature [14, 17].

According to our data, fever was absent statistically significantly more often in older patients with sepsis than in younger patients which coincides with the results of the study by Bhavani et al., where the average age in the febrile group with rapid/slow rise in temperature was 54/56 years, while the average age in normothermic and hypothermic patients was 60 and 63 years [17]. Such data are in line with literature data claiming that old people are more often immunocompromised [1, 19]. A research by Norman DC et al. showed that the elderly, due to their "physiological immunodeficiency" often do not present with fever, leukocytosis, tachypnea or tachycardia [19–22]. In addition to the immunocompromised response, general activity decreases, causing lower daily rise in body temperature. Also, inherent mechanisms of thermoregulation are reduced. In his article, Yoshikawa T. confirmed that infections are one of the leading causes of morbidity and mortality in the elderly population [23]. The presence of comorbidities is observed in a significantly higher percentage of afebrile patients (≈3/4) compared to febrile patients (≈2/3).

This result corresponds to the results obtained in the study by Bhavani et al. [17]. One of the potential explanations is the well-known immunocompromised condition of chronically ill patients, which causes a weaker proinflammatory response, therefore lessening stimulation of the thermoregulatory center [1].

The values of the laboratory parameters show that statistically significantly lower values of fibrinogen were recorded in the group of afebrile patients. That may be interpreted as the reduced capacity of the pro-inflammatory response in these patients. The absence of differences in concentrations of other parameters of inflammation have been reported in numerous studies which confirmed these claims, and it has been pointed out that initially measured values of inflammation parameters have no prognostic significance, and that only their dynamic monitoring has prognostic significance in sepsis [24–29]. The patients with elevated body temperature had a significantly lower degree of organ dysfunction measured by the SOFA score compared to the afebrile patients, which differs from the study of Bhavani et al., where no statistically significant differences were found [17]. According to numerous literature data, a higher degree of organ dysfunction, as well as higher mortality can be associated with a weaker inflammatory response in afebrile patients [1, 2]. It is known that an increase in body temperature occurs due to pyrogenic cytokines (interleukin-1, interleukin-6, tumor necrosis alpha, interferon alpha), so the assumption is that the inability to increase body temperature is based on a weak immune response [14]. Statistically significantly higher mortality was found in the group of afebrile patients, where almost every third patient died (29.2%), compared to febrile patients, where every fifth patient died (18.4%). If we exclude patients older than 65 years, the result of higher mortality in the afebrile group does not change, like reported by other researchers [19, 30]. One advantage that is widely attributed to elevated body temperature is an immune protective mechanism. Namely, the defense against pathogens involves a tight temporal and spatial connection between the regulators of the immune system. The absence of elevated body temperature as a part of the response to infection could be a reflection of the weakened immune capacities of the individual, regardless of his/her age, indicating the necessity of greater caution in the treatment of these patients, their intensive monitoring, and a greater possibility of a complicated course and outcome of the disease.

Conclusion

Two out of five patients diagnosed with sepsis presented with a normal body temperature. Elevated body temperature, as a clinical symptom of sepsis, is more often absent in the elderly.

In the group of afebrile patients, a higher percentage of people presented with comorbidities. Afebrile patients have statistically significantly lower values of fibrinogen than febrile patients, while the mean values of other parameters of inflammation were not statistically significantly different in the observed groups of patients. Afebrile patients with sepsis showed a higher degree of organ dysfunction. Higher mortality was recorded in the group of afebrile patients compared to the group of febrile patients.

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MODERN CONCEPTS OF IMPROVING PROCEDURES AND PROCESESS IN HEALTHCARE FACILITIES – EFFECTS OF THE LEAN CONCEPT

SAVREMENI KONCEPTI UNAPREĐENJA PROCEDURA I PROCESA U ZDRAVSTVENIM ORGANIZACIJAMA – UTICAJ LEAN KONCEPTA

Edin MEĐEDOVIĆ[1-3], Sabina ŠEHIĆ KRŠLAK[4], Zlatan ZVIZDIĆ[5], Edin BEGIĆ[3, 6], Alma SULJEVIĆ[1] and Fahira IMAMOVIĆ[1]

Summary

Introduction. Lean principles have been successfully adapted to the healthcare environment, enabling hospitals and clinics to streamline their operations and focus on value as perceived by their patients. Many healthcare facilities have implemented lean principles to improve their efficiency. The subject of this paper is the lean concept, the essence of which is implementation of methods that affect the efficiency and quality of providing health services. Our aim was to point out the necessity of applying modern concepts in healthcare. **Material and Methods.** The primary sources of data were obtained through research on the opinions and possibility of applying the lean concept in hospitals in Bosnia and Herzegovina. We presented the results on the effectiveness of the lean concept in hospitals that apply it. **Results.** After implementation of the lean concept in an Italian hospital, the results showed a positive impact on the waiting time for admission, faster discharge, and faster flow of information. The results of the research in Bosnia and Herzegovina showed that there were positive attitudes towards the effects that would be achieved by implementing the lean concept. **Conclusion.** The implementation of the lean concept would reduce medical waste, which would positively affect the quality of health care services.

Key words: Health Services; Delivery of Health Care; Quality Improvement; Efficiency, Organizational; Evidence-Based Medicine

Sažetak

Uvod. *Lean* principi su uspešno prilagođeni zdravstvenom okruženju, omogućavajući bolnicama i klinikama da pojednostave svoje poslovanje i da se fokusiraju na vrednost koju vide njihovi pacijenti. Mnoge zdravstvene organizacije su implementirale *Lean* principe, kako bi poboljšale svoju efikasnost. **Predmet istraživanja.** Predmet istraživanja ovog rada je *Lean* koncept čija je suština određena primenom metoda koje utiču na brzinu i kvalitet pružanja zdravstvenih usluga. Cilj rada je da se ukaže na neophodnost primene savremenih koncepata u zdravstvenim organizacijama. **Materijal i metode.** Primarni izvor podataka su podaci dobijeni istraživanjem o mišljenju i mogućnosti primene *Lean* koncepta u bosanskohercegovačkim bolnicama. Prezentirani su rezultati o efikasnosti *Lean* koncepta u bolnicima koje ga primenjuju. **Rezultati.** Rezultati nakon implementacije u italijanskoj bolnici pokazuju pozitivan uticaj na vreme čekanja na prijem, brži otpust i brži protok informacija. Rezultati istraživanja u Bosni i Hercegovini pokazuju postojanje pozitivnog stava o efektima koji bi se postigli implementacijom *Lean* koncepta. **Zaključak.** Implementacija *Lean* koncepta smanjila bi „medicinska rasipanja", što bi pozitivno uticalo na kvalitet zdravstvenih usluga.

Ključne reči. zdravstveni sistem; pružanje zdravstvene nege; unapređenje kvaliteta; organizaciona efikasnost; medicina zasnovana na dokazima

Introduction

Lean concept is a system of leadership, management and organization of the work process, with a focus on eliminating all types of waste (resources, time, energy). The basic premise of lean management (LM), which has its origins in the automotive industry, is that greater efficiency can be achieved through a process of continuous improvement aimed at eliminating waste and maximizing value-adding activities [1–4]. The expected effect of the lean concept implementation is to reduce business costs, through the elimination of wastage. Implementation of modern models at the level of tertiary health care is particularly popular. Khamidullina and Puryaev claim that companies that are world leaders in their industries actively apply the lean concept [5]. It first appeared in production [6]. Pro-

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Abbreviations

BH – Bosnia and Herzegovina
LM – lean management
5S – Sorting, Simplifying, Sweeping, Standardizing, Self-Discipline
VSM – value stream mapping

duction and health care differ in many ways, but there are also similarities that enable the application of lean principles when providing health services.

The lean concept (suppliers, inputs, process, outputs, customers) has found application in the management of various organizations [7, 8], but the challenge is to apply it. Despite the successful implementation of the lean concept, many obstacles have also appeared in its application. Elkhairi et al. [9] refer to the research of Bajjou and Chafi [10] emphasizing that they classified these barriers into three different categories: economic, managerial and technical, and social. Managerial and technical barriers include lack of planning, lack of expertise, lack of top management commitment, lack of strategic perspective, and lack of understanding the lean production. The economic barrier means limited resources, and social barrier means resistance to change.

The expected improvements resulting from the implementation of the lean concept are intended for: patients, healthcare workers, and healthcare institutions.

Patients [11]:
– Decrease in the time spent in hospital
– Increase in satisfaction
– Decrease in waiting time
– Improvement of service quality
– Decrease in the number of errors
– Improvement of information flow;

Healthcare workers [12]:
– Elimination of waste
– Decrease of overtime
– Decrease of the workload
– Increase in satisfaction
– Peaceful and better organized work environment;

Healthcare institutions [13]:
– Decrease in equipment
– Increase in the number of examined patients
– Decrease in costs
– Improvement of information flow.

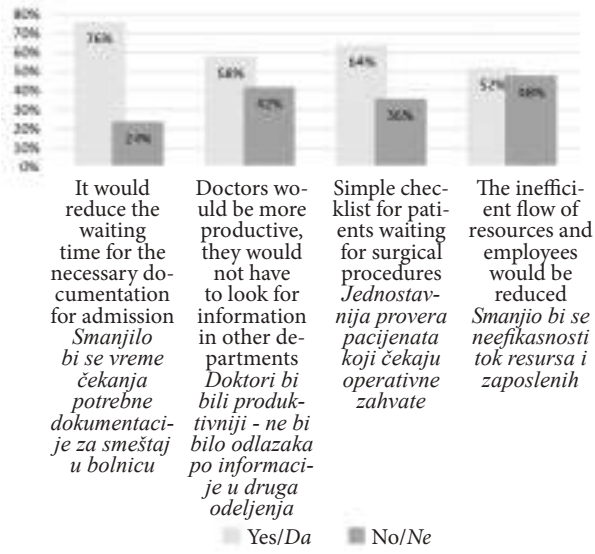
Generally, the lean concept is considered to be the "antidote" to waste in organizations [14]. Lean consists of a set of tools in identifying and eliminating waste with value stream mapping (VSM), Sorting, Simplifying, Sweeping, Standardizing, Self-Discipline (5S), Single-Minute Exchange of Die, and standardized work that focuses on aspects of the manufacturing process to eliminate waste, improve quality, reduce time and cost. Among these tools, VSM gets more attention for using process improvement with a systematic approach [15]. The VSM method is widely used in the efforts to reduce waste [16]. The research was conducted [17] by VSM approach.

Material and Methods

Data were collected from the latest relevant scientific articles and books, and health systems applying modern concepts of optimization of clinical processes were analyzed. The methods used in this paper are analytical and synthetic. The analytical method was used for the purpose of analyzing the available literature that deals with the given subject of research, and for the purpose of analyzing the obtained research results. The inductive method was used as a logical reasoning procedure, based on the analysis of research problems and research results. The deductive method was used for making conclusions about whether the goal of the research was achieved and making general conclusions reached during the research. The synthetic method was used in order to connect all elements into an integral whole and reach the general conclusion of the paper. The primary sources of data were obtained through research on the opinions and possibilities of applying the lean concept in hospitals in Bosnia and Herzegovina (BH).

Results

Graph 1 presents the opinions of healthcare workers about the effects that would be achieved by implementing the lean concept. The highest agreement is about the reduction of the waiting time for documents necessary for admission. One of the fundamental principles of the lean concept is the satisfaction of end users, in this case of patients. The second-ranked effect according to the respondents is a simple checklist for patients waiting for surgical procedures. The lowest degree of agreement among respondents is about the reduction of the inefficient flow of resources and employees **(Tables 1 and 2)**.



Graph 1. Opinions of healthcare workers about the effects that would be achieved by implementing the lean concept
Grafikon 1. *Mišljenje zdravstvenih radnika o efektima koji bi se postigli implementacijom lean koncepta*

Table 1. Examples of waste at the Department of Oncology
Tabela 1. *Primeri medicinskih rasipanja na odeljenju onkologije*

Type of wastage *Tip rasipanja*	Mislabeled tubes *Pogrešno označene epruvete*	Oncology patients *Onkološki pacijenti*
Errors/*Greške*	Unused tubes *Neiskorištene epruvete*	Inadequate therapy for the patient *Neadekvatna terapija za pacijenta*
Excess production *Višak proizvodnje*	Different sampling and testing sites *Različita mesta uzimanja uzoraka i testiranja*	Waiting for chemotherapy *Čekanje hemoteraija*
Transport/*Prevoz*	Waiting for the sample to be tested *Čekanje da se uzorak testira*	Distance between the place of residence and the place of chemotherapy/*Udaljenost između mesta stanovanja i mesta hemoterapije*
Waiting/*Čekanje*	Test reagents have expired *Isticanje roka reagensima*	Expired chemotherapy drugs *Istekli rokovi lekova za hemoterapiju*
Supplies/*Zalihe*	Too many reagents *Previše reagenasa*	Delay of patients due to overcapacity of doctors/*Kašnjenje pacijenata zbog preopterećenosti lekara*
Motion/*Kretanje*	Label printing time *Vreme štampanja nalepnica*	Nurses searching for misplaced medical supplies/*Medicinske sestre u potrazi za medicinskim materijalom*
Redundant processing *Suvišna obrada*	Repeating the entire examination due to one bad result/*Ponavljanje celog pregleda zbog jednog lošeg rezultata*	Time spent creating a schedule that is not followed/*Vreme utrošeno na kreiranje rasporeda koji se ne poštuje*
Human potentials *Ljudski resursi*	Ignoring employee ideas *Ignorisanje ideja zaposlenih*	

Table 2. Examples of successful lean implementation in hospitals [18]
Tabela 2. *Primeri uspešne implementacije lean koncepta u bolnicama [18]*

Organization/*Organizacija*	Impact/*Uticaj*
Scotland Cancer Treatment Center *Škotski centar za lečenje onkoloških bolesti*	Reduction in patient waiting times for the first appointment from an average 23 to 12 days/*Skraćivanje vremena čekanja pacijenata na prvi pregled u proseku sa 23 na 12 dana* Patient flow time improvement by 8%/*Poboljšanje usluge pacijentima za 48%*
Royal Bolton Hospital *Kraljevska Bolton bolnica*	Direct savings of £3.1 millions/*Direktne uštede 3.1 mil. funti* Reduction of time taken to process important categories of blood from 2 days to 2 hours/*Skraćivanje analiza krvi sa dva dana na dva sata* Average turnaround time in pathology from over 24 hours to 2 - 3 hours *Prosečno vreme patoloških pretraga sa preko 24 sata na 2 - 3 sata*
Nebraska Medical Centre *Medicinski centar Nebraske*	Reduced staff walking distance/*Smanjivanje prostorne udaljenosti administrativnog osoblja* Reduced lab space and specimen processing turnaround time by 20% *Smanjenje vremena laboratorijskih obrada za 20%* Reduced manpower and their transfer to other critical points/*Smanjeno premeštanje osoblja na druge kritične tačke* Decrease average patient stay from 6.29 to 5.72 days/*Smanjen prosečan boravak pacijenata sa 6,29 na 5,72 dana*
Pittsburgh General Hospital *Opšta bolnica u Pitsburgu*	Intensive care unit cost reduction by almost $0.5 million per year/*Smanjenje troškova intenzivne nege za skoro 0,5 miliona dolara godišnje* A 90% reduction in the number of recorded infections after 90 days of using a changed procedure for intravenous line insertion/*90% smanjenje broja evidentiranih infekcija nakon 90 dana primene izmenjene procedure za intravensko uvođenje linije*

Discussion

The lean concept also focuses on processes that do not add value [19]. Health care systems in BH are focused on traditional business processes. They are more precisely focused on business processes that add value. The basic principle of the lean concept is to learn to see waste. The first to observe medical wastage were Dutch and British hospitals [20, 21]. By comparing research, differences in ranking types of wastage according to priorities and according to the frequency of occurrence were analyzed. Based on the comparison of results, it can be concluded that the emphasis in Dutch and British hospitals is on improving efficiency (speed of service), while in BH health institutions, the emphasis

is more on effectiveness, i.e. on the mode of operation (reduction of defects).

The aforementioned results confirm the necessity of improving the efficiency of providing health services in BH. In BH healthcare institutions, a common obstacle to the implementation of modern models is the lack of motivation. In British and Dutch hospitals, recognized wastages are eliminated through modern improvement concepts and integral indicators are applied: process efficiency and workforce productivity. In BH health institutions, it is necessary to work more on determining indicators, above all the productivity of the workforce, which is aimed at reducing defects that are part of everyday work according to the results of the research.

According to characteristics of the situation and problems in health care systems, the solution lies in the implementation of modern business process improvement concepts [22, 23]. In support of this, the results in **Graph 1** show how employees at the tertiary level of health care see the implementation of the lean concept. The effects that the respondents expect to achieve through the implementation of the lean concept to a significant extent coincide with the effects that are evident in hospitals that apply the lean concept.

Beyond the limited range of research conducted on the human outcomes of lean concept in healthcare, the review also reveals the lack of both methodological diversity and rigor that characterizes the existing literature. Most of the included studies lacked a theoretical conceptualization of the staff related to outcomes of lean concept and were constrained by reporting descriptive results with relatively limited analytical reach.

According to different researchers, there are positive and negative classifications of the effects achieved by the implementation of the lean concept in healthcare organizations. According to some researchers, positive outcomes are: teamwork, communication, coordination learning, innovation and personal development, morale, motivation, and job satisfaction [24–28].

Furthermore, despite examining the use of multiple LM tools and techniques, only one of the studies considered lean holistically, as an organizational, system-wide approach designed to target waste and improve the production of value [29, 30]. Negative outcomes are: work intensification, job strain, anxiety, stress, and dehumanization [31, 32].

The results of this review are reflective of the broader literature on lean concept and its impact on staff working in other industries. A recent review also pointed to the restricted number of studies focusing on the impact of lean concept on employees [33]. They highlighted the inconsistent nature of the research findings on this topic. Further research that holistically examines lean concept and encompasses its socio-technical and human dimensions is therefore crucially needed, especially given the demonstrated potential of this approach that can help increase the capacity and improve the efficiency of health systems. The contribution of this research is updating the topic of the necessity of implementing modern business process improvement concepts in order to improve health services for patients at the tertiary level of health care. Based on the principles of lean thinking, the medical directorate of the Cardarelli Hospital in Naples decided to review the patient's path from arrival to the ER to admission, recovery and discharge. This path is transversal to several operating units and includes processes pertinent to hospitals and others of territorial relevance. In detail, a re-engineering process that improves the management of medical reports and the creation of a web application that provides notifications on the arrival of reports in real time have been employed and/or developed to reduce the waiting time related to the doctors' consultation.

A study by Dickson et al. on the implementation of the lean methodology at emergency departments of four public hospitals in Massachusetts, Worchester, Orlando, and Iowa City, showed that with help of the lean methodology, the patients' waiting time was reduced. The decreased waiting time directly affected the increase in the satisfaction of patients [34].

A study by Zoe Radnor showed that the implementation of this methodology at the Scotland Cancer Treatment Center resulted in a reduction of waiting time for examinations, as well as in the improvement of patient flow through the system of service provision by 48% [35]. Based on the review of the literature dealing with the research topic of the present study, a research hypothesis was formulated: application of lean concept can positively affect the efficiency of the clinical process.

The results of this review are reflective of the broader literature on lean concept and its impact on staff working in other industries. In a recent review, authors [36] also pointed to the restricted number of studies focusing on the impact of lean concept on employees. Improvements in teamwork were also self-reported by staff after LM was applied to the perioperative otolaryngology workflow in an American university hospital [37].

Whilst piecemeal implementation of the lean concept could be effective in reaching desired performance and efficiency goals, there is little evidence on the long-term sustainability of such gains [38].

Improving patient workflow was also targeted in a study performed at the Department of Radiology, Medical College of Wisconsin, USA [39]. Application of lean principles to screening mammography workflow has improved the efficiency and decreased patient waiting time. The implementation of the lean philosophy started with patient-centered approach, analyzing patients-defined valuable activities and problems to be solved. The lean tools included VSM, identification of waste, 5S tool, creation of process map, and visual management based communication. Among other things, portable electronic devices were used to verify patient identifiers, electronic work lists were formed, and images were digitized before patient`s appointment. After implementation of the lean philosophy, patient waiting time was reduced by amazing 70% (from 11.1 to 3.3 minutes). Also, total

visit length was reduced by 23.4% (from 33.7 minutes to 25.8 minutes) and reading time of a mammogram by 40% (from 4.8 minutes to 2.9 minutes per case).

The observed healthcare systems, obviously, had a high level of organization and management in the initial phase, yet they realized remarkable results thorough the lean concept, which should serve as inspiration to all the others, regardless of their present condition and performances.

The motivation and job satisfaction of healthcare workers are the basis for providing quality healthcare [40].

Conclusion

The implementation of the lean concept would reduce medical waste, which would positively affect the quality of healthcare services.

1. Reduce patient wait times (Solutions include moving to in-room testing instead of transporting patients around a facility and delivering test results via technology).

2. Manage inventory (Health care facilities can use tracking systems to understand what supplies are in high demand and order accordingly or rely on an automated order system).

3. Decrease errors (The names of tests, prescriptions, and diagnoses can often be similar. One way to reduce errors is to switch to a technology-based information system. Doctors and nurses can track patient records without relying on patient recall which may not always be accurate).

4. Elimination of overproduction (In healthcare, overproduction includes ordering unnecessary tests, providing higher levels of care than required, or having doctors perform tasks that can be done by other qualified health care providers that charge less per encounter).

5. Limit movement (Movement looks at how inventory, information, and staff move between floors and departments).

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CORRELATION BETWEEN THE PERCEIVED PAIN INTENSITY AND PSYCHOPHYSICAL TESTS IN PATIENTS WITH CHRONIC PAIN

KORELACIJA PERCIPIRANOG INTENZITETA BOLA SA PSIHOFIZIČKIM TESTOVIMA KOD PACIJENATA SA HRONIČNIM BOLOM

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Summary

Introduction. Pain perception varies due to many factors. Quantitative sensory testing is a panel of diagnostic tests used to assess somatosensory function. The aim of the study was to determine how psychophysical variables are related to the perceived pain intensity in patients with chronic pain. **Material and Methods.** The cross-sectional study included 88 subjects (average age 51.3 ± 9.4 years, 76 (86.4%) women) diagnosed with chronic pain syndrome and fibromyalgia or chronic neuropathic pain associated with lumbosacral radiculopathy. Current and average pain intensities in the past 4 weeks were rated on a numerical rating scale. Quantitative sensory testing included pressure pain thresholds, heat pain thresholds, and cold pain thresholds. Patients filled out the Fear Avoidance Component Scale, a questionnaire that examines the fear avoidance phenomenon. **Results**. The highest correlations were found between the Fear Avoidance Component Scale scores and current and average pain intensity (r = 0.438 and r = 0.253, respectively); between pain duration and current and average pain intensity in the past 4 weeks (r = 0.340 and r = 0.308, respectively). Moderate and negative correlations were found between pressure pain thresholds and current and average pain intensity (r = - 0.233 and r = -0.300, respectively). **Conclusion.** Low to moderate, significant positive correlations were found between fear-avoidance and pain intensity. Significant but low negative correlations were found between pressure pain threshold and current pain intensity, as well as between pressure pain threshold and average pain intensity.

Key words: Chronic Pain; Pain Perception; Pain Measurement; Sensory Thresholds; Avoidance Learning

Sažetak

Uvod. Percepcija bola varira usled mnogih faktora. Kvantitativno senzorno testiranje predstavlja panel dijagnostičkih testova koji procenjuju somatosenzornu funkciju. Cilj studije je bio da se utvrdi kako su psihofizičke varijable povezane sa percipiranim intenzitetom bola kod pacijenata sa hroničnim bolom. **Materijal i metode**. Studija preseka obuhvatila je 88 ispitanika (prosečne starosti 51,3 ± 9,4 godine, 76 (86,4%) žena) sa sindromom hroničnog bola, uz dijagnostikovanu fibromialgiju ili hronični neuropatski bol od lumbosakralne radikulopatije. Trenutni i prosečan intenzitet bola (u poslednje četiri nedelje) određivani su na *Numeričkoj skali bola*. Kvantitativno senzorno testiranje je uključivalo ispitivanje praga bola pritiskom, praga bola toplotom i praga bola hladnoćom. Pacijenti su popunili *Skalu komponenti izbegavanja straha*, upitnik koji ispituje fenomen izbegavanja usled straha. **Rezultati.** Najveće korelacije su dobijene između vrednosti *Skale komponenti izbegavanja* usled straha i trenutnog intenziteta bola (r = 0,438) i prosečnog intenziteta bola (r = 0,253), između trajanja bola i trenutnog intenziteta bola (r = 0,340) i prosečnog bola (r = 0,308). Nađena je umerena i negativna korelacija između praga bola na pritisak i trenutnog intenziteta bola (r = - 0,233) i prosečnog intenziteta bola (r = -0,300). **Zaključak.** Uočene su male do umerene, značajne i pozitivne korelacije između izbegavanja aktivnosti zbog straha i intenziteta bola. Prisutne su značajne, ali male negativne korelacije između praga bola na pritisak i trenutnog intenziteta bola, kao i između praga bola na pritisak i prosečnog intenziteta bola.

Ključne reči: hronični bol; percepcija bola; merenje bola; senzorni pragovi; skala izbegavanja usled straha

Introduction

Pain perception is a complex process and it is still not fully understood. There are four steps of pain pathway: transduction, transmission, modulation, and perception. Transduction (conversion) is the ability of nociceptors to convert painful stimuli (mechanical, chemical, thermal) into an action potential. Transmission is the conduction of nerve impulses of A-delta myelinated fibers and C non-myelinated fibers from nociceptors to the posterior horns of the spinal cord, and then via ascending pathways to the higher centers of the central nervous system. Modulation is the processing and transformation of nociceptive information. Perception (experiencing pain) is the phase in which there is a projection of nerve pathways for pain transmission to the cerebral cortex and the conscious experience

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Abbreviations

QST – quantitative sensory testing
NRS – numerical rating scale
PPT – pressure pain threshold
HPT – heat pain threshold
CPT – cold pain threshold
FACS – fear avoidance component scale

of pain [1]. Subcortical structures, i.e. the limbic system, are responsible for emotional reactions to pain, increased alertness, anxiety, and depression that accompany chronic pain [2]. Several cortical regions are active at the same time during pain perception; activity in the cortical pain matrix undergoes changes over time producing a complex network of pain perception. Dysfunction at any level carries the risk of developing dysregulated, persistent pain [3].

Pain perception is known to vary from person to person in the general population. Some factors, such as spontaneous neural fluctuations, attention, expectation of pain, cognitive and emotional states, sleep habits, and stress, may impact the pain perception [4]. How one experiences a painful stimulus depends on his psychological state and the influence of the environment, which may intensify it (sadness, fear) [5, 6] or alleviate it (rest, joy, social well-being, hope) [7].

Diverse processes can happen along the nociceptive pathways which may result in the gain or loss of nociceptive impulses. This change in incoming nociceptive signals may play an important role in the development of chronic pain with all known functional limitations [8–12]. Some authors believe that a phenomenon such as fear avoidance could be responsible for the transition of pain from acute to chronic [13, 14].

Psychophysical tests quantify perception based on verbal or other overt conscious responses on the part of a subject [15]. Psychophysics today is used primarily in experiments to determine absolute thresholds for various senses [16]. Skin sensation tests have been developed to detect various physical stimuli that elicit sensations of touch-pressure, vibration, cooling, warming, heat, or mechanical stimuli inducing pain, movement, or static position. In research settings or as an additional tool in the diagnosis of somatosensory disorders, such as pain insensitivity and painful and painless neuropathy, quantitative sensory testing (QST) is a panel of diagnostic tests that assess somatosensory function. The QST is a validation of various neurological tests already in use into a standardized battery intended to identify minute changes in sensory function [17]. A thorough assessment of somatosensory function is believed to help identify different types of pain and as a potential technique to detect silent neuropathy [18].

Although we can expect that lower pain thresholds are associated with higher levels of perceived pain intensity, findings in the literature are conflicting [19].

Therefore, the main goal of the present study was to determine how psychophysical variables are related to the perceived pain intensity in chronic pain patients. The additional goal was to investigate the connection between the perceived pain intensity and the level of fear-avoidance phenomenon.

Material and Methods

This cross-sectional study included 88 subjects (average age 51.3 ± 9.4 years) with chronic pain syndrome. The research was approved by the Ethics Committee of the Clinical Center of Vojvodina.

Subjects were consecutively recruited from the medical records. The inclusion criteria were: fibromyalgia or chronic neuropathic pain associated with lumbosacral radiculopathy. The diagnosis of fibromyalgia was established according to the 2016 American College of Rheumatology criteria [20] and the diagnosis of neuropathic pain associated with lumbosacral radiculopathy was established according to the criteria given by Finnerup et al. [21]. Additional inclusion criteria were average pain intensity in the past 4 weeks > 4/10, duration of pain > 3 months, and age over 18 years.

Exclusion criteria included: malignancy, back surgery in the previous 12 months, rheumatic inflammatory disorders (e.g. rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, etc.), diabetes mellitus, neurological disorders (e.g. polyneuropathy, multiple sclerosis, Parkinson disease, etc.), and patients who were using neuroleptics, strong opioids, and/or benzodiazepines regularly.

Demographic and anthropometric data included gender, age, height, weight, and education level (years of education), as well as if the patients had a partner, and how long they slept on average (in hours) in the past 4 weeks.

Subjects rated their pain intensity (current at the time of testing and average over the past 4 weeks) on a numerical pain scale (NRS). The NRS values ranged from 0, meaning no pain, to 10, meaning the worst imaginable pain. Information on pain duration (in months) was also recorded.

The QST involved examining the pressure pain threshold (PPT), heat pain threshold (HPT), and cold pain threshold (CPT) in the forearm area. The testing was conducted according to the procedure routinely performed in our laboratory [19, 22, 23]. A digital algometer (Wagner Instruments, FDX-50) with a 1 cm rubber tip was used to test PPT. The HPT and CPT were determined using the Medoc Pathway Pain and Sensory Evaluation System. The respondents were informed about the procedure and devices before the examination. Pain thresholds (PPT, HPT, and CPT) were measured in the area of the forearm opposite to the side of the painful side of the back. In case the pain was bilateral, the testing side was contralateral to the more painful side of the back. The PPT was examined on the proximal part of the body of the extensor carpi radialis longus muscle. A digital pressure algometer was applied over the standardized test sites with pressure increasing at a rate of approximately 5 N/s, and the subject said "stop" at the moment when the feeling of pressure turned into a feeling of pain, burning, stinging, or stabbing, and the value in N/cm^2 was recorded. Three measurements were made, with a 10s interval, and the average value was taken as the final value. The HPT and CPT were

Table 1. Characteristics of subjects and examined parameters
Tabela 1*. Karakteristike ispitanika i testirani parametri*

	Maximum *Maksimum*	Minimum *Minimum*	Mean *Srednja vrednost*	Standard deviation/*Standardna devijacija*
Age (years)/*Starost (godine)*	19	65	51.3	9.4
Body height (cm)/*Telesna visina (cm)*	150	193	167.5	8.5
Body mass (kg)/*Telesna masa (kg)*	50	126	76.8	15.1
Years of education/*Godine obrazovanja*	4	16	11.28	2.28
Pain duration (months)/*Trajanje bola (meseci)*	4	360	70.1	67.5
Current pain intensity (NRS)/*Trenutni intenzitet bola (NRS)*	2	10	6.85	1.99
Average intensity of pain in the past 4 weeks (NRS) *Prosečan intenzitet bola u poslednje 4 nedelje (NRS)*	3	10	7.33	1.62
FACS	12	66	60.65	18.54
Average sleep time (h)/*Prosečno vreme spavanja (h)*	3	8	5.65	1.31
PPT (N/cm^2)	7.3	56.2	25.39	9.32
HPT (^oC)	33.1	48.7	40.26	4.60
CPT (^oC)	0	31.2	18.81	9.54

Legend: NRS - numerical rating scale; FACS – Fear Avoidance Component Scale; PPT - pressure pain threshold; HPT - heat pain threshold; CPT - cold pain threshold
Legenda: NRS - numerička skala bola, FACS – skala komponenti izbegavanja aktivnosti usled straha, PPT – prag bola za pritisak, HPT – prag bola za toplo, CPT – prag bola za hladno

examined on the proximal volar forearm (C8 dermatome). During the HPT/CPT testing, the applied temperature via thermode was gradually increased or decreased, and the subject pressed the stop button immediately when the sensation of heat or cold changed to a sensation of pain, burning, stinging, or stabbing. Four stimuli for hot and then 4 stimuli for cold were performed with an intermediate interval of 10 s, and mean values of the last 3 measurements were taken as the final value of HPT and CPT.

All subjects were instructed not to consume alcohol, take analgesics or sedatives, or engage in intense physical activity 24 hours before the test [19, 22, 23]. Also, it was necessary for them to get enough sleep the night before and not to consume caffeine products 4 hours before the test.

In addition, patients filled out the Fear Avoidance Component Scale (FACS) questionnaire which examines the fear avoidance phenomenon. The FACS included 20 items on a six-point Likert scale from 0 (strongly disagree) to 5 (strongly agree). The FACS score ranges from 0 to 100, where the higher score indicates a greater degree of avoidance [14, 24, 25].

The SPSS 20.0 software package was used for data processing. For the analysis and description of the sample in regard to relevant variables, frequency and percentage displays were used. Descriptive statistics methods were used to determine measures of central tendency (arithmetic mean) and measures of variability (standard deviation). To determine the degree of connection between variables, Pearson's correlation coefficient was used, and Cohen's criteria were used for interpretation (small $r < 0.29$, medium $0.3 < r < 0.49$, large $r > 0.5$). The overall significance level was set at $p < 0.05$.

Results

The sample included 88 patients and the majority of respondents were women (76, 86.4%) **(Table 1).** The study sample included patients with fibromyalgia (45, 51.1%) and patients with neuropathic pain due to lumbosacral radiculopathy (43, 48.9%). In the group with neuropathic pain due to lumbosacral radiculopathy, 30.3% of patients experienced pain on the left side, 34.9% on the right, and 34.9% on both sides. The most frequently affected roots were L5 (28, 65.1%) and S1 (15, 34.9%), while L4 damage was detected in 10 (23.3%) patients. Upper radiculopathy was not detected in the examined sample. Both, current and average pain intensity in the past 4 weeks were high (6.85 ± 1.99 and 7.33 ± 1.62, respectively) **(Table 1).**

The highest correlations were found between FACS scores and current and average pain intensity in the past 4 weeks ($r = 0.438$ and $r = 0.253$, respectively), between pain duration and current and average pain in the past 4 weeks ($r = 0.340$ and $r = 0.308$, respectively) and finally, moderate and negative correlation between pain threshold for pressure in the forearm area and current and average pain intensity in the past 4 weeks ($r = -0.233$ and $r = -0.300$, respectively). All the above-mentioned correlations were significant **(Table 2)**.

Discussion

Chronic pain is a growing problem in both developed and undeveloped countries. It is estimated that over 20% of the global population has chronic pain. It is known that the intensity of pain is associ-

Table 2. Correlation between the perceived pain intensity and the investigated parameters
Tabela 2. *Korelacija percipiranog intenziteta bola drugih ispitivanih parametara*

	Current pain intensity *Trenutni intenzitet bola*		Average pain intensity in the past 4 weeks *Prosečan intenzitet bola u poslednje 4 nedelje*	
	r/*r*	p/*p*	r/*r*	p/*p*
Age/*Starost*	0.109	0.314	0.043	0.692
Body height/*Telesna visina*	-0.168	0.119	-0.177	0.101
Body weight/*Telesna masa*	-0.032	0.772	-0.058	0.597
PPT	**-0.233***	0.029	**-0.300****	0.005
HPT	-0.189	0.078	**-0.243***	0.023
CPT	0.197	0.066	**0.276****	0.009
Pain duration/*Trajanje bola*	**0.340****	0.001	**0.308****	0.003
Years of education/*Godine obrazovanja*	-0.14	0.193	-0.019	0.858
FACS	**0.438****	<0.001	**0.253***	0.017
Sleep/*San*	-0.06	0.58	-0.209	0.051

Legend: ** p < 0.01; * p < 0.05; FACS – fear avoidance component scale; PPT - pressure pain threshold; HPT - heat pain threshold; CPT - cold pain threshold
Legenda: $^{**}p < 0,01$; $^{*}p < 0,05$; *FACS- skala komponenti izbegavanja aktivnosti usled straha. PPT- prag bola za pritisak. HPT- prag bola za toplo. CPT- prag bola za hladno*

ated with a reduced level of functionality and quality of life [9, 26], but there are still doubts about the relationship between the perceived pain intensity and the psychological and psychophysical characteristics of patients [19]. Our research included patients with lower back pain and fibromyalgia, which are very common causes of pain in the general population [9]. We wanted to find out how anthropometric, psychological, and psychophysical variables are related to the perceived pain intensity.

Duration of pain is a determining factor for defining chronic pain. Our results indicate that pain duration is related to the perceived pain intensity. This indicates that the longer the pain is present in patients, the higher is the perceived severity. In the literature, there are many articles that discuss the connection between the pain duration and the pain intensity [27]. One of the processes that can explain this association is central sensitization [8]. It is defined as the increased function of neurons in pathways that transmit pain resulting from increased excitability and decreased inhibition [28]. Referring to this definition, it is expected that the pain thresholds in persons with existing central sensitization will be lower and that the intensity of pain will be higher [8, 29, 30]. A part of our results confirms these assumptions, namely the inversely proportional relationship between perceived pain intensity and pain thresholds for heat and pressure. Therefore, the higher the pain intensity experienced by the patients, the lower are the pain thresholds for pressure and heat. Similar results were found by Hooten et al., showing a significant negative correlation between HPT and pain intensity [31]. In the study of Kamper et al. in 2011, neck PPT and neck pain intensity were examined and a significant negative correlation was observed between the two variables [32].

Our results did not show the expected correlation between the cold pain threshold and pain intensity. This result can be explained by the difficulty of detecting pain to a cold stimulus, which was discussed by some authors [28]. In the paper of Gehling et al., a high variability in the perceived cold pain intensity was explained by the lack of individualized calibration of the cold stimulus [33].

In our study, the FACS score showed the highest correlation with the pain intensity, which indicates a significant degree of avoidance of activities due to fear. The fear-avoidance phenomenon shows the influence of fear on activities and it is widely present in patients with chronic pain, furthermore, fear avoidance is blamed for the transition from acute to chronic pain [14]. This kind of correlation is expected given that patients with chronic pain participated in our study. Similar results were obtained in the meta-analysis by Kroska et al. which highlights the positive association between these two variables [34]. Therefore, fear of pain and avoidance of activity due to fear lead to each other. The explanation of such results lies in the fact that, according to some authors, it is precisely this fear of activity that leads to less and less physical activity which is the basis for the development and maintenance of chronic pain. Possible mechanisms are misinterpretations of bodily sensations, inaccurate predictions about pain, hypervigilance, deconditioning, and muscle reactivity [9, 35].

Greater sleep disturbance is associated with greater pain intensity, greater pain-related dysfunction, greater psychosocial distress, and pain catastrophizing [6, 36]. Finan et al. suggest that sleep disturbance and pain are reciprocally related, so poor sleep at night worsens the pain later during the day and vice versa [37]. In our research, no significant correlations between hours of sleep and pain intensity were found. In part, the explanation may lie in the fact that we considered the average number of hours of sleep during the past four weeks, which is

a variable insufficient to explain pain intensity, in the way other characteristics, besides sleep duration, could influence the perceived pain intensity [38].

Conclusion

Longer duration of pain is associated with higher perceived pain intensity. Small to moderate significant positive correlations were found between fear avoidance and pain intensity. Therefore, addressing this phenomenon may be very important for chronic pain treatment. Significant but small negative correlations were found between pressure pain threshold and both present and average pain intensity in patients with chronic pain.

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REVIEW ARTICLES
PREGLEDNI ČLANCI

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ROLE OF PHYSICIANS IN ELIMINATING RISK OF CANCER CAUSED BY COMBUSTIBLE TOBACCO SMOKE

ULOGA LEKARA U ELIMINISANJU RIZIKA OD RAKA UZROKOVANOG KOMUBUSTIBILNIM DUVANSKIM DIMOM

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Summary

Introduction. Combustible tobacco smoking accounts for nearly 30% of all cancer deaths in the United States of America and about 7 million deaths worldwide each year. Nowadays, e-cigarettes are increasingly used, especially among young people, but nicotine addiction that develops by such smoking easily converts to smoking combustible tobacco. Therefore, public health efforts must be directed to the prevention of initiation of smoking all nicotine-containing products. **Role of Physicians.** Medical doctors are very influential in smoking-related changes in local society, especially those who work in primary care, and they have an important role in both prevention and cessation of tobacco smoking. Tobacco smoking should be eliminated among medical doctors, yet many of them still smoke. The lowest percentage of smoking among physicians is in Oceania and North America (less than 11%) and the highest in Eurasia (25%). Smoking prevalence among medical students is higher than 35% in Georgia, Greece, Spain, and Italy, but less than 5% in the United States of America and Australia. In Serbia, 23% of physicians smoke. The age of physicians does not affect the number of smokers, but gender has a significant effect; women smoke less than men. **Smoking Prevention and Cessation.** Education about the effects of combustible tobacco smoking is a critical issue for successful smoking prevention and cessation; the best way is to provide educational programs on smoking at medical schools by introducing a mandatory course on combustible tobacco smoking at the beginning of the first year of study, especially in societies with a large percentage of smokers. **Conclusion.** In this paper, we showed how smoking can be eliminated among physicians and how they can affect the patients, public health policies, and antismoking campaigns.

Key words: Tobacco; Smoking; Physician's Role; Risk Factors; Neoplasms; Smoking Cessation; Smoking Prevention

Sažetak

Uvod. Sagorevanje duvana dovodi do blizu 30% karcinoma s letalnim završetkom u Sjedinjenim Američkim Državama i oko sedam miliona umrlih godišnje u svetu. Danas se elektronske cigarete sve češće koriste, posebno u mlađoj populaciji, ali navika na nikotin koja se razvije takvim pušenjem lako pređe u naviku na pušenje kombustibilnog duvana. **Zato je javno zdravstvo** usmereno na prevenciju početka pušenja svih produkata nikotina uloga doktora medicine. **Uloga lekara.** Doktori medicine mogu snažno uticati na promene pušenja u lokalnoj sredini, posebno oni koji rade u primarnoj zaštiti i njihova je uloga veoma važna kako u otpočinjanju, tako i u prekidu pušenja. Pušenje lekara mora se eliminisati, ali mnogi lekari još uvek puše. Najmanji procenat lekara-pušača je u Okeaniji i Severnoj Americi (manje od 11%) a najveći u Evropi i Aziji (25%). Prevalencija pušenja studenata medicine je viša od 35% u Gruziji, Grčkoj, Španiji i Italiji, a manja od 5% u Sjedinjenim Američkim Državama i Australiji. U Srbiji puši 23% lekara. Životno doba lekara ne utiče na broj pušača, ali pol ima značajan uticaj − žene puše manje od muškaraca. **Prevencija i prekid pušenja**. Edukacija o efektima pušenja kombustibilnog duvana veoma je važna za prevenciju i prekid pušenja; najbolje je obezbediti edukacione programe o pušenju na medicinskim fakultetima uvođenjem obaveznog kursa o kombustibilnom duvanu na početku prve godine studija, naročito u društvima u kojim postoji veliki procenat pušača. **Zaključak**. U ovom članku ukazujemo kako može da se eliminiše pušenje lekara i kako lekari mogu da utiču na pacijente, propise javnog zdravlja i antipušačke kampanje.

Ključne reči: duvan; pušenje; uloga lekara; faktori rizika; neoplazme; prestanak pušenja; prevencija pušenja

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Abbreviations

WHO – World Health Organization
USA – United States of America
COPD – chronic obstructive pulmonary disease
CAD – coronary artery disease
CHF – congestive heart failure
ENDS – electronic nicotine delivery systems
ICD-10 – International Classification of Diseases, Tenth Revision

Introduction

According to the International Classification of Diseases 10 Tenth Revision (ICD-10), tobacco smoking is a behavioral disease. The World Health Organization (WHO) described smoking as an epidemic, because it causes premature death of several million individuals per year among about a billion smokers worldwide [1]. Disease and death in individuals who smoke are caused by combustible products in burning tobacco; these include cigarettes, pipe tobacco, cigars, or other products that allow inhalation of smoke from the burning tobacco. A smoker inhales about 1.0 - 1.8 mg of nicotine from each cigarette smoked to the end. Nicotine is a powerful drug and it induces addiction [2]. A cigarette contains about 600 other chemicals, including several chemicals added to correct the taste and absorption of nicotine in the final products. After combustion, tobacco smoke contains an estimated 7,000 chemicals, including about 70 carcinogens [3]. All other combustible tobacco products used for smoking yield similar amounts of chemicals and carcinogens in the smoke. Smoking of combustible tobacco is the leading global cause of morbidity and mortality [4–7]. Yet, nearly two-thirds of lung cancer deaths attributable to smoking worldwide may be prevented through effective tobacco-control policies and regulations. In the INTERHEART study, smoking accounted for 35.7% of acute myocardial infarction worldwide [8, 9]. Because smoking causes many other adverse effects to health, including pharmacokinetic and pharmacodynamic drug interactions [10], elimination of tobacco use remains an important public health priority that requires special attention to prevent smoking by young people, and it must include all nicotine-containing products. Many adult smokers are interested in quitting, but self-quitting is not an easy process and it is not often successful. Motivation and encouragement for smokers to quit could be increased by firm public policy and regula-

Table 1. Policies and measures to reduce the prevalence of tobacco smoking
Tabela 1. *Propisi i mere kojima se smanjuje prevalencija pušenja duvana*

Place/*Mesto*	Methods/*Metode*
Country or area *Država ili region*	Implementation of public health polices/*Implementacija propisa javnog zdravstva* Offering help to quit tobacco use/*Ponuda pomoći za prekid pušenja* Anti-smoking campaigns/*Antipušačke kampanje* Prohibition of tobacco advertisement, promotion and sponsorship *Zabrana reklamiranja duvana, promocija i spozorstva* Warning about the dangers of combustible tobacco *Upozorenje o opasnosti kombustibilnog duvana* Rising tobacco taxes*/*Povećanje poreza na duvan**
Health institutions *Zdravstvene institucije*	'No-smoke policy'*/*"Zabrana pušenja"** Short-term intervention to smokers/*Kratkotrajna pomoć pušačima* Intensive smoking cessation support*/*Pomoć za intenzivno odvikavanje** Training of medical personnel in tobacco control *Obuka medicinskog osoblja za odvikavanje pušača*
Medical schools *Medicinski fakulteti*	"No-smoke policy"/*Zabrana pušenja* Mandatory module/s on tobacco smoking/*Obavezni kurs o pušenju duvana* Intensive smoking cessation intervention/*Intenzivna pomoć za prekid pušenja*
Dormitories for students *Studentski domovi*	"No-smoke policy" *Zabrana pušenja*
Local cancer societies and sports organizations/*Društva za borbu protiv raka i sportske organizacije*	Rapid elimination of combustible tobacco *Hitra eliminacija kombustibilnog duvana*
At home *Kod kuće*	Isometric and/or isotonic exercise* during and after smoking cessation/*Izometrijske i/ili izotonične vežbe za vreme i posle prekida pušenja*

Legend: *Most young people, including university students, have limited financial means, and increasing the price of tobacco would result in a drop of students smoking; *"No-smoke policy" means that smoking is only permitted at certain locations outside the buildings and all closed spaces; Penalties for violating smoking regulations (cigarettes, e-cigarettes or other 'vapor' products); *Intensive smoking cessation support includes help to smokers in specific situations to obtain temporary or permanent abstinence; *Isotonic physical exercises are recommended to younger smokers (up to 65); Isometric exercises for smokers in the geriatric age are recommended to prevent relapse
*Legenda: *Većina mladih osoba, uključujući studente nema dovoljno novca i porast cene duvana dovodi do pada pušenja studenata. "Zabrana pušenja" znači da je pušenje dozvoljeno samo u određenim mestima izvan zgrade i svih zatvorenih prostora; kažnjavaju se svi prekršaji pušenja (cigarete, e-cigarete, pušeneje "vodene pare"). *Intenzivna pomoć za prekid pušenja dešava se pri specijalnim situacijama kada je nužna privremena ili trajna apstinencija. *Izotonične vežbe preporučuju se mlađim pušačima (do 65 godina); izometrijske vežbe preporučuju se pušačima u gerijatrijskim godinama da se suzbije relaps pušenja.*

tions within the environment **(Table 1).** The proof for successful impact of such factors on tobacco smokers was studied recently within the context of acculturation [11]. The best way to help smokers to quit smoking is to provide adequate information about combustible tobacco products and smoking cessation [12]. The WHO emphasized the potential role of physicians in this fight against tobacco smoking [13], because even a short-term clinical intervention by a physician was highly effective in the cessation of cigarette smoking in patients. In addition, many countries employ various ways to help people quit tobacco use, such as the World No Tobacco Day, 31 May, and National No Smoking Day; for example 31 January, which was introduced in Yugoslavia by medical students from Tuzla **(Figure 1).** Today, it is accepted in Serbia and Bosnia and Herzegovina since 2000.

Figure 1. The postal stamp released on January 31, 1990 in recognition of the anti-smoking campaign in the whole Yugoslavia led by medical students from Tuzla and Banja Luka which started in 1980

Slika 1. *Poštanska marka je puštena u promet 31. januara 1990. u znak priznanja studentima medicine iz Tuzle i Banjaluke koji su vodili ani-pušačku kampanju u Jugoslaviji otpočetu 1980. godine*

Physicians have a key role in the fight against tobacco; they can educate their patients, support anti-smoking policies, lead smoking cessation programs within their communities, and support national tobacco control efforts. However, some physicians remain smokers themselves [14]. The aim of this paper is to consider how to reduce smoking prevalence among physicians and medical students. Because high smoking rates among physicians in some countries are still an important public health issue, one might assume that these doctors-smokers cannot help to curb tobacco use among the general population. According to Smith and Leggat [15], the reduction in smoking occurs more rapidly among doctors than among other healthcare workers. To gain even more rapid results, it will be necessary to reduce smoking prevalence among medical students, who may become physicians-smokers. Therefore, tobacco use among medical students is included in this report, with particular attention to countries where high smoking rates are documented.

Combustible and noncombustible tobacco smoke products

Tobacco plants (Nicotiana tabacum) have been cultivated for centuries by Native American tribes around Peru and Ecuador [2]. When Columbus and his crew brought tobacco to Europe, smoking was considered to be an evil practice. However, the purported medical properties of tobacco smoke were accepted, especially for its presumed cure and prevention of cancer. The manufacture of cigarettes stimulated a global increase in tobacco smoking, probably related to the convenience of the device, as well as the use of a milder sort of tobacco. The small and convenient form of the cigarette enabled smokers to inhale and thus deliver greater amounts of product to a huge area of respiratory epithelium. The cigarette thus provided more rapid satisfaction than pipe or cigar by means of a rapid nicotine delivery via the vast area of the lungs to the brain and other tissues by the vascular system. In addition, an increase in absorption of nicotine through the lungs potentiates nicotine addiction.

In the nineteenth century, some European physicians believed that smoking may be harmful, but there was no proof to substantiate such a claim. Nonetheless, the opinion was expressed in the current artistic literature, and in 1886, A. P. Chekhov, a doctor/writer, published a one-act play: On the Harmful Effects of Tobacco [16]. Epidemiological studies done in Germany before the Second World War showed an association between smoking and lung carcinoma [17, 18]. These observations stimulated an extremely robust anti-smoking campaign in Germany [19]. Documentation of smoking contributing to lung carcinoma was published in 1950 and gained wide acceptance [20]. Nevertheless, Ronald A. Fischer, who is considered to be the father of modern statistics, continued to smoke a pipe and did not believe that smoking causes lung carcinoma. In 1957, Fisher published a letter in the British Medical Journal denying any connection [21]. Despite the fact that the observed association between smoking and tissue damage is the most extensively documented cause of various diseases, governments worldwide have been slow to reduce smoking, and this view prevails primarily only in culturally advanced countries.

In 2003, Hon Lik, a pharmacist and smoker in Beijing, created an electronic cigarette [22]. He created this device after his father, a heavy smoker, died of lung cancer. The terms "e-cigarettes" and "vaping" are used as synonyms, although the term "vaping" originates from "vapor", which is not formed by such devices; both kinds of delivery systems form aerosols by using a variety of electronic battery-operated devices. These devices do not burn liquids to release nicotine and other substances, so the era of electronic nicotine delivery systems (ENDS) was born. It refers to the combination of liquids containing nicotine, water,

Table 2. Elements of teachable moments for combustible tobacco or nicotine smokers
Tabela 2. *Elementi poučnih trenutaka za pušače kombustivnog duvana ili nikotina.*

Carcinomas/*Karcinomi* Elective surgery *Elektivni hirurški zahvat* Planned pregnancy *Planirana trudnoća* Pregnancy/*Trudnoća* COPD/*HOBP* CAD/*KAB* CHF/*KSI* All smokers who use combustible tobacco and/or nicotine/*Svi pušači koji koriste kombustibilni duvan ili nikotin*	Perceived risk & new social perception of smoking *Percipirani rizik i nova društvena percepcija pušenja*	Emotions increase & social role redefined *Emocije se povećavaju i društvena uloga se redefiniše*	Increased motivation *Povećana motivacija*	Smoking cessation (immediate or after relapse/s) *Prekid pušenja (odmah ili nakon relapsa)*

Legend: COPD – chronic obstructive pulmonary disease; CAD – coronary artery disease; CHF – congestive heart failure
Legenda: HOBP – hronična opstruktivna plućna bolest; KAB – koronarna arterijska bolest; KSI – kongestivna srčana insuficijencija

propylene glycol and flavorings that are heated, not burned, in e-cigarettes. For that reason, ENDS are much less harmful than combustible tobacco products used for smoking. However, non-combustible smoking also has its own risks and benefits [12]. The ENDS can be used as a smoking cessation option, but it is not recommended to be used by youths because they often turn to cigarettes.

Role of physicians in the cessation of tobacco smoking

Involvement of the medical community in smoking cessation is not equally pronounced across various medical specialties [23]. Ophthalmologists, specialists in infectious diseases, and general surgeons may lack an interest in smoking cessation, while pulmonologists, as well as thoracic surgeons, cardiologists and ear, nose, and throat specialists may be more inclined to influence their patients' smoking status. It should be in the interest of all physicians, regardless of their specialization. They should use their unique professional position to eliminate smoking in all patients. The harmful effects of smoking and the association of disease with combustible tobacco smoking may motivate patients to quit.

If a physician devotes only a few minutes to the patient who is a smoker, it can cause reduction in cigarette smoking by 5% to 15% [4, 23]. In such a brief time, the physician does not always have time to apply highly recommended 5A's (Ask, Advise, Assess, Assist, and Arrange) smoking cessation intervention [24]. Doctors should rather ask the patient if he/she smokes, when they light the first cigarette in the morning, and how many cigarettes they smoke daily. A doctor can then instantly decide whether the patient is a "light" or "heavy smoker" and whether the patient is psychologically or physically (or both) dependent on cigarettes. This will also help doctors to predict what type of smoking cessation should be applied if the patient decides to quit smoking [25].

The family physicians should obviously record the smoking status of each patient and provide smoking-cessation advice through brief oral information about associated health risks of combustible tobacco smoke. However, in special circumstances, e.g., chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), congestive heart failure (CHF), planned pregnancy, confirmed pregnancy, and elective surgery, a high intensity smoking-cessation intervention is indicated **(Table 2).** Interestingly, the percentage of general practitioners who have never distributed a high intensity smoking-cessation intervention is lower in men (41%) than in women (45%) [26]. The patient may be offered a prescription for pharmacotherapy (bupropion, varenicline, cytisine) or for short-time usage of nicotine patches, gums, or e-cigarettes, and biochemical validation may be sometimes verified for smoking abstinence [27–30].

Prevalence of smoking among physicians

Almost a quarter of the global population smokes tobacco products and the majority of them smoke cigarettes, at least once a day. Four decades ago, the incidence of smoking among medical doctors in many European and Asian countries was almost as high as the prevalence in the general population (about 30%). Smoking habits of doctors and medical students often mirror those of the society in which they live, but additional factors sometimes contribute to maintaining the habit, such as the stress of academic studies, workload stress, and poor working conditions. However, from the very beginning of the third millennium, the perception of smoking has changed in many countries. The culture of the country influences tobacco use in both the general population and physicians. The smoking prevalence rate among female doctors is generally significantly lower than in their male counterparts at the same health institution. In some countries, e.g., China, India, Thailand, and Malaysia, smoking is considered an inappropriate behavior for women. This cultural reluctance also produces gender differences not only in the population's smoking rates but also among physicians [15].

Recent systematic review and meta-analysis on the predominance of smoking among physicians included 246 studies [14]. It showed that the total prevalence of smoking was high, around 21%. The

global smoking percentage of physician-smokers dropped from 28% before 1985 to 16% after 2015. The smoking prevalence among physicians is lowest in Oceania and North America (less than 11%) and highest in Eurasia (25%). In Serbia, about 34% of physicians used to smoke in 2010 [31], but ten years later the prevalence of smoking among physicians dropped to 23% [30]. Health care and educational facilities in the Republic of Serbia are completely smoke-free. However, in the indoor offices, restaurants, cafes, and bars designated smoking rooms are allowed under the current legislation. The prevalence of smoking among medical students is less than 5% in the USA and Australia, but over 35% in Georgia, Greece, Spain, and Italy [5, 14, 32]. The prevalence of smoking in medical students in Serbia is less than 25% [28]. Thus, smoking of physicians and future physicians in many regions still presents an acute public health issue in many countries [33].

The smoking prevalence is not affected by the age of physicians, but it is affected by gender; the prevalence of smoking is lower in women than in men. Education on the effects of combustible tobacco is a critical issue for successful smoking prevention and cessation. The best way to provide educational programs on smoking in medical schools is to introduce a mandatory module, a course on combustible tobacco, at the beginning of the first year. Setting up the unit for smoking counseling and intensive smoking cessation intervention at the university health office may also help to reduce the prevalence of tobacco smoking among medical students, especially in societies with a significant percentage of smokers [30].

In some countries, lung cancer accounts for more deaths than three other types of cancer together (breast, colon**,** and prostate) [12]. For this and other health damages, combustible tobacco should be eliminated. Nowadays, e-cigarettes are increasingly used, especially by young people, including medical students, and nicotine addiction developed by noncombustible smoking can easily be changed to combustible tobacco smoking. Therefore, public health efforts must be directed to the prevention of all nicotine-containing products.

In order to reduce the use of all combusted tobacco products, it is necessary to eliminate smoking among physicians [3, 13]. When a medical doctor decides and succeeds to quit, this influences and encourages both smokers in his medical institution and the community [25]. Many physician-smokers try to quit themselves. Their success may be enhanced by public policy interventions, such as smoke-free hospitals and the support of friends and family members. In addition, the perception of smoking has recently changed. In earlier times, smoking was both socially acceptable and rewarding, but today it has a distinctly negative image, which generates strong motivation to quit.

Self-quitting approaches, in the majority of smokers, often require multiple attempts before achieving long-term abstinence. Many physician-smokers often struggle to maintain nicotine abstinence. With that in mind, it is useful to consider the methods of enhancing their success. To maximize the chances of achieving the desired outcome, prevent relapse, and obtain permanent smoking cessation, it is vital to increase physical activity [30]. Additionally, it also strengthens the negative connotations associated with the modern image of smoking in social life. Subsequently, it generates a strong sentiment supported by other members of society in support of smoking cessation.

Nonetheless, even backed by public policy intervention and the use of anti-smoking medications, the self-quitting approach often requires multiple attempts before achieving long-term abstinence. Increased physical activity boosts the endogenous opioid peptides in such an individual to deal with withdrawal symptoms, and later prevents smoking relapse. This phenomenon can be attributed to the release of enkephalins and endorphins [34]. These peptides are under the influence of exercise and by increasing the level of exercise, it is easier to resist the temptations of smoking [35].

Conversely, studies show that smoking works as an external drug to stimulate endogenous peptides. In other words, a lot of people enjoy the feeling of pleasure when smoking; it presents a kind of psychological hedonism [36]. In the same manner, physical activity can be seen as an alternate method of increasing the production of endogenous peptides and pleasure. Hence, both smoking and physical exercise may have the same hedonistic value, and exercise ought to be considered a relevant factor in combating addiction. On that account, physical exercise can be perceived as a way of complementing public policy interventions in smoking cessation [32].

The prevalence of smoking among medical students varies between different countries and between male and female students within the same country. A major reason for this variation is the population-based influence on the student's decision to smoke [33]. Limited overall knowledge regarding health among university students is another motivation for taking up smoking and continuing the habit. Because it also affects the general adult communities in which medical students live, education about the effects of combustible tobacco is a critical issue in smoking cessation. The best way may be to provide medical schools with a mandatory module, a specific course on combustible tobacco, for all medical students at the beginning of the first year. This would apply especially to schools with a significant percentage of smokers. Setting up the unit for smoking counseling and intensive smoking cessation intervention at universities may help to reduce the prevalence of tobacco smoking in both medical and other university students. Later, in the final years of medical studies, a second module on the fight against tobacco should be optional. Taxes on tobacco products are very effective in reducing use, especially in students [37]. These measures, including smoke-free hospitals, can significantly reduce smoking prevalence of tobacco smoking in medical students and provide useful means for new generations of physicians to eliminate smoking in their patients and in society, as well [33, 38–41].

Conclusion

Combustible tobacco use is responsible for the majority of all cancer deaths in the United States of America, and about 7 million deaths globally. For this reason, combustible tobacco should be eliminated, and it should become the most important public health priority. To prevent relapse and obtain permanent abstinence, in addition to anti-smoking medications, smokers should take on physical exercise which initially also reduces withdrawal symptoms, and later on leads to long term abstinence. Public health efforts should be directed to limiting usage of all nicotine-containing products, and physicians have an important role in prevention and cessation of tobacco smoking in each society. The first step to be accomplished is eradication of smoking in all health institutions, including medical schools.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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CALCIFYING FIBROUS TUMOR IN THE ABDOMEN – A CASE REPORT

FIBROZNI KALCIFIKUJUĆI TUMOR U ABDOMENU – PRIKAZ SLUČAJA

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Summary

Introduction. Calcifying fibrous tumor is a rare benign neoplasm of soft tissue origin. The tumor is commonly found in young adults. In most cases it is an incidental finding, because patients do not have obvious symptoms. This tumor may appear in different anatomical locations mimicking other stromal lesions. The diagnosis is made based on pathohistological characteristics and an appropriate immunohistochemical profile. The treatment is surgical, and the prognosis is good. **Case Report.** A 19-year-old female patient was admitted for abdominal surgery presenting with abdominal pain and pressure. Abdominal ultrasonography and multislice computed tomography of the abdomen showed a tumor mass in the right hemiabdomen. The patient underwent surgical treatment and the tumor was completely removed. Macroscopic analysis showed that the tumor was encapsulated and had a smooth surface. Microscopically, the tumor consisted of bundles of partially hyalinized collagen fibers with calcifications in the form of psammoma bodies that were permeated with mononuclear inflammatory infiltrates. **Conclusion.** Given the higher incidence of other mesenchymal tumors in the abdomen, due to its rare occurrence, calcifying fibrous tumor presents a diagnostic challenge.

Key words: Neoplasms, Fibrous Tissue; Abdominal Neoplasms; Calcinosis; Morphological and Microscopic Findings; Immunohistochemistry; Diagnosis, Differential

Sažetak

Uvod. Fibrozni kalcifikujući tumor je retka benigna neoplazma porekla mekih tkiva. Tumor je češći kod mladih odraslih osoba. U većini slučajeva se otkriva slučajno jer pacijenti nemaju očigledne simptome. Ovaj tumor se može javiti na različitim anatomskim lokalizacijama imitirajući druge stromalne lezije. Dijagnoza se postavlja na osnovu patohistoloških karakteristika i određenog imunohistohemijskog profila. Tretman je hirurški, a prognoza je dobra. **Prikaz slučaja.** Pacijentkinja, 19 godina, primljena je na abdominalnu hirurgiju sa simptomima u vidu bola i pritiska u abdomenu. Ultrazvučnom sonografijom i kompjuterizovanom tomografijom abdomena verifikovano je prisustvo tumorske mase u desnom hemiabdomenu. Pacijentkinja je podvrgnuta hirurškom tretmanu i tumorska promena je otklonjena u celosti. Makroskopskom analizom tumor je inkapsulisan i glatke površine. Mikroskopski, tumor je sačinjen od snopova kolagenih vlakana delom hijalinizovanih sa kalcifikacijama u vidu psamoznih telašaca koji su prožeti mononuklearnim inflamatornim infiltratom. **Zaključak.** S obzirom na veću incidenciju drugih mezenhimalnih tumora u abdomenu, postavljanje dijagnoze fibroznog kalcifikujućeg tumora je delikatno, imajući u vidu njegovu retku pojavu.

Ključne reči: fibrozne neoplazme; abdominalne neoplazme; kalcifikacija; morfološki i mikroskopski nalazi; imunohistohemija; diferencijalna dijagnoza

Introduction

Calcifying fibrous tumor (CFT) is a benign mesenchymal tumor with a low rate of recurrence after removal [1]. Histologically, it should be distinguished from other, more aggressive, rare mesenchymal lesions [2], especially because it can affect soft tissues at different anatomical sites (intra-abdominal and intrathoracic) [1]. We present a case of a 19-year-old woman with a diagnosed CFT in the abdominal cavity to provide more information about this extremely rare entity.

Case Report

A 19-year-old female patient was admitted for abdominal surgery presenting with abdominal pain and pressure**.** On physical examination, the abdomen was at chest level and palpably soft. Abdominal ultrasonography and multislice computed tomography of the abdomen revealed a tumor, 14 cm in maximum diameter in the right hemiabdomen. The patient underwent surgical treatment. Intraoperatively, it was found that the tumor was in contact with the duodenum, head of the pancreas, and the portal vein. It did

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Abbreviations
CFT – calcifying fibrous tumor
IgG – imunoglobulin G

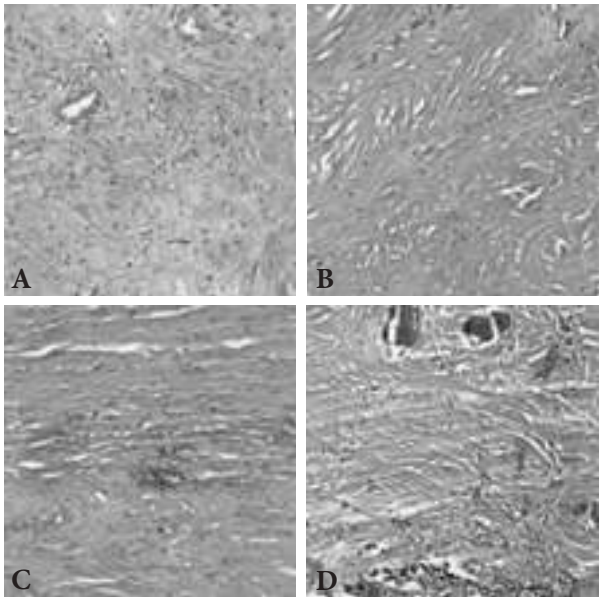

Figure 1. Microscopic appearance of CFT: (a) HE, x 10; (b); HE, x 10; (c) HE, x 10; (d) HE, x10
Slika 1. *Histološki izgled fibroznog kalcificirajućeg tumora: (a) HE, x 10; (b); HE, x 10; (c) HE, x 10; (d) HE, x 10*

not infiltrate the surrounding structures and was removed completely. On gross examination, the tumor was oval, encapsulated, and hard in consistency, with a smooth and shiny surface, measuring 11 x 9 x 7 cm. On cross-section, the tumor had a whirling pattern and it was pale with a darkly colored central area. Microscopic examination with hematoxylin and eosin staining showed circumscribed bundles of collagen fibers partially hyalinized and with sparse areas of inflammatory infiltrates composed of lymphocytes and plasma cells with folliculoid appendages **(Figures 1a, 1b and 1c)**. The bundles of collagen contained rare spindle cells, sparse cytoplasm and elongated nuclei and foci of dystrophic calcifications in the form of psammoma bodies **(Figure 1d).** The immunohistochemical staining showed that the spindle cells were partially positive for bCl2 and CD34, and negative for beta-catenin, STAT6, anaplastic lymphoma kinase, CD117, and DOG1. The plasma cells showed high ratio of IgG4-positive to IgG-positive plasma cells **(Figure 2)**. The proliferation index (% Ki-67 positive cells) was 1%.

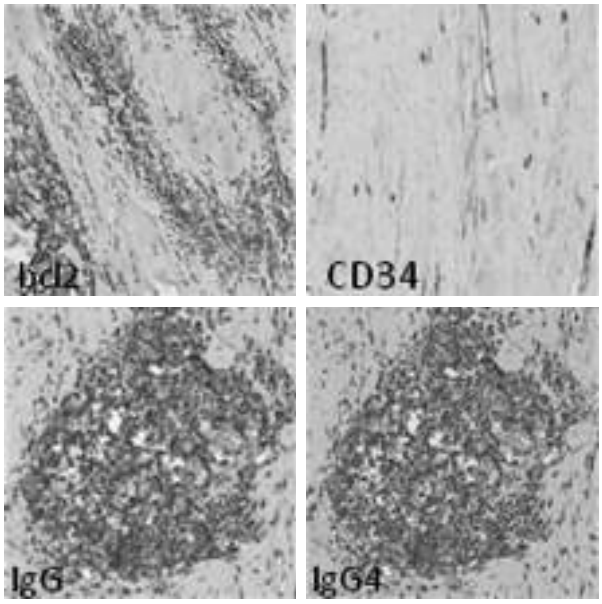

Figure 2. Immunohistochemical analysis showing: (a) bcl2 positivity, HE, x 10; (b) CD34 positivity, HE, x 10; (c) IgG positivity, HE, x 20; (d) IgG4 positivity HE, x 20
Slika 2. *Imunohistohemijska analiza pokazuje: (a) bcl2-pozitivnost, x 10; (b) CD34 pozitivnost, x 10; (c) IgG pozitivnost, x 20; (d) IgG4 pozitivnost, x 20*

According to the histomorphological features and immunophenotype of the tumor cells, the diagnosis of CFT was made. The postoperative course was uneventful and the patient was discharged in good general condition. The patient was followed up for 3 months after surgery and recovered well.

Discussion

The CFT was first described by Rosenthal and Abdul-Karim as a childhood fibrous tumor with psammoma bodies [3], but it was renamed by Fetsch et al., as a calcifying fibrous pseudotumor [4]. In 2002, the World Health Organization established the name for this lesion as CFT, in the new classification of soft tissue tumors that originated from fibroblasts/myofibroblasts [1, 5]. Meta-analysis by Chorti et al. shows a trimodal pattern of age distribution with the first peak from birth to 4 years, the second in the mid-20s, and the third in the mid-30s [1, 2]. It mainly affects women and the average age at the time of diagnosis is 33.58 years [2]. However, our patient was an exception. The etiopathogeny of CFTs is unclear; several theories have been developed about posttraumatic or genetic pathogenesis, as well as a relationship between IgG4-related disease and inflammatory myofibroblastic tumors [2]. Histopathological characteristics of CFT are abundant hyalinized paucicellular collagen, dystrophic calcifications and mononuclear inflammatory infiltrates [2, 6]. Spindle cell mesenchymal lesions and inflammatory conditions are included in the differential diagnosis of CFT [6]. Immunohistochemical analysis of CFT shows uniformly negative staining for anaplastic lymphoma kinase, which is typically positive in inflammatory myofibroblastic tumors [6–8]. Considering the location of the tumor in our case, the use of CD117 immunohistochemistry is important to delineate the gastrointestinal stromal tumor from CFT, because the spindle cells are negative for CD117 in CFTs [6]. Solitary fibrous tumor is immutable CD34 positive as in our case, and reactivity for BCL-2 is not described in CFT [6], but in our case it was positive. In some cases of CFT, the plasma cell population may stain positively for IgG and IgG4

and show increased IgG/IgG4 ratio [8, 9]. High IgG4-to-IgG ratio (41%) supports the view that CFT may be a manifestation of IgG4-related disease (IgG4-RD) [8, 10]. In our case, CFT showed a significant IgG4-postive plasma cell infiltrate and IgG/IgG4 ratio higher than the 40%. However, the major criterion of IgG4-related disease is obliterative phlebitis, but it is not a feature of CFT [6, 8]. The IgG4-related disease usually responds to corticosteroid therapy, but its efficacy in CFT has never been established [6]. Surgical excision is the appropriate treatment for abdominal CFT [11].

Conclusion

Calcifying fibrous tumor is a rare neoplasm of soft tissue origin with benign biological behavior. The diagnosis is based on histological features, because it has no specific clinical and radiological characteristics. We should keep in mind the rare occurrence of this entity and a difficult differential diagnosis, especially when it is localized in the abdomen.

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UTEROCUTANEOUS FISTULA AFTER CESAREAN SECTION − A RARE DIAGNOSIS NOT TO BE MISSED – A CASE REPORT

UTEROKUTANA FISTULA NAKON CARSKOG REZA, RARITET KOJI SE NE SME ZABORAVITI – PRIKAZ SLUČAJA

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Summary

Introduction. Uterocutaneous fistula is a rare complication of cesarean section which is challenging to diagnose and treat. The aim of this paper is to present a case of uterocutaneous fistula in order to contribute to the literature and help in the therapy and diagnosis of this rare complication. **Case Report.** A 29-year-old patient was referred to our clinic two months after her second cesarean section. The immediate postpartum course was complicated by endometritis treated with antibiotic therapy. At the time of admission, she was afebrile, without complaints other than a 2 cm long wound dehiscence on the anterior abdominal wall. The uterocutaneous fistula was confirmed by injecting methylene blue through the dehiscence on the anterior abdominal wall, which then spread into the vagina through the cervix. After laboratory tests, ultrasound and clinical examination, the patient underwent surgery. A total excision of the fistula was performed by laparotomy. Histopathological findings confirmed the diagnosis of uterocutaneous fistula. The postoperative recovery was uneventful. At the follow-up examination, three months after surgery, the patient had no complaints; the menstrual cycles were normal, as well as the transvaginal ultrasound findings. **Conclusion.** Uterocutaneous fistula is a rare complication following cesarean section. Timely identification of the fistula, its complete resection, and adequate antibiotic therapy in case of infection are necessary.

Key words: Cutaneous Fistula; Uterine Diseases; Cesarean Section; Postoperative Complications; Treatment Outcome

Sažetak

Uvod. Uterokutana fistula je retka, ali terapijski i dijagnostički vrlo zahtevna komplikacija nakon carskog reza. Cilj rada bio je prikaz slučaja uterokutane fistule i dati doprinos literaturi i pomoći u terapiji i dijagnostikovanju ove retke komplikacije. **Prikaz slučaja.** Pacijentkinja stara 29 godina javlja se na Kliniku dva meseca nakon drugog carskog reza. Neposredni postpartalni tok bio je komplikovan endometritisom, koji je tretiran antibiotskom terapijom. U momentu prijema pacijentkinja je afebrilna, bez tegoba, osim dehiscencije u predelu incizije na prednjem trbušnom zidu u dužini od 2 cm. Uterokutana fistula je potvrđena ubrizgavanjem metilenskog plavila, kroz dehiscenciju prednjeg trbušnog zida, koje se potom kroz grlić izlilo u vaginu. Nakon laboratorijske, ultrazvučne i kliničke obrade, pacijentkinja je operisana. Tokom laparotomije, načinjeno je odstranjenje fistule u celosti. Patohistološki nalaz potvrdio je dijagnozu uterokutane fistule. Postoperativni tok protekao je uredno. Na kontrolnom pregledu, tri meseca nakon operacije, pacijentkinja je bez tegoba, urednih menstrualnih ciklusa i urednog ultrazvučnog nalaza. **Zaključak.** Uterokutana fistula je retka komplikacija nakon carskog reza. Neophodna je pravovremena identifikacija fistule, kompletna resekcija fistule kao i adekvatna antibiotska terapija u sličaju postojanja infekcije.

Ključne reči: kožna fistula; bolesti uterusa; carski rez; postoperativne komplikacije; ishod lečenja

Introduction

A fistula is an abnormal communication between two epithelial surfaces that is most commonly found between the urinary and genital tract [1]. Pathological communication between the skin and the uterus (uterocutaneous fistula) is extremely rare, but it may be a complication in gynecology and obstetrics [2]. Approximately 120 cases have been reported over the past 200 years, 25 cases in the past 50 years, and 15 cases in the past 20 years [3]. We have not found any reported cases in the Serbian medical literature. This case report is bridging the gap and serves as a reminder that, although rare, uterocutaneous fistula is a possible complication after cesarean section that requires timely diagnosis and treatment.

Case Report

A 29-year-old patient was referred to the Department of Gynecology and Obstetrics two months after her second cesarean section. She was admitted to the Clinical Center due to partial dehiscence of the abdominal wound. An elective cesarean section was performed at 39 weeks of gestation because the

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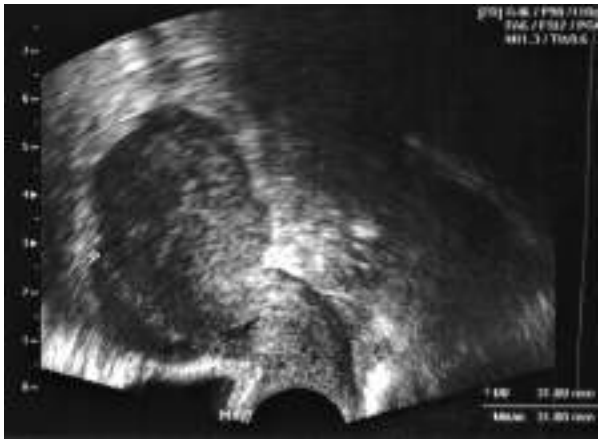

Figure 1. Transvaginal ultrasound before surgery shows an echogenic formation in the area of the uterine incision
Slika 1. *Transvaginalni ultrazvučni pregled pre operativnog zahvata pokazuje ehogenu promenu u predelu reza na uterusu*

previous pregnancy ended with a cesarean section as well.

The postoperative course was complicated by the development of endometritis. During the postpartum period, she received a parenteral combination antibiotic therapy (cefuroxime and metronidazole) which led to an improvement, so the patient was discharged on the thirteenth day after the cesarean section. Staphylococcus aureus was isolated from the wound swab, and oral antibiotic therapy was administered according to the antibiogram (ciprofloxacin).

At the control examination, after the toilet of the wound on the anterior abdominal wall with an antiseptic solution, the patient noticed a discharge of the solution through the vagina. The examination of the anterior abdominal wall revealed a Cohen incision with partial 2 cm long wound dehiscence in the central part with initial granulations. On speculum examination, the cervix and vagina were normal. Since uterocutaneous fistula was suspected, methylene blue solution was injected through the area of dehiscence of the incision on the abdominal wall, and it was seen coming through the cervix into the vagina. The ultrasound examination showed an echogenic formation, 31 x 24 mm in size, in the area of the uterine incision, which was connected with the skin **(Figure 1)**.

On admission, the patient was afebrile, with normal vital parameters, peristalsis and no difficulty urinating. Laboratory test results were normal with negative markers of infection (white blood cell count: 5.8 x 10^9/l, C-reactive protein: 3.9 mg/L). After clinical, ultrasound and anesthesia examination, the patient underwent surgery. Methylene blue solution was injected immediately before the surgery through the scar to determine the direction of the fistula. After opening the anterior abdominal wall by Pfannenstiel laparotomy, uterine adherence to the anterior abdominal wall was noticed. Within

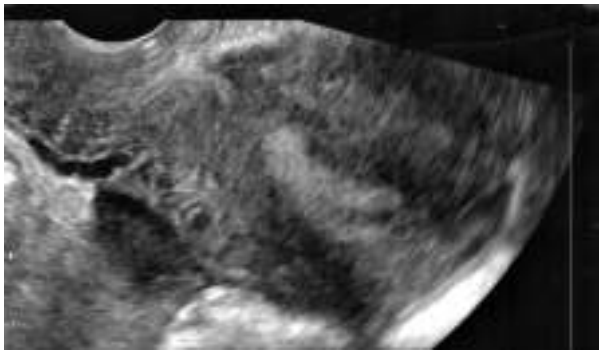

Figure 2. Transvaginal ultrasound three months after surgery shows a normal finding of the uterus without pathological changes
Slika 2. *Transvaginalni ultrazvučni pregled tri meseca nakon operacije pokazuje uredan nalaz, bez patoloških promena*

the connection, there was a 5 mm wide fistula. The entire fistula channel connecting the skin to the uterus with the surrounding tissue was excised, and the sample was sent for histopathological analysis. Uterine opening and debridement were performed, so individual sutures were placed on the layers of the uterus. Adhesiolysis of the omentum from the anterior abdominal wall adhesion was performed. After the drains were placed in the pouch of Douglas and anterior uterine space, 48 h after the surgery the drains were removed.

Postoperative antibiotics and analgesia were administered. Pathological examination showed inflammatory necrosis of the uterine muscle with a fistula tract in the muscular wall of the uterus with hemorrhage and fibrin deposition. The patient was discharged on the seventh postoperative day. She had a menstruation 4 weeks after surgery, and she had no complaints. There was no sinus on the abdomen discharging blood. The follow-up ultrasound examination 3 months after surgery was normal **(Figure 2).** She was advised to use contraception.

Discussion

Our patient presented with a fistula following cesarean section, but there are other recognized risk factors for uterocutaneous fistula. The most common are septic abortion, postoperative sepsis, pelvic abscesses, intrauterine device-related actinomycosis, abdominal drainage, operative delivery, endometriosis and true intra-abdominal pregnancy because of incomplete placenta removal, congenital anomalies [4–10]. Studies have shown that the onset of symptoms varies from 2 months to even 6 years after the last surgery [6]. Our patient was referred to the hospital barely 2 months after the cesarean section. The dominant symptom of the uterocutaneous fistula is a retrograde effusion of menstrual blood simultaneously with normal menstruation [9]. In our patient, this symptom was not found, probably due to lactation amenorrhea. The diagnosis of

uterocutaneous fistula is made by fistulography [11] and magnetic resonance imaging [6]. In case of a small opening in the skin and suspicion of uterocutaneous fistula, hysterosalpingography with methylene blue injection through the cervix may be helpful [12, 13]. There is no standard treatment for uterocutaneous fistula, because it is a rare clinical condition (less than 15 cases reported in the last 20 years worldwide) [14]. Some authors used a minimally invasive surgery (laparoscopy) to excise the fistula tract [15]. Some papers report a novel successful treatment of uterocutaneous fistula with gonadotropin-releasing hormone agonists [16, 17]. In our case, a fistulectomy was performed to preserve the patient's fertility.

Conclusion

Certain studies have shown that congenital anomalies and earlier curettage of the uterus can be the reasons for both uterine rupture and uterocutaneous fistula. However, cesarean section remains the most significant risk factor for the occurrence of this rare complication. An uterocutaneous fistula should be suspected in any patient who presents with cyclic bloody discharge from a surgical scar. Given the increased incidence of cesarean section, obstetricians must be aware of the potential complications of surgical delivery. Uterocutaneous fistula is a rare complication of the cesarean section that should be considered and recognized on time so that the patient can receive adequate treatment.

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LIMITED SCLERODERMA – A CASE REPORT

OGRANIČENA SKLERODERMA – PRIKAZ SLUČAJA

Snežana KNEŽEVIĆ and Slavica ĐORĐEVIĆ

Summary

Introduction. Systemic sclerosis is a rare autoimmune disorder of the connective tissue, gastrointestinal tract, lungs, kidneys, and musculoskeletal tissue. It predominantly affects women. The localized variant is limited scleroderma. **Case Report**. We present a 64-year-old female patient with the diagnosis of limited scleroderma that has lasted for thirteen years. She had hyperpigmentation, telangiectasias, and progressive skin tightening of the face and fingers. Her blood test was positive for antinuclear antibodies. Sclerodactyly began in the distal phalanx. Tender and painful calcium deposits appeared subcutaneously on the surface of palms and knees, radiographically confirmed. The patient was treated with surgical debridement, vasodilating agents, corticosteroids, diltiazem, sildenafil, nitro paste, antiplatelet drugs, and physical therapy. **Conclusion.** It is necessary to control numerous factors that affect daily functioning, including nutrition, pain therapy, musculoskeletal dysfunctions, and emotional and social aspects caused by deformities. Targeted therapy in the early stages of the disease, before irreversible damage occurs, improves the overall quality of life.

Key words:Scleroderma, Limited; Calcinosis; CREST Syndrome; Autoimmune Diseases; Risk Factors

Sažetak

Uvod. Sistemska skleroza je redak autoimuni poremećaj vezivnog tkiva, gastrointestinalnog trakta, pluća, bubrega i koštano-zglobnoh tkiva. Pretežno obolevaju žene. Lokalizovana varijanta bolesti je ograničena skleroderma. **Prikaz slučaja**. Predstavljamo pacijentkinju starosti 64 godine, sa dijagnozom ograničene skleroderme koja traje 13 godina. Postojale su hiperpigmentacija, teleangiektazije i progresivno zatezanje kože lica i prstiju. Uzorak krvi je bio pozitivan na antinuklearna antitela. Sklerodaktilija je započela na distalnim falangama prstiju. Osetljive i bolne naslage kalcijuma pojavile su se supkutano na površini dlanova i kolena, radiografski potvrđene. Pacijentkinja je lečena hirurškim uklanjanjem depozita, vazodilatatornim agensima, kortikosteroidima, diltiazemom, sildenafilom, nitro-pastom, antitrombocitnim lekovima i fizikalnim terapijama. **Zaključak**. Potrebno je kontrolisati mnogobrojne faktore koji utiču na svakodnevno funkcionisanje, uključujući ishranu, terapiju bola, disfunkciju mišićno-skeletnog sistema, emocionalne i socijalne aspekte uzrokovane deformitetima. Ciljana terapija zahvaćenih organa u ranom stadijumu bolesti, pre nego što nastupe nepovratna oštećenja, poboljšava ukupan kvalitet života.

Ključne reči: ograničena skleroderma; kalcinoza; CREST sindrom; autoimuna oboljenja; faktori rizika

Introduction

Systemic sclerosis is a rare autoimmune connective tissue disorder. The prevalence is estimated at 1/12,500 adults, with a higher incidence among women (female to male ratio around 4:1) [1, 2]. It typically affects various organs, including the skin, gastrointestinal system, lungs, kidneys, skeletal muscle tissue, and pericardium. Systemic sclerosis or scleroderma is a generalized form, whereas limited scleroderma, also known as calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias (CREST) syndrome, is the localized variant [3]. Limited scleroderma may lead to the development of progressive pulmonary arterial hypertension, rarely seen in diffuse scleroderma, with a prevalence of 10% [3]. Prominent findings include the intimal proliferation of small and medium-sized pulmonary arteries. While biliary cirrhosis is uncommon in systemic sclerosis, it may develop in limited scleroderma. Various peripheral nervous system symptoms are associated with direct auto-inflammatory processes, vasculitis, or median neuropathy due to compression [1, 3]. In this report, we present a case of limited scleroderma and provide a summary of current knowledge about its treatment, along with all the criteria for its definition.

Case Report

We present a 64-year-old woman with a diagnosis of limited scleroderma. The first symptoms appeared on the acral areas of the hands thirteen years ago. She visited a primary healthcare physician due to numbness in the fingers and toes upon exposure to cold, which resulted in discoloration of her digits from white to blue. Upon exposure to warmth, her digits became red, painful, swollen, and stiff. After physical examination, the primary healthcare physician found telangiectasia in the skin on the palms, and sclerodactyly, which started in the distal fingers of both hands. Skin thickening was also observed on

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Abbreviations
CREST – calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias

the hands. The laboratory tests showed abnormal results for the following: erythrocyte sedimentation rate of 66, red blood cell count of 3.7 x 10^{12}/L, hemoglobin level of 8.8 g/L, positive antinuclear antibody 1:580 with a centromere pattern, and negative anticentromere antibody. There was no family history of a similar condition, and the patient reported no other serious diseases. According to physical examination and laboratory test results, Raynaud's phenomenon was suspected and a rheumatologist was consulted. During the diagnostic procedures, the rheumatologist found nail fold capillary abnormalities, and no pathologic radiologic findings. As she met at least 3 of the following clinical features: Raynaud's phenomenon, sclerodactyly, and telangiectasia, the diagnosis of limited scleroderma was made by a rheumatologist, three months after consulting the primary healthcare physician. In the first stage of the disease, the patient received anti-inflammatory drugs, vasodilators, hydroxychloroquine, anti-anemic drugs, corticosteroid hand creams, and was advised to wear gloves and warm socks when cold, physical therapy and regular exercise, avoid smoking, stress, and eliminate sympathomimetic medications.

The face was affected five years after the appearance of the first symptoms. The facial skin was tight, thin, and hard, which made it look smaller, and wrinkles appeared around the mouth. A dry mouth caused difficulty smiling, laughing, talking, and chewing food. The patient also developed firm yellowish nodules on the finger joints and had regurgitation after large meals. She also reported difficulty swallowing and heartburn, and additional tests were performed to identify any complications related to the lungs, heart, and gastrointestinal system. Esophageal dysfunction was found using esophagogastroduodenoscopy and it was treated with proton pump inhibitors and prokinetic agents, in addition to the therapy she was already using. At that stage of the disease, she complained about muscle weakness.

In 2019, the patient reported tender and painful subcutaneous calcium deposits with a chalk-like consistency on the palms and knees. The X-ray showed calcinosis of variable opaque densities ranging in size from 10 x 10 to 10 x 15 mm lying superficially within the soft tissues **(Figure 1)**.

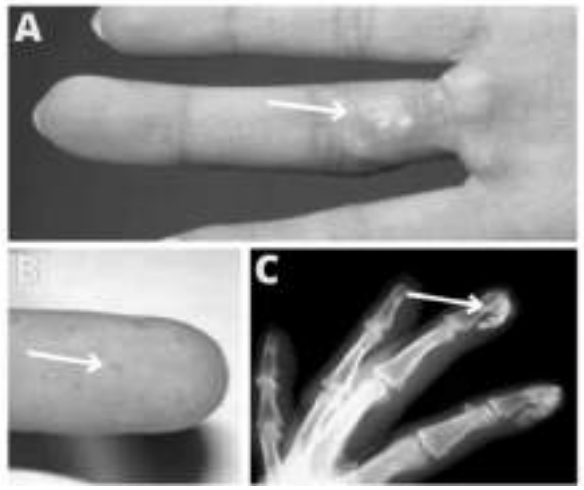

Figure 1. Calcinosis of the right hand (A); Telangiectasias of the left hand (B); Left hand X-ray shows calcification (C)
Slika 1. *(A) Kalcinoza na desnoj šaci; (B) teleangiektazije na levoj šaci; (C) radiografija leve šake prikazuje kalcifikaciju*

The patient underwent surgical debridement due to infection, which was treated with antibiotics. Paraspinal calcifications also occurred, resulting in local pain and radiculopathy. Antinuclear antibodies (1:640) were consistent in the patient's blood, along with mild leukocytosis, normocytic anemia, thrombocytosis, elevated erythrocyte sedimentation rate and C-reactive protein. The computed tomography did not indicate any lung fibrosis or pulmonary arterial hypertension. The patient received vasodilating agents, corticosteroids, diltiazem, sildenafil, nitro-paste, antiplatelet drugs, proton pump inhibitors, physical therapy, and hand and foot coverings. Regular multidisciplinary clinical follow-ups were necessary, which were coordinated by the primary healthcare physician.

Discussion

We presented a case of limited scleroderma from our clinical practice. Systemic sclerosis, also known as scleroderma, is an uncommon autoimmune disorder affecting connective tissues. Scleroderma can be classified into two main types: diffuse scleroderma

Table 1. CREST Syndrome
Tabela 1. *CREST sindrom*

(**C**) - Calcinosis ***(C)*** *- Kalcinoza*	Calcium deposits in the connective tissues *Depoziti kalcijuma u vezivnom tkivu*
(**R**) - Raynaud's phenomenon ***(R)*** *- Rejnoov fenomen*	Fingers and toes turn white and cold and then blue *Prsti na rukama i nogama postanu beli i hladni, potom modri*
(**E**) - Esophageal dysfunction ***(E)*** *- Disfunkcija jednjaka*	Swallowing difficulties *Poteškoće pri gutanju hrane*
(**S**) - Sclerodactyly/***(S)*** *- Sklerodaktilija*	Thick and tight skin on the fingers/*Debela i zategnuta koža na prstima*
(**T**) - Telangiectasias/***(T)*** *- Teleangiektazije*	Small red spots on the hands and face/*Male crvene mrlje na rukama i licu*

or systemic sclerosis, and localized scleroderma or limited scleroderma, which is characterized by calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias [4]. Scleroderma primarily affects organs such as the skin, gastrointestinal tract, lungs, kidneys, skeletal muscles, and pericardium [1]. Patients with CREST syndrome must meet at least three of the clinical features shown in **Table 1**, according to the American College of Rheumatology classification criteria [5].

In contrast to diffuse scleroderma, limited scleroderma affects only the skin of the extremities and is associated with a gradual and less severe progression of internal organ involvement. Calcinosis is a common complication and 22% of patients develop this condition within the first or second decade after diagnosis [6]. Despite normal calcium metabolism, chronic ischemia can lead to the calcium deposition in inflamed tissues. The subcutaneous tissues and fascia of the hands and feet, as well as the extensor surfaces of the forearms, elbows, and knees, are particularly prone to developing these deposits due to recurrent microtrauma [7]. Although calcific deposits can be asymptomatic, they may be tender and painful and can lead to ulceration, drainage of a chalky substance, and secondary infection. Paraspinal calcifications are rare, but can cause local pain, radiculopathy, and diffuse weakness [8].

Pharmacological treatment methods have been used to treat calcinosis, but there is no effective treatment to date. A variety of drugs such as warfarin, colchicine, probenecid, bisphosphonates, minocycline, salicylates, aluminum hydroxide, and diltiazem have been studied, but their effectiveness is variable [9]. Surgical intervention is necessary for distinct deposits accompanied by extrusion, wound infection, or discomfort. However, asymptomatic deposits should not be excised as they tend to recur.

Raynaud's phenomenon is common in individuals with scleroderma, affecting 96.3% of patients, and it is characterized by excessive vasospastic response to stress or exposure to cold [7]. This phenomenon results in the hands and digits turning cyanotic, pale, and flushed [7]. Esophageal dysfunction is also common, with 90% of cases caused by smooth muscle atrophy in the lower two-thirds of the esophagus. Gastrointestinal reflux caused by esophageal dysfunction can lead to Barrett's esophagus, esophagitis, hemorrhage, and/or strictures [6]. Another hallmark of scleroderma is sclerodactyly, which involves swelling, glossy skin, difficulty bending, and contractures in the fingers [1].

Telangiectasia occurs due to vascular dysfunction, intimal proliferation, thrombosis, and vasospasm. These are caused by abnormal vascular endothelial cells with mononuclear infiltration, disturbances in type 1 T helper and type 2 T helper cells activity, and abnormal fibroblast activity leading to increased collagen deposition [10]. Although biliary cirrhosis is uncommon in systemic sclerosis, it may occur in limited scleroderma. Pulmonary hypertension typically occurs in the absence of interstitial fibrosis (in 3 - 14% of cases) [8]. While seizures and headaches are the most common neurological symptoms in limited scleroderma, involvement of the peripheral and autonomic nervous systems is more common in systemic sclerosis [1].

To diagnose scleroderma, a comprehensive diagnostic approach includes physical examination and additional diagnostic testing. In particular, the presence of anticentromere antibodies is found in a large proportion of patients, ranging from 82 - 96%. However, this test is typically negative in cases of limited scleroderma. Additionally, various nonspecific indicators of inflammation, such as leukocytosis, normocytic normochromic anemia, thrombocytosis, elevated erythrocyte sedimentation rate, and elevated C-reactive protein, may be present and may help to make the diagnosis [11].

In the context of scleroderma, treatment involves various options, such as vasodilating agents, corticosteroids, diltiazem, sildenafil, topical nitroglycerin paste, antiplatelet drugs, physical therapy, and covering in case of Raynaud's phenomenon. However, there is currently no established treatment that can modify the overall course of the disease [1]. Nonetheless, organ-specific treatment can improve the quality of life and survival rate. For instance, in case of progressive pulmonary fibrosis, low doses of corticosteroids along with immunosuppressive agents are typically required. Pulmonary vasodilators are administered in case of pulmonary arterial hypertension. Given that scleroderma is a systemic disease with a variable clinical presentation, a multidisciplinary treatment approach is necessary, including early identification of affected individuals, prompt referral to rehabilitation, and attention to psychological comorbidities such as neuroticism and anxiety, which are closely related to somatization [12, 13].

Conclusion

This case report highlights the significance of a multidisciplinary approach in the management of limited scleroderma. The primary objective of treating limited scleroderma is to reduce the impact of specific organ involvement and enhance the quality of life. Several factors affecting the daily functioning of patients, including pain, musculoskeletal disuse, comorbidities, and emotional issues such as fear, depression, and social isolation caused by physical disfigurement, need to be addressed. Further studies are necessary to gain better understanding of this disease.

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MEDICAL TERMINOLOGY IN MODERN SERBIA – MORE THAN ONE AND A HALF CENTURY LONG JOURNEY (1841 – 1872 – 2022)

VELIKA GODIŠNJICA MEDICINSKE TERMINOLOGIJE U SAVREMENOJ SRBIJI – PUT DUG 1,5 VEK I VIŠE (1841-1872-2022 GODINE)

Ankica JELENKOVIĆ[1] and Rade BABIĆ[2]

Summary

Introduction. Linguistic expressions in a certain country, used in new or less developed sciences and professions, are commonly associated with difficulties due to the mother-tongue poverty. This also applies to the medical terminology. In modern Serbia, despite an eight-century-long hospital tradition, an institutional approach to the medical terminology was first established 180 years ago by the Society of Serbian Letters, founded in 1841, lasting until 1885. It was continued 30 years later by the Serbian Medical Society, founded in 1872. **Society of Serbian Letters.** The work of the Society of Serbian Letters on the Serbian language and terminology was very short, because Vuk Karadžić, among others, pointed out that the Society had to provide accurate and reliable terminology, which was not possible at the time. The work of Dr. Jovan Stejić and his translations of the books Macrobiotics and Anthropology are significant for medical terminology. **Serbian Medical Society.** Precisely set goals related to medical terminology and the preservation of the Serbian language in medicine were an integral part of the first Constitution of the Serbian Medical Society. However, during the continuous, 150-year- long work of the Society and the beginning of medical terminology standardization, for reasons still not explored, medical terminology has disappeared from its highest legal act, including the current Statute. **Conclusion.** Not even 180 years since the first short-term and 150 years since the long-term process of institutional approach to medical terminology was enough to develop and standardize medical terminology in modern Serbia. In order not to leave it to the arbitrariness of individuals, medical terminology must be a national strategy, such as, for example, the terminology of 33 professions in the Republic of Croatia called Croatian Professional Nomenclature.

Key words: Terminology as Topic; History of Medicine; Physicians; Famous Persons; Societies, Medical

Sažetak

Uvod. Jezički izraz nove ili do tada manje razvijene nauke i struke u jednoj zemlji neminovno nailazi na teškoće zbog siromaštva maternjeg jezika. Ovo važi i za medicinsku terminologiju. U savremenoj Srbiji, uprkos osmovekovnoj bolničkoj tradiciji, institucionalizovan pristup medicinskoj terminologiji prvi put je pre 180 godina uspostavilo Društvo srpske slovesnosti, osnovano 1841, trajalo do 1885. Nastavilo ga je 30 godina kasnije Srpsko lekarsko društvo, osnovano 1872. godine. **Društvo srpske slovesnosti**. Rad Društva srpske slovesnosti na srpskom jeziku i terminologiji bio je veoma kratak jer je Vuk Karadžić, između ostalih, isticao da Društvo mora da pruži tačne i pouzdane terminološke podatke, što u to vreme nije bilo moguće. Za medicinsku terminologiju značajan je rad dr Jovana Stejića i njegov prevod knjiga Makroviotika i Antropologija. **Srpsko lekarsko društvo.** Precizno postavljeni ciljevi u medicinskoj terminologiji i očuvanje srpskog jezika u medicini bili su sastavni deo Prvog ustava Srpskog lekarskog društva. Međutim, tokom ovih tačno 150 godina neprekidnog rada Društva i početka uspostavljanja medicinske terminologije, iz još uvek neistraženih razloga, medicinska terminologija je nestala iz njegovog najvišeg pravnog akta, uključujući i današnji statut. **Zaključak**. Ni 180 godina od prve kratkotrajne i 150 godina od dugogodišnje institucionalizacije medicinske terminologije nije bilo dovoljno da se u savremenoj Srbiji ona razvije i standardizuje. Da to ne bi bilo prepušteno samovolji pojedinaca, medicinska terminologija mora da bude nacionalna strategija, kao što je, na primer, terminologija 33 struke u Republici Hrvatskoj nazvana STRUNA.

Ključne reči: terminologija kao tema; istorija medicine; lekari; poznate ličnosti; medicinska društva

Introduction

The evolution of the medical profession and science, as well as of all other scientific and professional disciplines, is inevitably associated with the evolution of language of the environment in which they are applied. This especially applies to environments in which they are new or have been less de-

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Abbreviations
SSL – Society of Serbian Letters
SMS – Serbian Medical Society
STRUNA– Croatian Professional Nomenclature

veloped compared to other areas/countries. It is the same with medicine in Serbia. Although it has a very long tradition, starting with the founding of the first hospitals in Hilandar and Studenica by Saint Sava in 1198 and 1207, respectively, slavery under the Turks lasting about 3.5 centuries, necessarily led not only to stagnation, but also to regression of medicine. In contrast, countries of Europe, many of which were physically defended and protected from the Turkish invasion by the Serbs, experienced no delays in their development. That is why it is not surprising that, in the 18th and 19th centuries, the citizens of Serbia mostly studied medical science in the countries of Western Europe. Upon returning to the country, newly graduated doctors, due to the lack of appropriate medical terms in the Serbian language, encountered difficulties or even impossibility of expressing themselves in Serbian language in their profession, either in communication with each other, or in communication with the largest number of patients who, just like today, mostly had no medical education. Thus, there was a need to introduce a large number of previously unknown terms into the Serbian language, to come up with completely new words - terms denoting certain concepts in science. This implied the formation of scientific terminology.

Figure 1. Dr. Jovan Stejić
Slika 1. *Doktor Jovan Stejić*

And the number of new words directly depended on the development of the native language at that time.

In Serbia, the need for establishing and improving medical terminology was expressed by medical professionals in the 19th century. These activities took place within the framework of appropriate scientific and professional societies, primarily the Society of Serbian Letters (SSL) and the Serbian Medical Society (SMS). Their members were medical doctors educated outside of Serbia, because such education was not possible in Serbia yet. To date, this process, with its ups and downs, has neither been completed, nor can it be expected, precisely because of the nature of language and the nature of medicine itself as a scientific field.

Development of medical terminology in modern Serbia

Institutional approach began 180 years ago (1841 - 2022): Society of Serbian Letters

With the founding of the Lyceum in Kragujevac in 1838, which was moved to Belgrade in 1841, it turned out that there were linguistic inconsistencies in teaching. In order to achieve, among other things, "dissemination of science in Serbian language, as well as education and improvement of language" [1], including the the creation of professional terminology, that were necessary due to rapid development of the society and science in general, the SSL, i.e. literacy in the broadest sense of the word, was founded under the patronage of Prince Mihailo Obrenović in 1841, and lasted until 1845. The members of the Society were learned and important people of that time in the fields of science and literature, including Jovan Sterija Popović, Jernej Kopitar, Petar II Petrović Njegoš, Sava Popović Tekelija. The first institutional approach to the creation of terminology in general, including medical terminology, was established by this Society.

One of the founders and the member of the SSL, its secretary and vice-president was Jovan Stejić (1803, Arad, Austria-Hungary – 1853, Belgrade), a medical doctor, writer, and educator **(Figure 1)**. He was educated thanks to the help of Sava Tekelija and Jevrem Obrenović. He started studies of medicine in Pest (Austria-Hungary) and finished in Vienna in 1829, after which he came to the Principality of Serbia [2]. Dr. Stejić held respectable and important positions in the social and political life of the Principality of Serbia. He contributed a lot to the development of civil healthcare.

Dr. Jovan Stejić actively participated in the work of the SSL. He had a notable role in the reform of the Serbian language and orthography and its development and standardization at a time when the modern Serbian literary language was at its very beginning. Although he was in favor of them to a large extent, he did not always agree with Vuk Karadžić on the issues of language reform that he implemented. And "in his writings he advocated a middle way in the development of the Serbian literary language, especially in terms of its orthography

... When it comes to newly created words, Stejić was prone to purist understanding, but also allowed the use of foreign words, but selectively". He advocated a language "known to the priest and the judge, the merchant and the craftSMSn, the farmer and the servant" [3].

He worked on the creation of terminology, including medical terminology. "He is considered the founder of medical literature and medical terminology in this area" [2]. He came across medical terminology at a very young age, during his studies, translating from German into Serbian the book "Macrobiotics - the Science of Prolonging Human Life" (1826), whose author was the Berlin professor of the Faculty of Medicine, Johann Peter Huferland. "It was the first medical book in Serbian language in the Principality of Serbia" [4]. In the translation, he had to introduce some new and "changed" words, which did not lose their significance in relation to the text he was translating.

Later on, Dr. Stejić gave new medical terms in the translation of the book "Anthropology or Science of Man" (1850) by an unknown author, on the cover of which he wrote that he adapted it to Serbian rather than translated it. In an analysis of this book, it was determined that out of 245 terms in the field of anatomy, as many as 210 were domestic and a SMSll number of words were of foreign origin, Latin, Greek, Slavicisms and a few Turkishisms, which he opposed. Today, 105 of those terms are still in use [5].

The systematic work of the SSL on developing a terminology system in general, including medical terminology, was interrupted in 1845, mostly under the influence of Vuk Karadžić, a member of this Society. "Vuk criticized this experiment (creation of terminology in the SSL, author's note) both in writing and orally, stating that the main reason was that the participants did not know their native language well. An individual would also be allowed to propose new words, said Vuk, so others would accept or reject them; but the SSL is an authority, and it must not propose mistakes" [6]. This action clearly showed the understanding and attitudes towards terminology: it was not a matter of an individual, but it had to be approached in an organized manner. Also, it should be done by experts with exceptionally good education and knowledge. Therefore, their work would give no reasons for any doubt. Unfortunately, such conditions did not exist at the time of the beginning of the work of the SSL, but also many years later, so the creation of terminology was left to the good will of individuals. Dr. Jovan Stejić was among them. This was the case until the founding of the SMS in 1872.

Institutional approach continued 150 years ago (1872 - 2022): Serbian Medical Association

In 1872, the conditions were met for the establishment of the SMS. It was founded on April 22, 1872, by 15 doctors, five of whom were Serbs, three Czechs, two Poles, three Germans, one Greek and one Slovak. One of the aforementioned founders and initiator was Dr. Vladan (Hippocrates) Đorđević (1844, Belgrade - 1930, Baden, Austria), a military surgeon, founder of the military medical service and the Red Cross Society in Serbia, minister, ambassador, and writer. At the very first meeting of the SMS, Dr. Đorđević was presenting a case of a patient he was treating, and tried to find the appropriate term for the Latin term nodus, which was then named in the Serbian language for the first time as "gromuljica". Much earlier, Milan Jovanović-Batut (1847, Sremska Mitrovica - 1940, Belgrade), while still a medical student in Vienna, asked himself a question, for which he had no answer at the time, namely what was the word for scapula (Latin) in Serbian. He devoted his entire life to collecting materials for medical terminology. In 1886, his book "Materials for Medical Terminology" **(Figure 2)** was published, as the first of its kind in our country [7]. Unfortunately, although he collected 60,000 words, and this number is not definitive, he never translated them into a medical dictionary [8]. However,


ГРАЂА

ЗА МЕДИЦИНСКУ ТЕРМИНОЛОГИЈУ

САБРАО

ДР МИЛАН ЈОВАНОВИЋ-БАТУТ.

(ПРЕШТАМПАНО ИЗ ЛЕТОПИСА „МАТИЦЕ СРПСКЕ" ЗА ГОД. 1886.)

У НОВОМ САДУ

СРПСКА ШТАМПАРИЈА ДРА СВЕТОЗАРА МИЛЕТИЋА

1886.

Figure 2. Materials for Medical Terminology (Novi Sad, 1886)

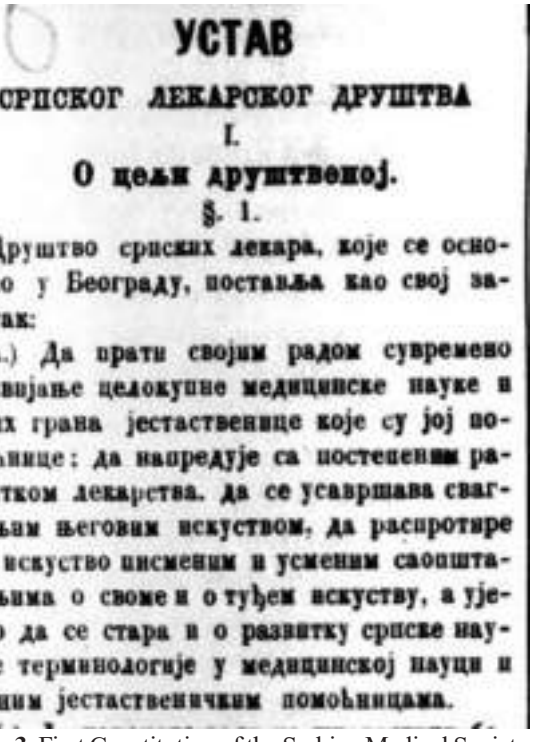
Slika 2. *Građa za medicinsku terminologiju (Novi Sad, 1886)*

Prof. Aleksandar Kostić, our famous histologist, managed to publish "Multilingual Medical Dictionary", perhaps his most famous work [9]. The first edition is from 1956. Professor Kostić worked persistently and systematically on our medical terminology.

At the meetings of SMS, since the beginning of its work, the members realized that there were no corresponding word in Serbian language for many medical terms they learned during their studies. The SMS Constitution is an excellent indicator that the issue of medical terminology has been approached extremely seriously. In the first paragraph, under point a, it is stated that SMS "takes care of the development of Serbian scientific terminology in medical science and its disciplines" **(Figure 3)** [10].

At the suggestion of the president of the SMS, Aćim Medović, the conclusions of the fourth meeting of the SMS (September 16, 1872), formulated in three points, were printed in the Serbian Archives of Medicine, journal established at the first meeting of the SMS. The first issue of the journal was published in 1874. Among other things, the journal published professional presentations from SMS meetings and conclusions reached at SMS meetings on issues of importance for the medical profession, health and well-being of people in Serbia, including medical terminology. Some of the conclusions from the fourth meeting were as follows [11]:

"a) The Society uses terms used by the people, and if they have not yet been collected, it collects them from the people for its own needs and progress;



УСТАВ

СРПСКОГ ЛЕКАРСКОГ ДРУШТВА

I.

О цељи друштвеној.

§. 1.

Друштво српских лекара, које се основало у Београду, поставља као свој задатак:

а.) Да прати својим радом савремено развијање целокупне медицинске науке и оних грана јестаственице које су јој помоћнице: да напредује са постепеним развитком лекарства. да се усавршава свагдањим његовим искуством, да распростире то искуство писменим и усменим саопштавањима о своме и о туђем искуству, а једно да се стара и о развитку српске научне терминологије у медицинској науци и њеним јестаственичким помоћницама.

Figure 3. First Constitution of the Serbian Medical Society (July 25, 1872)
Slika 3. *Prvi Ustav Srpskog lekarskog društva (25. 7. 1872.)*

b) The newly coined terms should not to be submitted for publication, until they are formally accepted within the limits of the freedom of expression, and

c) Instead of other folk terms, until the society learns the place of newly coined terms, which are not adopted, Greek and Latin terms should be used, as the greatest scholars in other nations do".

The basic task of the SMS in terms of medical terminology was also confirmed in the amended First Constitution from 1873, which was formulated in point 3 of Article 1:

"To (SMS - author's note) take care of Serbian terminology in medical science and its basic disciplines according to the laws of science and idiomatic Serbian language and above all by collecting and critically adopting words that exist in the Serbian nation" [12].

In the creation of medical terminology, SSL and SMS preferred Serbian to foreign words. They were searched for, if they were not already in practice. Yet, there were always individuals or groups who intensively advocated internationalism and/or foreign words. If something is a historical legacy of SMS, it is certainly the clearly expressed awareness and foresight of the first generation of doctors, founders and members of SMS, about the need and importance of the development of medical terminology. The proposed terms could be used only after they were adopted by the SMS. It was expected that a professional approach to the creation and development of medical terminology, one of the basic achievements of the SMS set at the very beginning of its work, would be a continual and permanent responsibility of the SMS. How successful was it?

Medical terminology in Serbia today

Today, the SMS does not have a Constitution, but it does have a Statute, and the last one was adopted on December 28, 2018. In Article 4, the first paragraph is entitled "Goals and Tasks of the Society" [13]. The beginning of the first sentence reads: "The objectives of the Society are to preserve the historical heritage of Serbian healthcare and to take care of IT...". There is no mention of medical terminology in the Goals, or in other parts of the Statute, although it is a historical heritage. Do these relentless facts indicate that the terminology in the amendment to the first Constitution of the SMS has become absolutely outdated?

It has not yet been investigated when medical terminology, as a task of the SMS, disappeared from its basic legal act or why. This may have been the result of an assessment that:

– The process of creating medical terminology in our country has already been completed and there is no need for an institution such as SMS to further take care of it;

– Medical terminology is an unimportant part of medicine and there is no need for SMS to deal with terminology;

Figure 4. Prof. Radivoje Pavlović
Slika 4. *Prof. Radivoje Pavlović*

– Another institution took over the care of medical terminology from the SMS and it will continue to work on it, etc.

Radivoje Pavlović (1893, Chip, south of Budapest, Austria-Hungary - 1938, Belgrade), the first Serbian professor of pharmacology at the Faculty of Medicine in Belgrade **(Figure 4)**, could have helped us understand the current situation. With his extraordinary medical, general and musical education, knowledge of many foreign languages, including Hungarian, Latin and ancient Greek, and his completely developed attitude to the state of medical terminology in our country, with scientific precision, clearly, reliably and uniquely he explained many important aspects on this topic in his unique work "On Medical Terminology" from 1928. He wrote: "... the development of our medical literature brought the creation of new words ... new words must be created for new terms". He continues: "Medical terminology in no language will be elaborated and can never be elaborated, arranged and definite in all details, as long as a language is alive." In order for this process of creating new words to be as successful as possible, there must be some rules and "certain instructions must be created on the main issues, there must be a platform".

The Republic of Croatia is a good example of how to take care about the native language today and it may be a guide to others. Along with several state institutions, in 2007 it launched a national program for the creation of professional terminology in Croatian language, whose acronym is STRUNA (Croatian Professional Nomenclature), which is financed by the state [15]. "STRUNA is a terminological database of Croatian professional terminology in which the terminology of various professions is systematically collected, created, processed and interpreted in order to build and harmonize terminology in Croatian language." Medical science is one of the 33 professions covered by the STRUNA program.

If the concept of institutional approach is replaced by an individual approach and the development of medical terminology is left to individuals, there will be inconceivable consequences, both due to the creation of inappropriate new words in the Serbian language, and due to uncritical and incorrect adoption of foreign words. Professor Pavlović points out where the danger may come from: "Semiliterate intellectuals, so numerous in their professions, do not learn well their mother tongue during schooling, and become susceptible to the influence of grammar, syntax and stylistics of foreign languages, especially if they stay abroad for a long time. This is where countless errors of all kinds originate from, not only in journalistic, popular and professional literature, but even in fiction" [14].

Although the medical profession, for the most part, has for a very long time resisted accepting, perception or trends in terms of unreserved acceptance of foreign terms [16], in recent decades, however, mostly wrongly, foreign words, regardless of whether they are Greek, Latin, English or from some other language, have violently invaded our medical terminology. They are often introduced into the Serbian language by the process of "Serbization", incorrect and inaccurate translations. There are many studies that clearly show how improperly this is done [17].

Adoption of foreign words has its good sides, because the language is enriched, but there are also bad sides, because they squeeze out native words, as well as the obligation of the society to create appropriate terms in the Serbian language if they do not already exist, which impoverishes the language. Proponents of using foreign words, including internationalism, are not only medical doctors, but also experts in the Serbian language. This is especially emphasized in the case of the so-called obscene words, selected according to their own standards: "In modern medical terminology, international terms are also mandatory, in order to avoid obscene words" [18]. Since the meaning of a foreign and native word must not differ, the only question is: why is a foreign word not obscene, but the Serbian is?

Conclusion

Newly formed words, which are often incorrectly, unprofessionally coined and classified as medical terms, are very dangerous for future gen-

erations, because, in the absence of criticism, these terms are imposed as the only correct and acceptable solution, and young people, almost as a rule, in these cases trust the authorities because they encounter these terms for the first time. Thus, the avalanche of bad medical terms is becoming more and more established. It will be like that until the creation of terminology in general, not only medical, is established by the state, as its national interest in nurturing and preserving the Serbian language and, consequently, clear principles of terminology creation are established. Also, from the point of view of the current state of this important field of medical science, the statement of Dr. Batut from 1886 must be genuinely analyzed: "At this moment, our medical terminology is so incomplete ..." [7]. Experts, in the true sense of the word, with different professional education, not only linguists or medical doctors, should continue working on medical terminology, which was systematically started more than 1.5 centuries ago, and it is a great aniversary today. The last 180 years were not enough for Serbia to establish a standardized medical terminology, rather, it has not been done even to a significant extent.

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

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

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

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

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

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Rukopis treba da sadrži sledeće elemente:

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

2. Sažetak

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

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

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

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

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

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

3. Tekst članka

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

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

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

Uvod

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

Materijal i metode

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

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

Diskusija

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

Zaključak

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

4. Literatura

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

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

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Elektronski materijal

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∗ Monografija u elektronskom formatu

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

∗ Kompjuterska datoteka

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

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

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

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

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

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

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

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

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

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

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

6. Dodatne obaveze

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

INFORMATION FOR AUTHORS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Preparation of the manuscript

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

The covering letter:

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

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

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

The manuscript:

General instructions.

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

The manuscript should contain the following elements:

1. The title page.

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

2. Summary.

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

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

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

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

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

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

3. The text of the paper.

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

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

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

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

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

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

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

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

Articles in journals

∗ *A standard article*

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

∗ *An organization as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

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

∗ *An issue with supplement*

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

∗ *A summary in a journal*

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

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

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

∗ *A chapter in a book*

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

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

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

∗ *Monographs in electronic format*

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

∗ *A computer file*

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

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

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

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

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

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

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

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

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

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