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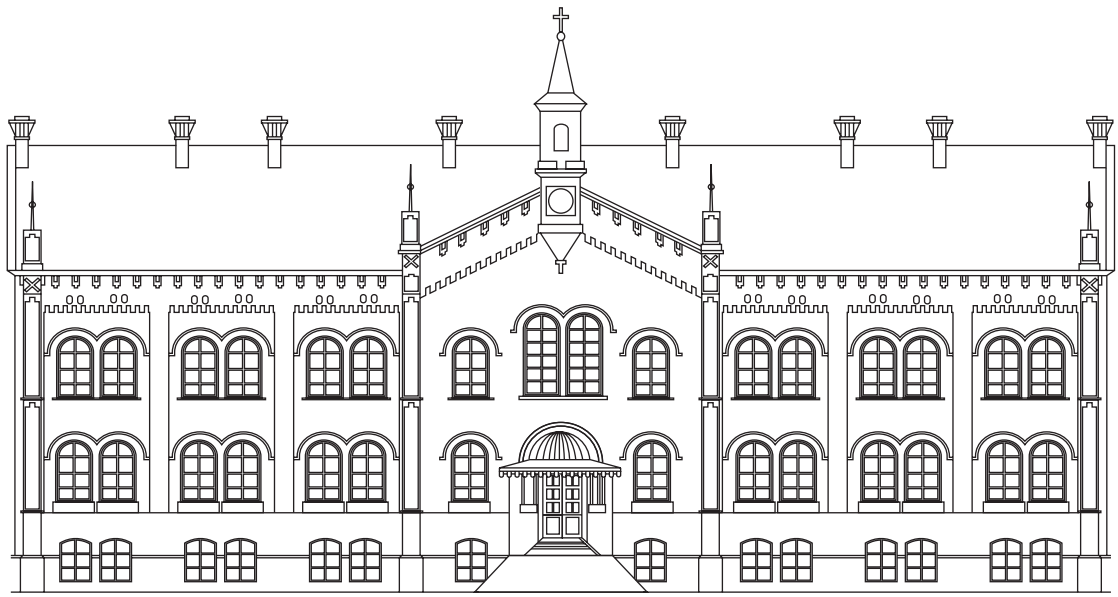

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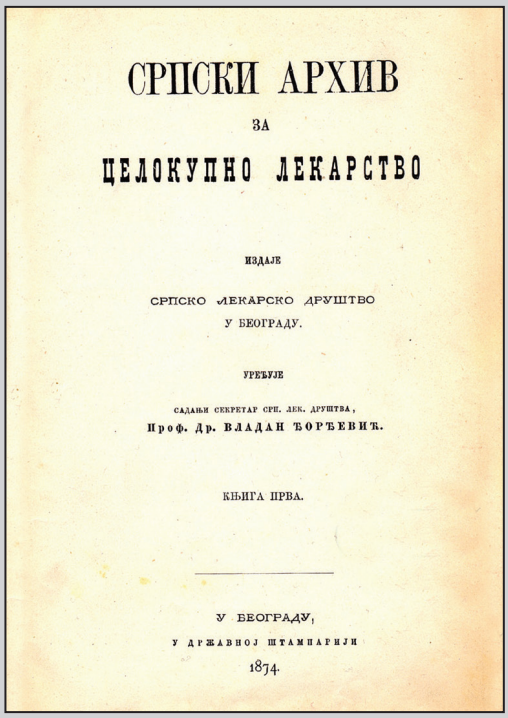

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ЗА

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1874.

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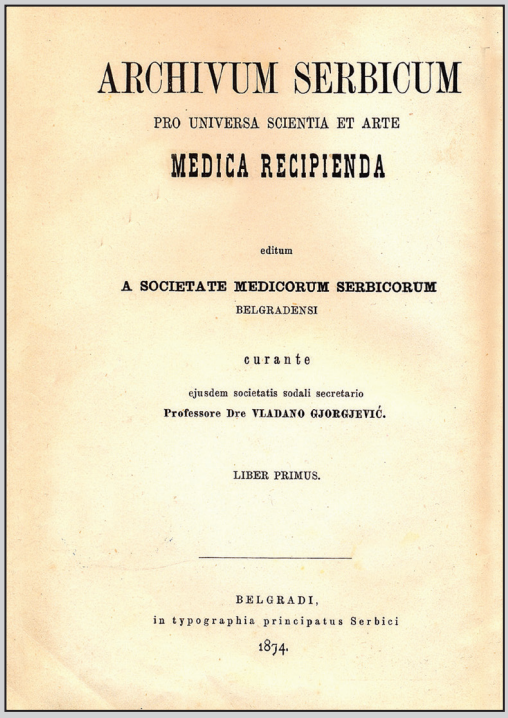

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1874.

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Depression and insomnia among students during the COVID-19 pandemic – a cross sectional study

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SUMMARY

Introduction/Objective In the first year of the COVID-19 pandemic, global prevalence of anxiety and depression increased by a massive 25%, according to the World Health Organization. The objective of the study was to determine the level of depression and insomnia among students in North Macedonia during the COVID-19 pandemic.

Methods A cross-sectional study was performed among students of the Ss. Cyril and Methodius University in Skopje during May–July of 2021. The anonymous online survey contained questions regarding their sex, age, their opinion and attitude towards the COVID-19 infection, if they had any infection/isolation, and about physical activity during the pandemic. We used scales for assessment of insomnia (Insomnia Severity Index – ISI) and depression (Patient Health Questionnaire 9 – PHQ-9).

Results The study was completed by 355 participants, 28.4% of them had clinically important insomnia scores and almost 47.5% of the participants presented clinically important depression scores. Female and younger participants had higher scores for both scales. A highly statistically significant, positive correlation was detected between ISI and PHQ-9 scores ($\rho = 0.646$, $p = 4.05 \times 10^{-43}$), suggesting that during the examined cross-sectional period of the COVID-19 pandemic, depression and insomnia were mutually connected.

Conclusion The COVID-19 pandemic caused a serious impact on mental health of the population, especially on young people, girls, students, and those who live alone. Therefore, we should be prepared for support and treatment of these vulnerable groups, not only as health care services, but also as educational institutions, to provide support to students in terms of consultation and motivation.

Keywords: pandemic; COVID-19; adolescents; insomnia; depression

INTRODUCTION

Nowadays, depression is a considerable cause of disability worldwide and a leading causation of a mental health-related disease burden [1]. On the other hand, sleep is extremely important for the overall function of the body, so cumulative long-term effects of insomnia have health consequences such as increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke [2].

Contrary to fear, which is a natural physiologic reaction that prepares our body for action in case of real danger, anxiety is an emotional state that occurs even when no real danger is present. Anxiety can affect and influence both depression and insomnia. With appearance of the virus COVID-19 in early 2020, anxiety was pushed to new levels, because of many reasons: change of daily routines, threats of illness and possible death, social isolation, living in small, sometimes crowded living spaces [3].

Clinical signs of COVID-19 infection were unknown and uncertain in the beginning of the pandemic and changing with time because of virus mutations. Fear of infection, other health, economic, and sociological challenges such as temporary unemployment, expensiveness, home-schooling/studying, and lack of physical contact with other family members, friends and colleagues contributed to different psychological problems during the pandemic.

In the first year of the COVID-19 pandemic, global prevalence of anxiety and depression increased by a massive 25%, according to a scientific brief released by the World Health Organization [4]. COVID-19 pandemic has had a tremendous impact on people's lives, affecting both physical and mental health [5]. Sleep disorders have been associated with infectious disease hazard, the incidence and progression of many diseases including depressive disorder [6]. During the COVID-19 pandemic depression, anxiety and insomnia were very prevalent [7]. The prevalence of anxiety, depression, and stress was 74.9%, 43.3%, and 78.9%, respectively, among medical students in North Macedonia during December 2020 [8].

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It is well known that depression, anxiety, and insomnia are important issues that could worsen mental wellbeing especially during a pandemic.

The objective of the study was to determine the level of depression and insomnia among students in North Macedonia during the COVID-19 pandemic.

METHODS

Study design and procedures

We designed and performed an anonymous online survey among students of the Ss. Cyril and Methodius University in Skopje, North Macedonia, for the period from May to the end of July 2021. The questionnaire especially created for this study consisted of questions regarding the sex and age of the participants, questions about their opinion of and attitude towards the COVID-19 infection, questions whether they had infection and/or isolation, and questions about physical activity during the pandemic. We used scales for the assessment of insomnia (Insomnia Severity Index – ISI) and depression (Patient Health Questionnaire 9 – PHQ-9). The ISI is a reliable and valid instrument consisting of seven-item assessment of insomnia symptoms over the prior two weeks, with items rated on a scale ranging from 0 ("no problems") to 4 ("very severe"). Total scores are categorized as not clinically significant (0–7), subthreshold insomnia (8–14), moderate insomnia (15–21), or severe insomnia (22–28) [9]. PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring depression severity and consists of nine questions that are relevant for rough estimation of the depression level. Each item is rated on a scale ranging 0–3. Total score below 4 suggests minimal depression and there is no need for treatment; 5–9 suggest mild depression; 10–14 suggest moderate depression, where clinical judgment based on duration of symptoms and functional impairment is necessary. Scores 15–19 suggest moderately severe depression, and severe depression is 20–27 points [10].

The study complied with the principles of Declaration of Helsinki, and we received an approval from the Human Research Ethics Committee within the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje (No 03-2092/1). Participants in the survey were informed about the research study and gave their consent to participate.

Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as the percentage of individuals, and the differences in the frequencies among the groups were calculated with the contingency coefficient and the χ^2 tests. Since the distribution of the values of all ordinal variables (age; ISI; PHQ-9 depression score) differed significantly from normality (Shapiro–Wilk's test, $p < 0.001$, Figure 1a–c), these results were expressed as median and interquartile range (IQR, reported as values of Q1–Q3). The Kruskal–Wallis F-test (followed by Mann–Whitney U-tests) was used to compare the differences in the central tendencies among the groups. The bivariate statistical analyses were performed using non-parametric correlation with Spearman's ρ-coefficient. In all cases, the level of statistical significance was defined as $p < 0.05$ (marked as *), i.e., $p < 0.001$ for highly significant (***).

RESULTS

The study was completed by 355 participants, response rate was 76%, the study group was characterized by dominantly female participants (83.4%), with an age range 18–36 years (median of 21; 20–23 interquartile range). Most of the respondents lived in a family accommodation with equal to or more than four members (42.5%), or less than four members (35.2%) (Table 1).

Table 1. Descriptive statistics of the study participants (n = 355)

Variable	Frequency[a]/ median (Q1–Q3)[b]
Age	21 (20–23)
Sex	
male	16.6%
female	83.4%
Type of household	
family accommodation with equal to or more than 4 members	42.5%
family accommodation with less than 4 members	35.2%
in a student dormitory	4.2%
alone in an apartment	18%
Insomnia Severity Index score	10 (5–15)
PHQ-9 Depression Score	9 (5–15)
Fear of COVID-19 infection	
not present	32.7%
mild	38.6%
moderate	21.1%
severe	7.6%
Previous infection with COVID-19	
have not been infected and have not got sick with COVID-19	55.8%
have not been infected with COVID-19, but underwent isolation	17.7%
have been infected and got sick with COVID-19	26.5%
Psychological changes and connection with COVID-19	
not related	36.9%
probably connected	47.3%
certainly connected	15.8%
Physical activity in the past months of COVID-19 pandemics	
yes	63.1%
no	36.9%
Weekly physical activity	
less than 150 minutes	69.9%
equal to or more than 150 minutes	30.1%

[a]Categorical variables are expressed as percentage of individuals;
[b]ordinal variables are expressed as median and interquartile range (as Q1–Q3)

The analyses of distribution of frequencies have shown that variables age, ISI, and PHQ-9 scores differ significantly from normality (Shapiro–Wilk's test $p < 0.001$). Most of our participants (207 participants, i.e., 58.6%) were

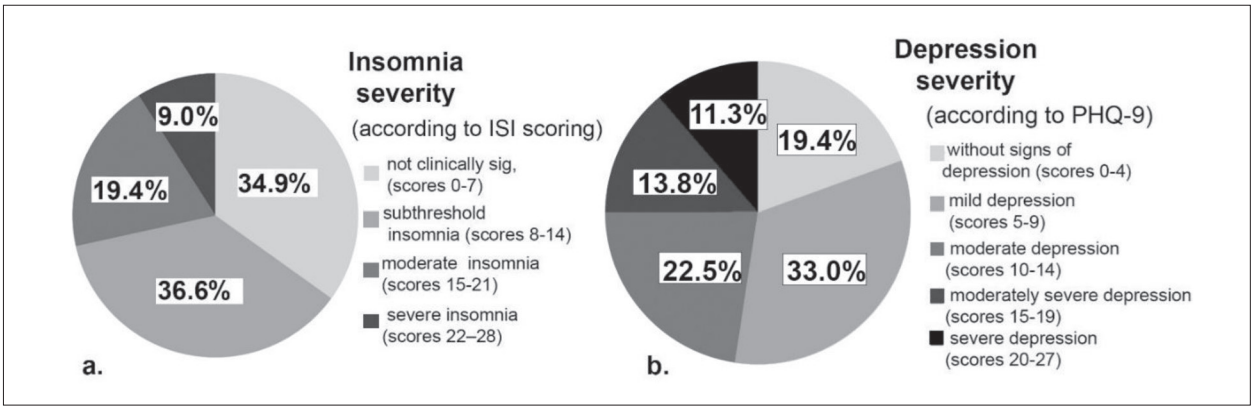

Figure 1. Insomnia (a) and depression severity (b) among the study participants

19–21 years old, characterized by subthreshold insomnia scores (maximal frequency of ISI results score was 8), and PHQ-9 scores corresponded to mild depression (maximal frequency of PHQ-9 score was 5). Concerning the connections with COVID-19, only 26.5% of the participants had been infected and had got sick with COVID-19 (most of the study participants were not infected with COVID-19 and did not undergo isolation – 55.8%); nevertheless, most of the participants answered that they had mild fear from the COVID-19 infection (38.6%). Only 15.8% of the study participants reported that their psychological changes were probably connected with COVID-19, while 47.3% stated that these changes were probably connected with COVID-19. Regarding the physical activity, most of the participants were not physically active during the previous months of COVID-19 pandemics (63.1%) or were physically active for less than 150 minutes for one week (69.9%).

After categorization of ISI scores, 34.9% of the participants were without any signs of insomnia (scores 0–7), 36.6% were expressing subthreshold insomnia (scores 8–14), and 28.4% had clinical important scores higher than 15 (i.e., 19.4% of the participants with moderate insomnia and 9% with severe insomnia) (Figure 1a).

Mild depression was detected in 33% of the participants (scores 5–9), moderate depression in 22.5% (scores 10–14), moderately severe depression was present in 13.8% (scores 15–19), and severe depressive episode was present in 11.3% (scores 20–27) of the examinees (Figure 1b).

Although our study group was mainly dominated by female participants, still the statistical tests were able to detect clear significant effects of sex on the ISI and PHQ-9 scores; namely, female participants had higher scores both for the ISI insomnia index ($U = 6989$, *p = 0.015; Figure 2a) and the PHQ-9 (U = 5885, ***p = 0.00007; Figure 2b), suggesting that females were more susceptible to psychological changes during COVID-19 pandemics. The results were more evident for PHQ-9 depression score, where analyses of frequencies showed that only 12.5% of the female participants suffered from severe depression, while only 5.1% of the male population was characterized with severe depression (contingency coefficient = 0.206, $\chi^2 = 15.73$, *p = 0.003).

The type of household has shown mild effect only on the insomnia ISI score, statistically significant higher insomnia ISI scores were detected in participants who lived alone in the apartment, when compared to the participants accommodated in a family with equal to or more than four members (U = 4600, *p = 0.039; Figure 2c).

Younger participants were shown as more susceptible to both insomnia and depression; the bivariate statistical analyses revealed negative, mild, but statistically significant correlations of age with both the ISI score ($\rho = -0.208$, ***p = 0.0009; Figure 2d) and especially the PHQ-9 depression score ($\rho = -0.264$, ***p = $4.9 \cdot 10^{-7}$; Figure 2e). From the scatters (Figures 2d–e; trend of the relation along with 95% confidence interval is shown) it can be noted that for both scores, younger participants have more diverse specter of scores, but as age increases, participants older than 26 years expressed only low scores (up to score 10 for ISI and up to score 6 for PHQ-9). Further analyses disclosed that this relation of age with ISI and PHQ-9 scores was not affected by sex, since similar correlation coefficients were assessed for both male and female participants.

A highly statistically significant, positive, and strong correlation was detected between ISI and PHQ-9 scores ($\rho = 0.646$, p = $4.05 \cdot 10^{-43}$, Figure 2f), suggesting that during our examined cross-sectional period of the COVID-19 pandemic, depression and insomnia were mutually interrelated and interconnected. Higher ISI scores were associated with higher PHQ-9 scores and vice versa. The analyses of frequencies confirmed highly significant elevated percentage of severe insomnia in participants assessed with severe depression, when compared to the ones with absence of depression (46.9% *vs.* 3.1%, respectively; contingency coefficient = 0.553, $\chi^2 = 156.188$, ***p = 3.14×10^{-27}; Figure 2g).

DISCUSSION

This study confirmed a high level of insomnia and depression in students, expressed with high percentage of fear (mild was 38.6% and moderate to severe in 28.7% of the examinees), although 55.8% of the participants had not been infected, against 26.5% of them who had got sick with

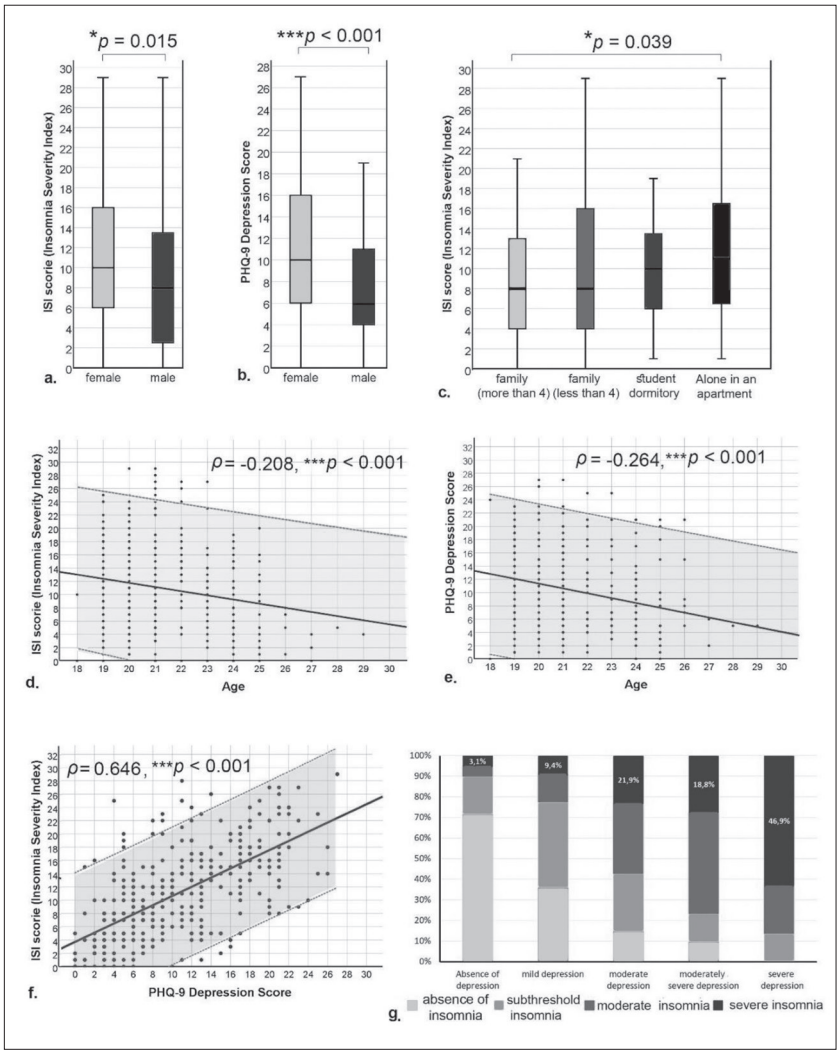

Figure 2. Effects on sex, age, and type of household on the Insomnia Severity Index (ISI) score and the PHQ-9 depression scores; mutual relations between ISI and PHQ-9;
a. female participants showed significantly higher scores for the ISI index (*p = 0.015); results shown as median and interquartile range (IQR), depicted with boxplot;
b. female participants had highly significantly elevated depression scores according to PHQ-9 (***p = 0.00007); results shown as median and IQR, depicted with boxplot;
c. significantly higher insomnia ISI scores were detected in participants who live alone in the apartment, when compared to the participants accommodated in a family with more than four members (*p = 0.039); results shown as median and IQR, depicted with boxplot;
d. effects of age on the ISI score; negative, mild, but statistically significant correlation of age was shown with the ISI score (ρ = -0.208, ***p = 0.0009); the scatter depicts the linear trend, with the 95% confidence interval;
e. effects of age on the PHQ-9 score; negative, mild, but statistically highly significant correlation of age was shown with the PHQ-9 depression score (ρ = -0.264, ***p = 4.9×10^{-7}); the scatter depicts the linear trend, with the 95% confidence interval;
f. a highly statistically significant, positive, and strong correlation was detected between the ISI and the PHQ-9 scores (ρ = 0.646, p = 4.05×10^{-43}); the scatter depicts the linear trend, with the 95% confidence interval;
g. a highly significant elevated percentage of severe insomnia (46.9%) in participants assessed with severe depression, when compared to the ones with absence of depression (3.1%; $\chi^2 = 156.188$, ***p = 3.14×10^{-27}); analyses based on comparison of frequencies with a contingency table

need for medical care and treatment seems indubitably warranted. Statistically significant higher insomnia ISI scores were detected in participants who lived alone in the apartment. Younger participants were more susceptible to both insomnia and depression. Highly statistically significant, positive, and strong correlation between the ISI and the PHQ-9 scores (ρ = 0.646, p = $4.05 \cdot 10^{-43}$, Figure 3f) proved that during our examined cross-sectional period of the COVID-19 pandemic, depression and insomnia were mutually interrelated and interconnected.

Based on the U.S. Census Bureau Household Pulse Survey data, the United States Centers for Disease Control reported significant increases in symptoms of anxiety and depressive disorders among adults aged ≥ 18 years from August 19, 2020 to February 1, 2021, with the largest increases among adults aged 18–29 years and among those with less than secondary education. Across the entire study period, the frequency of anxiety and depression symptoms was positively correlated with the average number of daily COVID-19 cases [11].

The study performed before COVID-19 pandemic in Thailand showed that psychological problems associated with depression were anxiety, sleep problems, internet addiction, and loneliness [12]. One review found that students experienced moderate to extremely severe scores and depression (34%) during the first weeks of confinement and points out to females, especially adolescents, as more susceptible to psychological changes [13]. The systematic review and meta-analysis found pooled prevalence of depression of 43.3% in university students and 25% of anxiety connected with females and somatic disorders [14].

This is in line with the data by WHO, according to which it should not surprise us that COVID-19 pandemic triggered a 25%-increase in prevalence of anxiety and depression worldwide and most affected were young people and women [4]. Young people were at higher risk of developing mental health problems than adults [15]. Young respondents reported more severe insomnia symptoms, subjectively poorer sleep quality, and

COVID-19. Almost half of the examined students (47.32%) thought that the psychological changes were probably connected to the COVID-19 pandemic and 16% of them confirmed that they were certainly connected.

Clinically important depression scores were detected in 47.5% of the participants and 28.4% of the participants had clinically important insomnia scores; therefore, the

a more prevalent disruption of sleep habits (bedtime, get-up time, nap) than the elderly. On the other hand, older participants showed shorter sleep duration. Finally, the younger population displayed higher levels of depression and perceived stress [16]. Recently performed meta-analysis has shown that female participants from the general population and university students experienced a statistically significant change in depression symptoms by minimal to small amounts during the pandemic [17]. One Chinese study also reported very high rates of clinically significant insomnia (20%), acute stress (15.8%), anxiety (18.5%), and depression (24.5%). The sample was composed predominantly of females (70%), similar to our study, and insomnia was generally more prevalent among females [18]. Researchers from Serbia reported moderate to severe depression in 28.9%, anxiety in 36.9%, and stress symptoms in 38.1% of the adult population, but students had a significantly higher level of depression and stress, while older age was protective against anxiety and stress [19]. A study performed in England has shown that higher number of COVID-19 deaths was associated with increased depressive and anxiety symptoms, and they found also longitudinal association of mental health with individual level factors, like COVID-19 knowledge, COVID-19 stress, COVID-19 infection, and social support [20].

In the cross-sectional study conducted in Brazil, with participants aged 13–18 years, more than half (58.2%) had worsened their sleep quality during the pandemic. The authors found significant associations between sleep and decreased school motivation ($p = 0.005$), and between sleep and sex ($p = 0.015$). The pandemic affected more females, 25.5% reported poorer sleep quality, 67% had sleep disorders; 30.1% students reported stress and anxiety [21].

Analyzed relation and interplay between insomnia and depression severity confirmed that they are mutually interrelated and interconnected. Insomnia, anxiety, and depression were very prevalent during the pandemic. Anxiety and depression were more severe in the insomnia than in the non-insomnia group, and insomnia and mental health care were closely related [22]. The COVID-19 pandemic has resulted in numerous life changes that may be conceptualized as precipitating events for the development of insomnia symptoms [23]. ISI scores showed that one third was without signs of insomnia, but the rest expressed subthreshold insomnia (36.62%) and clinical important scores were present in 28.45% of them. Statistically significant higher scores of insomnia were present in participants living alone. This result is in line with other studies [24]. The results indicated that insomnia is more severe in people who are female, young, and are experiencing a high degree of threat from COVID-19. The prevalence of insomnia was highly variable between sites, but the predictors appeared to be the same everywhere. Insomnia was significantly related to mood disorders, anxiety disorders, substance use disorders, and psychotic disorders [25]. According to a study during the first COVID-19 outbreak, insomnia was more severe in females, young people and those experiencing high threat [26].

Females, physically non-active people, people who fear COVID-19, are associated with insomnia [27, 28]. Almost two-thirds (63.1%) of the examinees said that they had less than 150 minutes (69.9%) of weekly physical activity and the rest had equal to or more than 150 minutes that are recommended as minimum for good physical and mental health according to WHO. Physical activity can prevent future depression [29]. According to this meta-analysis, there is an association between physical activity and incident depression. Assuming causality, one in nine cases of depression might have been prevented if everybody in the population was active at the level of current health recommendations [30].

Our study has some limitations because the data was derived from a single center and with a small sample group that consisted mainly of females. Nevertheless, many studies have similar biases, and this can be overcome with meta-centric studies and close follow-up in the future. In addition, studies across different geographical locations with detailed and strong methodology are needed.

CONCLUSION

COVID-19 pandemic caused a serious impact on the mental health of the population, especially on young people, girls, students, those who live alone. Some of them with impaired mental health during the pandemic may have similar and more serious problems later in life. The health system has to be prepared for early diagnosis and treatment of these people.

We may consider this pandemic finished, but no one knows when a new threat will appear among the population. Therefore, support and treatment of vulnerable groups should be prepared, not only by health care services, but also by educational institutions, to provide support to students in terms of consultation and motivation. Primary and secondary interventions on the national and local levels are necessary in focusing on adolescents and youth mental health.

Conflict of interest: None declared.

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Депресија и несаница међу студентима током пандемије ковида 19 – студија пресека

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САЖЕТАК

Увод/Циљ У првој години пандемије ковида 19, глобална распрострањеност анксиозности и депресије повећана је за огромних 25%, саопштила је Светска здравствена организација.

Циљ студије био је да се утврди ниво депресије и несанице међу студентима у Северној Македонији током пандемије ковида 19.

Методе Ово је студија пресека међу студентима Универзитета Св. Ћирила и Методија у Скопљу током маја и јула 2021. Анонимна онлајн анкета садржала је питања за пол, године, мишљење и однос према инфекцији вирусом корона, да ли су имали било какву инфекцију/изолацију и о физичкој активности током пандемије. Користили смо скале за процену несанице (индекс озбиљности несанице – *ISI*) и депресије (упитник о здрављу болесника 9 – *PHQ*-9).

Резултати Студију је завршило 355 учесника, од којих је 28,45 одсто имало клинички важне оцене несанице и скоро половина учесника је имала клинички важне оцене депресије. Женски и млађи учесници имали су веће оцене за обе скале. Високо статистички значајна, позитивна корелација откривена је између резултата *ISI* и *PHQ*-9 ($\rho = 0{,}646$, $p = 4{,}05 \times 10^{-43}$), што указује на то да су током испитаног пресечног периода пандемије ковида 19 депресија и несаница били међусобно повезани.

Закључак Пандемија ковида 19 изазвала је озбиљан утицај на ментално здравље становништва, посебно на младе људе, девојке, студенте и оне који живе сами. Зато треба да будемо спремни на подршку и лечење ових рањивих група, не само као здравствене службе већ и као образовне установе, да подржимо ученике кроз консултације и мотивацију.

Кључне речи: пандемија; ковид 19; адолесценти; несаница; депресија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Self-harm in children and youth – impact of the COVID-19 pandemic

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SUMMARY

Introduction/Objective COVID-19 pandemic caused many disruptions in the daily routines of children and adolescents, which may have influenced their mental health.
This study aimed to examine the impact of the COVID-19 pandemic on self-harming behaviors, including non-suicidal self-injury (NSSI) and suicide attempts in children and youth seeking psychiatric help.
Methods Retrospective, cross-sectional study was conducted, analyzing data from medical documentation of 1129 outpatients, aged between 10 and 18, who had their first psychiatric examination at the Institute of Mental Health in Belgrade, Serbia between March 1, 2019 and August 31, 2021. The frequency of NSSI and suicide attempt during the pandemic was compared to a one-year period before the pandemic.
Results Proportions of patients with NSSI were higher in both years during the pandemic (18.1%; 27.7%) compared to the year before (12.6%), especially in the second year of the pandemic, with a marked increase in March 2021. NSSI was more frequent in girls, older adolescents, those living in incomplete families and those with a history of abuse. No significant change in the frequency of suicide attempts related to the COVID-19 pandemic was found.
Conclusion Significant increase in the frequency of NSSI, markedly during the second year of the pandemic, especially in children and youth with additional factors of vulnerability, calls for further attention from both professionals and policymakers, as well as preventive measures for this vulnerable group during stressful times.
Keywords: non-suicidal self-injury; suicidal attempt; child; adolescent; pandemic

INTRODUCTION

Suicide is the second leading cause of mortality among children and youth aged 10–24, and a global public health concern that requires more interest from the medical community. While youth mortality from major medical disorders has declined in recent years, the prevalence of child suicide has increased. Suicidal thoughts and behavior are more frequent than completed suicide [1, 2]. Self-injurious behavior is a broad category of behaviors in which an individual directly and deliberately causes harm to oneself. It can include non-suicidal self-injury (NSSI), as a direct, deliberate destruction of one's own body in the absence of intent to die; or suicide attempts, which refer to acts directed toward intentionally ending one's own life [3]. The rate of self-injurious behavior is low in early childhood but increases rapidly with the onset of teenage years [4]. Even though NSSI excludes explicit suicidal intention, it is associated with suicidal thoughts and behaviors.

Those who engage in NSSI are more than four times more likely to attempt suicide later in life [5]. Moreover, engaging in NSSI can predict the transition from suicidal thoughts to attempted suicide in youth [6].

Systemic changes have occurred due to the coronavirus disease (COVID-19) pandemic, including the temporary closure of academic institutions, limited accessibility to health and social services and the disruption of children's and their families' daily routines, having significant influence on their lives [7, 8]. The state of pervasive fear, the presence of stress, the lack of psychological support systems, and worsening socio-economic conditions in many families have led to the worsening of existing and the emergence of new mental health issues [9].

Many school-based social, healthcare, and mental health services were disrupted, potentially resulting in negative academic, emotional, behavioral, and social outcomes [10]. Job loss or working from home along with constant worry and uncertainty are important causes of stress for the parents, which can further cause negative effects on children, directly or indirectly [11]. On one hand, school closure, online classes, and the loss of extracurricular activities resulted in the lack of social support which could have influenced children and youths' mental health negatively. On the other hand, the pandemic caused a reduction of academic pressure and stress, peer conflicts and violence, which could have had some positive effects [12, 13].

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Within the population of psychiatrically hospitalized youth COVID-specific suicidal thoughts and behaviors occurred (engaging in purposeful COVID-19 exposure with suicidal intent) [14].

Understanding how the still current pandemic affects mental health of children and youth is critical for evaluating strategies to enhance outcomes for persons who are experiencing mental health deterioration. The aim of our study is the evaluation of the influence of the COVID-19 pandemic on the frequency of NSSI and suicide attempts among children and adolescents, as well as the possible contributing risk factors within this population.

METHODS

This research was conducted as a retrospective, cross-sectional study, including data from medical documentation of 1129 children and youth, aged 10–18 (mean age 14.17; 57.8% girls), who had their first psychiatric examination in the Institute of Mental Health in Belgrade, Serbia between March 1, 2019 and August 31, 2021. Presence of NSSI and suicidal attempt during the pandemic period (March 2020 – August 2021) was compared to a one-year period before the pandemic (March 2019 – February 2020). The presence of any type of abuse, family status and the presence of negative life events were also examined as possible risk factors.

Ethics approval

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Institute of Mental Health in Belgrade, Serbia (Date 14.12.2021/No.1060/2110/1).

RESULTS

Proportion of patients with NSSI has increased in the second year of the pandemic period (27.7%) compared to the year before (12.6%) and the first year of the pandemic (18.1%) (Table 1). Comparing the first year of the pandemic period with the prior year, there was a slightly higher proportion of patients with NSSI, with the effect size bordering on significance ($\chi^2 = 4.538$, p = 0.03, Cramer's V = 0.074 (weak effect)). When comparing the second year of the pandemic period with the first year, there was a significant increase in frequency of patients with NSSI ($\chi^2 = 7.247$, p = 0.007, Cramer's V = 0.113 (weak effect), Figure 1).

A marked rise in frequency of patients with NSSI occurred in March 2021, with frequencies in the following months on the same level for the remainder of the observed time period (that is, until August 2021). No significant differences were found between the prior period and the first year of the pandemic ($\chi^2 = 1.359$, p = 0.244), or the first and second year ($\chi^2 = 214$, p = 0.643).

The average age of patients with NSSI (mean = 14.82, SD = 1.718) was slightly greater (F = 23.305, p = 0.000) compared to the rest (mean = 14.02, SD = 2.211), with most patients in the NSSI group being girls (89.1%).

A similar pattern was observed with the frequency of suicidal behavior, with no differences between the pre-pandemic period (7.3%) and the first year of the pandemic (7%), and a significant increase in the second year (11.9%) ($\chi^2 = 6.893$, p = 0.032, Cramer's V = 0.078 (weak effect), Figure 2).

In regard to other sociodemographic variables, considered as possible risk factors, patients with NSSI more frequently came from incomplete families (55%) compared to the rest of the sample (39.3%, $\chi^2 = 16.741$, p = 0.000, Cramer's V = 0.122 (weak effect)). The presence of any type of abuse was also more frequently associated with NSSI (27.2% of NSSI patients compared to 19% of the rest, $\chi^2 = 6.923$, p = 0.009, Cramer's V = 0.078 (weak effect)). No significant differences were found in regard to the frequency of negative life events – 38.6% in the NSSI group, and 35.4% in the non-NSSI group ($\chi^2 = 0.752$, p = 0.386).

Table 1. Number of patients with non-suicidal self-injury and suicidal behavior distributed by time period

Time period	Non-suicidal self-injury n (%)	Suicidal behavior n (%)	Others n (%)	Total n
Pre-pandemic[1]	71 (12.6%)	41 (7.3%)	451 (80.1%)	563
First year[2]	49 (18.1%)	26 (7%)	195 (74.9%)	270
Second year[3]	82 (27.7%)	32 (11.9%)	182 (60.4%)	296

[1]March 2019 – February 2020;
[2]March 2020 – February 2021;
[3]March 2021 – August 2021

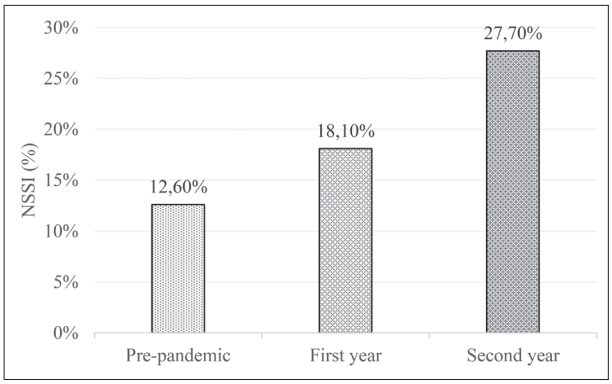

Figure 1. Non-suicidal self-injury trend

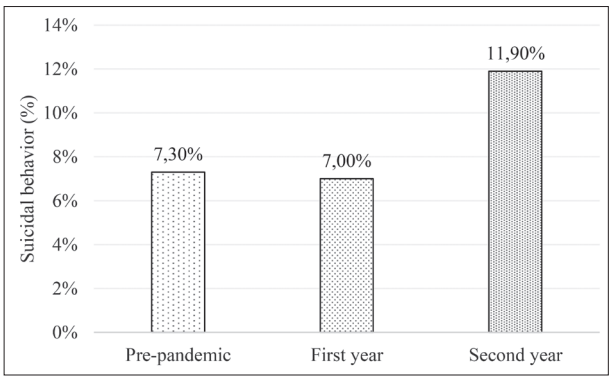

Figure 2. Suicidal behavior trend

Patients who attempted suicide were, on average, older (mean = 15.09, SD = 1.464) than patients in the non-suicidal group (mean = 14.08, SD = 2.188, (F = 20.390, p = 0.000). As was the case with NSSI, most patients that attempted suicide were girls (82.8%). No significant differences were found in regard to either family status, the presence of abuse, or negative life events.

DISCUSSION

Results of our study suggest that the proportions of children and adolescents with NSSI within our sample were higher for both periods during the pandemic (March 2020 – February 2021 and March 2021 – August 2021) compared to the one-year period before the pandemic (March 2019 – February 2020). The proportion of patients with NSSI during the first year of the pandemic was significantly higher than the year before (with a weak effect size), and in the second pandemic period (March 2021 – August 2021). This increase in frequency was even more significant compared to the first year of the COVID-19 pandemic, with a marked increase of frequency in March 2021. These results are consistent with other research regarding the effects of the pandemic on the frequency of NSSI in the adolescent population [15, 16, 17].

It is important to note that our sample was made up of children and adolescents seeking help from psychiatric services for the first time, it does not give us insight into the general population of children and adolescents where the number of those who self-harm without seeking help might be greater. Moreover, children and youth with a previous history of contact with the psychiatric service were also excluded from the sample, which could be a subject of a future study.

NSSI is mainly used by children and youth as a strategy for short-term emotional regulation. Previous research shows that stressors, depressive symptoms, hopelessness, the lack of adequate social support, negative interactions within close relationships as well as parental psychopathology are significant risk factors for NSSI [18, 19]. It is probable that many of the newly instituted restrictive measures and general changes in daily routines have led to increased stress in children, but also in their parents and other close relationships, making them feel hopeless and isolated, and therefore more prone to engage in NSSI.

The mean age of children and youth with NSSI was slightly greater compared to those not engaging in NSSI (mean = 14.82, SD = 1.718 *vs.* Mean = 14.02, SD = 2.211, p = 0.000), and most of the patients engaging in NSSI were female (89.1%). Finding that girls more often engage in NSSI compared to boys, both during and before the pandemic, is supported by previous studies [15, 16, 20, 21], as well as the fact that higher age is linked to NSSI among adolescents [21].

Children and adolescents engaging with NSSI more often came from incomplete families compared to those who do not self-injure (55% *vs.* 39.3%, p = 0.000). This was also the case with children and adolescents with a confirmed history of any type of abuse (27.2% *vs.* 19%, p = 0.009). However, comparing these two groups by the presence of negative life events did not yield a significant difference. Previous research on psychosocial factors related to NSSI in adolescents during the COVID-19 pandemic supports the connection between NSSI and living in an incomplete family and the experience of abuse (bullying) but differ in relation to negative life events [21]. This difference in negative life events could be because our data collection was not specific enough to determine the number and type of negative life events.

Regarding suicide attempts, no significant differences were found between the three examined periods, between the two pandemic years, nor the pandemic and pre-pandemic period. This result differs from other studies, where it was shown that the proportion of youth with recent suicide attempts was greater in the first year of the COVID-19 pandemic compared to a year before [22, 23]. Some studies also suggest there was an increase in suicide attempts in both pandemic years, but only after April and May 2020 (when there were strict lockdowns in most countries) [24]. This relative increase is dependent upon methodology and sampling. Especially in the clinical samples it could be a reflection of the decrease in help seeking related to other, less acute mental health problems, due to changes in the availability of care. There are also multiple studies that show no significant difference in the frequency of suicide attempts in the adolescent population compared to the pre-pandemic period overall [25, 26, 27] in concordance with our results.

Patients that have attempted suicide were, on average, older (Mean = 15.09, SD = 1.464) than the patients in the non-suicidal group (Mean = 14.08, SD = 2.188, p = 0.000). Most patients with suicide attempts were girls (82.8%). These results are supported by previous studies for both the pandemic, and the pre-pandemic period. Older adolescents are more likely to attempt suicide compared to younger children according to available research [26].

Girls seem to be more prone to suicide attempts compared to boys, probably more so when faced with stressors leading to internalizing problems, both in pandemic and pre-pandemic studies [24, 26, 28]. Comparing the patients that have attempted suicide with those who have not, no significant differences were found regarding either family status, the presence of abuse, or negative life events. This was an unexpected finding, considering that multiple pre-pandemic studies show that living in an incomplete family, the experience of abuse and other significant negative experiences are related to adolescents more often engaging in suicide attempts [29, 30].

CONCLUSION

Analyzing retrospective data from the COVID-19 pandemic period and the year prior to the pandemic, our study offers preliminary evidence that the pandemic may be a contributing factor in the increase in NSSI, especially in the year since the beginning of the pandemic. This increase was especially pronounced in girls and older adolescents, those living in incomplete families and those that have experienced abuse. This effect was not observed for suicide

attempts, as the frequencies did not significantly change during the pandemic, nor was the relationship proven for other examined psychosocial factors. Girls and older adolescents were more likely to attempt suicide, which is not a change in comparison to the pre-pandemic period. These findings call upon healthcare providers and related professionals, as well as policymakers, to pay closer attention to adolescents' mental health during a pandemic, especially young girls, having in mind that the presence of NSSI can predict the future transition from suicidal thoughts to attempted suicide in youth.

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Conflict of interest: None declared.

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Самоповређивање код деце и омладине – утицај пандемије ковида 19

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САЖЕТАК

Увод/Циљ Пандемија ковида 19 изазвала је бројне промене дневних рутина деце и адолесцената, што је могло утицати на њихово ментално здравље.

Циљ овог истраживања је да испита утицај пандемије ковида 19 на самоповређивање, укључујући несуицидно самоповређивање и покушаје суицида код деце и омладине којима је била потребна психијатријска помоћ.

Методе Спроведена је ретроспективна студија пресека, анализирани су подаци из медицинске документације 1129 амбулантно лечених болесника, узраста од 10 до 18 година, који су први пут прегледани на Институту за ментално здравље у Београду, између 1. 3. 2019. и 31. 8. 2021. Учесталост несуицидног самоповређивања и покушаја суицида је поређена са једногодишњим периодом пре пандемије.

Резултати Пропорција болесника са несуицидним самоповређивањем је била виша у обе године у току пандемије (18,1%; 27,7%) у поређењу са годином пре пандемије (12,6%), нарочито током друге године пандемије, са видним порастом у марту 2021. године. Несуицидно самоповређивање је учесталије код девојчица, старијих адолесцената, оних који живе у непотпуној породици или имају искуство злостављања. Није утврђена значајна разлика учесталости покушаја суицида у вези са пандемијом.

Закључак Значајан пораст учесталости несуицидног самоповређивања, нарочито у току друге године пандемије, посебно код деце и младих са додатним факторима осетљивости, указује на потребу за праћењем од стране стручњака и доносилаца одлука, као и превентивним мерама за ове осетљиве групе у периодима повишеног стреса.

Кључне речи: несуицидно самоповређивање; покушај самоубиства; деца; адолесценти; пандемија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Thromboembolic complications in patients with COVID-19 – experiences of the General Surgery Department of Zemun Clinical Hospital Center

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SUMMARY

Introduction/Objective More than three years have passed since the discovery of the new virus strain SARS-CoV-2, and the virus is still a challenge for all medical specialties. One of the most important characteristics is the tendency to develop thromboembolic complications, which are often lethal.
The aim of this paper is to present the experience of the General Surgery Department of the Zemun Clinical Hospital Centar in the surgical treatment of patients with thromboembolic complications.

Methods The research was conceived as a retrospective study conducted in the period from March 2020 to March 2021. A total of 42 patients participated in the study and were divided into a group diagnosed with small and large bowel ischemia and a group diagnosed with acute limb ischemia.

Results In both groups, males were predominantly represented. The first group consisted of nine patients, all of whom had a clinical finding of acute abdomen and ileus, while seven of them also had a severe computed tomography image of bilateral pneumonia. In the second group, a smaller number of patients were initially candidates for thrombectomy, while in others, primary amputation treatment was approached. Mortality from the underlying disease in both groups was high.

Conclusion Moderate and severe forms of SARS-CoV-2 infection are associated with an inflammatory response leading to endothelial dysfunction accompanied by a high incidence of thromboembolic complications despite pharmacological prophylaxis. The current consensus supports the use of anticoagulants in all hospitalized patients with moderate to severe disease, as well as in critically ill patients.

Keywords: COVID-19; SARS-CoV-2; thromboembolic complications; thrombosis

INTRODUCTION

More than three years have passed since the discovery of the new virus strain SARS-CoV-2 in Wuhan, People's Republic of China, and the virus is still present and poses a problem and challenge for all medical specialties. This disease is manifested by a different clinical manifestation, starting from asymptomatic cases, through symptoms and signs such as loss of taste and smell, fatigue, myalgia, gout, diarrhea and dry cough, which may or may not be accompanied by a fever. In addition to high transmissibility, the main feature of this disease is a significant tendency to develop complications at the level of various organ systems, which are often lethal. According to the data of the Institute of Public Health of the Republic of Serbia, over 200 million infected people are currently diagnosed in the world, with a fatal outcome in over 4 million patients. In our country there was 1,286,025 infected people until December 22, 2021, while the fatal outcome was confirmed in 12,488 patients.

One of the most significant complications of this disease is the dysfunction of the coagulation system. According to a study by Lazzaroni et al. [1] coagulation dysfunction itself can be observed through two main pathogenetic pathways, i.e., through inflammation with a consequent cytokine storm and through virus-specific mechanisms. Excessive immune response, hypoxia, diffuse intravascular coagulation and prolonged resting in patients are thought to be the main triggers for venous and arterial thromboembolic complications. A study conducted by Klok et al. [2] showed that the incidence of thromboembolic complications in patients treated in the intensive care unit is as high as 31%. Due to the high potential for the development of thromboembolic complications, we have a higher frequency of pulmonary embolism, deep vein thrombosis, coronary infarction, acute limb ischemia, ischemia at the level of the gastrointestinal tract and cerebrovascular strokes. A study by Omar et al. [3], which referred to radiological findings, showed the presence of thromboembolic complications in 10% of patients, where 45% of patients had pulmonary embolism, 25% cerebrovascular event, 13.7% limb ischemia, while 15.3% of patients were diagnosed with gastrointestinal thromboembolic disease.

The aim of this study is to present the experience of the General Surgery Department of KBC Zemun in the surgical treatment of patients with thromboembolic complications of SARS-CoV-2 infection.

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METHODS

Our research was conceived as a retrospective study, approved by the ethics committee of our Institution, and was conducted in the period from March 2020 to March 2021. The study involved a total of 42 patients hospitalized within the Department of General Surgery of KBC Zemun, who with their written consent underwent surgical treatment due to thromboembolic complications of SARS-CoV-2 infection.

We divided the patients into two groups. The first group consisted of nine patients with intraoperatively diagnosed ischemia of the small intestine and/or large intestine (Table 1), while the second group included 33 patients with diagnosed acute ischemia of the extremities (Table 2). In eight patients of the second group, acute arterial thromboembolism of the extremities was verified by clinical examination and via Color-Doppler, and they were operated on within six hours from the onset of the disease.

Table 1. Data on operated patients in COVID Zemun Clinical Hospital Center due to thromboembolic complications at the level of digestive tract

Gender		M = 6 (66.67%)	F = 3 (33.33%)
Age (years)		Youngest – 42	Oldest – 87
Pneumonia		(+) 9 (100%)	(-) 0 (0%)
PCR +/-		(+) 6 (66.67%)	(-) 0 (0%)
Ag +/-		(+) 7 (77.78%)	(-) 2 (22.22%)
Type of operation	Small bowel resection with primary anastomosis	6 (66.67%)	9
	Small bowel resection and right hemicolectomy	2 (22.22%)	
	Hartmann procedure	1 (11.11%)	
Mortality		6 (66.67%)	

Table 2. Data on operated patients in COVID Zemun Clinical Hospital Center due to thromboembolic complications at the level of extremities

Gender		M = 26 (78.79%)	F = 7 (21.21%)
Age (years)		Youngest – 49	Oldest – 81
Pneumonia		(+) 26 (78.79%)	(-) 7 (21.21%)
PCR +/-		(+) 28 (84.85%)	(-) 3 (9.1%)
Ag +/-		(+) 22 (66.67%)	(-) 11 (33.33%)
Type of operation	Thrombectomy/ Embolectomy	8 (24.24%)	33
	Femoral amputation	18 (54.55%)	
	Crural amputation	7 (21.21%)	
Mortality		16 (48.48%)	

The inclusion criteria were: confirmed SARS-CoV-2 infection (polymerase chain reaction or antigen method), both sexes, age over 18 years and verified acute abdominal events or acute limb ischemia.

All patients who were included in the study were preoperatively prepared according to the emergency admission protocol of the Surgery Clinic of KBC Zemun. Among the additional diagnostic procedures, computed tomography (CT) examination of the target topographic region, Doppler examination of the main blood vessels of the extremities, X-ray and ultrasonographic examination of the abdomen were applied. Consultative examinations of internists and anesthesiologists were also performed.

Methods of descriptive and analytical statistics were used in this study: absolute and relative numbers (n, %) and measures of central tendency (arithmetic mean, median). The necessary data were obtained by reviewing the protocol of surgical treatment, the patient's medical history, temperature list and anesthesia list, as well as by reviewing the histopathological findings.

RESULTS

In the group of patients with small intestine and/or large intestine ischemia, there was a statistically significant difference between the sexes, where male patients were dominant, accounting for two thirds of those treated. Out of a total of nine patients, small bowel resection with primary anastomosis was performed in six of them, there were two small bowel resections with right hemicolectomy, while Hartmann procedure was performed on one patient due to descending colon ischemia. All patients had a clinical finding of acute abdomen and ileus with radiographically diagnosed hydroaerial levels. As many as seven patients in this group had severe bilateral pneumonia with a CT score of 17–23. Since CT angiography was not available for preoperative diagnosis, mesenteric venous thrombosis was verified intraoperatively in seven patients. Postoperatively, one patient had an operative wound infection, one had dehiscence of the operative wound - treated with re-suturing, while one had dehiscence of the anastomosis which was treated with reoperation and stoma. In six patients, a lethal outcome occurred within 48 hours due to complications of the underlying disease, while the remaining three were discharged for further home treatment.

In the second group, there was also a statistically significant difference between the sexes, with 78% being male. Thrombectomy was performed in eight patients, seven of which were lower limb thrombectomies, while one was thrombectomy of the upper limb. Despite the application of adequate antithrombotic therapy, after 48 hours the complication in terms of retrombosis occurred in six patients, and due to the progression of the ischemic finding, we had to perform femoral amputation in four patients. Due to the consequences of the underlying disease, six patients from this subgroup died. From the remaining 25 patients, in 18 cases femoral amputation had to be performed due to the irreversible ischemic process, while in seven patients crural amputation was performed. Mortality in this group was recorded in as many as 16 patients or 48.48%, who had numerous comorbidities, progression of ischemia and very poor general condition caused by SARS-CoV-2 infection. Complications in the form of surgical wound infection were present in a relatively small number of cases, which can be explained by the protracted use of antibiotics preoperatively, rapid and atraumatic surgical technique, as well as a fairly high rate of postoperative mortality due to cardiovascular complications. Complications in the form of hematoma of the amputation stump and prolonged drainage activity were

recorded in a very low percentage of only 0.9% in relation to the type of pathology, regardless of the perioperative application of high doses of anticoagulant therapy.

DISCUSSION

The development of progressive endothelial thromboinflammatory syndrome, which leads to small blood vessel disease, is thought to be at the root of thromboembolic complications associated with SARS-CoV-2 infection [4]. A review of literature reveals that a large percentage of patients with a severe form of COVID-19 can develop venous and arterial complications [5].

COVID-19 is a multi-organ disease, causing acute complications through organ-specific pathogenesis followed by destruction of ACE2+ cells, including endothelium, cardiac microvasculature, alveolus and glomerulus. However, the fact that viral RNA is rarely detectable in patients' blood suggests that additional host-dependent factors may contribute to systemic endothelial dysfunction and vasculopathy in COVID-19, rather than just direct virus-dependent effects on endothelial cells [6].

The direct impact of Sars-Cov2 infection is achieved by binding the virus to endothelial cells. Endothelial cells are responsible for adequate hemostasis by maintaining the integrity of the blood vessel wall and maintaining the balance between fibrinolysis through the expression of coagulation inhibitors and blood clot enzymes, as well as maintaining the glycocalyx. SARS-CoV-2 alters vascular homeostasis by directly binding to endothelial cells via ACE2. Another piece of evidence is that in vitro, SARS-CoV-2 can successfully infect engineered organoids of human blood vessels, which further proves the tropism of SARS-CoV-2 for endothelial cells [7]. Binding to ACE2 results in internalization and down-regulation of ACE2, which further leads to reduced ACE2 expression and reduced angiotensin production. Angiotensin acts on the MAS receptor, and the consequent reduction of angiotensin leads to reduced activation of MAS, which promotes a local prothrombotic effect. In addition, the reduced expression of ACE2 can indirectly activate the kallikrein-kinin system and lead to an increase in vascular permeability [8].

On the other hand, the host's response can greatly affect endothelial dysfunction. As reviewed in a study by Perico et al. [9], hypercytokinemia and a massive proinflammatory host response may contribute to endothelial dysfunction in COVID-19 most likely through the action of IL-6 and TNF. The levels of these two cytokines are significantly increased in patients with severe forms of the disease [6]. In addition to the effect of cytokines, a number of studies have shown that reduced activity of endothelial nitric oxide synthase, decreased levels of nitric oxide and increased release of vascular endothelial growth factor due to hypoxia have also been suggested as key pathogenic processes [10]. Similarly, the complement system, as well as other components of the innate immune system, which helps control bacterial and viral infections, their unrestrained activation in prolonged SARS-CoV-2 infection can be harmful by causing direct tissue damage to the host. Activation of the complement system leads to damage and apoptosis of endothelial cells with subsequent vascular denudation and exposure of the thrombogenic basement membrane, which initiates the activation of coagulation cascades. These events result in inflammation, microvascular thrombosis, vessel edema, and hemorrhagic sequelae [11]. In Northern Italy, in a large series of autopsied lungs, platelet-fibrin thrombi were found in the largest number of cases in both small and large blood vessels of the lungs. Indeed, patients with SARS-CoV-2 infection are at increased risk of widespread coagulation of small and large vessels [12].

The results of a systematic review of the literature by Keshavarz et al. [13], which included 22 studies with 31 patients, suggest that thrombosis at the level of mesenteric blood flow was demonstrated in approximately half of patients diagnosed with intestinal ischemia. Based on all of the above, we see that the pathogenesis of thromboembolic complications in the gastrointestinal system is very complex. At the base is microvascular thrombosis involving the submucosal vessels of the intestine resulting from a combination of direct injury to the endothelium due to severe acute respiratory syndrome SARS-CoV-2, hyperviscosity as a consequence of the inflammatory response, and increased expression of von Willebrand factor with vascular stasis [14]. The clinical presentation of acute mesenteric thrombosis in COVID-19 manifests itself most often as an acute abdomen, and sometimes it is accidentally detected by more sophisticated radiological methods [15].

Serban et al. [16] performed a systematic review of 89 patients with acute mesenteric ischemia due to COVID-19. the average age of the patients was 59.3 ± 12.7 years with a slight predominance of men (61%), which is in accordance with our results. Among the clinical symptoms, abdominal pain was the most common symptom and was present in almost all patients. Fever was not differentially diagnostically significant because most hospitalized patients with COVID-19 either already have a fever or are receiving antipyretics. Other symptoms from the gastrointestinal tract such as nausea, anorexia, and vomiting are nonspecific and poorly sensitive and are present in only 30–40% of patients with mesenteric ischemia [16].

Our findings in terms of predominant venous thromboembolic events at the level of mesenteric blood flow coincide with the study by Omar et al. [3]. CT of the abdomen and pelvis with contrast is the method of choice for suspected mesenteric thrombosis. Ojha et al. [17] performed a systematic review of 75 patients with mesenteric thrombosis associated with COVID-19. It was shown that ischemia of the small intestine (46.7%) is more common than ischemia of the large intestine (37.3%). Arterial thrombosis was presented in about a quarter of patients, while venous thrombosis was verified in about 30% of patients [17]. In the case of the impossibility of CT diagnostics, native X-ray imaging can be of great help in the diagnosis of pneumatosis intestinalis and portal vein gas [18].

If we look at the study by Bhayan et al. [19], which included 412 patients with SARS-CoV-2 infection and was based on radiological diagnostic procedures performed

on the abdomen, we can note that abnormal findings at the level of the intestinal wall were verified in 31% of patients using CT imaging, by observing the presence of pneumatosis or gas at the level portal blood flow. Patients with this diagnostic finding underwent surgical treatment, where in two patients the finding was in favor of intestinal infarction, while the other findings were in favor of ischemic enteritis [19].

The surgical principles of treating acute abdomen in patients with COVID-19 infection are unchanged. By reviewing the literature, over 60% of patients with mesenteric thrombosis required surgical treatment. A smaller percentage of patients were treated conservatively or with endovascularly. The operative procedure that was carried out depended on the intraoperative findings, the time it took to diagnose mesenteric thrombosis, the location of the irreversible change on the intestines, but also the patient's general condition, as well as associated comorbidities. Hwabejire et al. [20] have described the undertaken surgical procedures. Based on their experience, over 85% of patients required bowel resection during the first exploratory laparotomy. Sometimes it is difficult to make a clear difference between an intestine with impending gangrene from a healthy intestine, so a second look is recommended. An individualization of the decision to perform an anastomosis or a stoma is required. According to their experience, about half of the patients could successfully undergo primary anastomosis [20].

The prognosis of mesenteric thrombosis in patients with COVID-19 is extremely poor. High mortality can be explained by the underlying disease but also by associated comorbidities [21]. A review of the literature by Kerawala et al. [22], which included 28 studies, indicated a high mortality rate in patients surgically treated for acute mesenteric ischemia, despite adequate follow-up, which agrees with our results. Numerous surgical series have reported a high mortality exceeding 50% [22].

As previously stated, the host's proinflammatory and procoagulant response, caused by virally induced vascular endothelial injury, can lead to arterial thrombosis and acute limb ischemia with a very poor prognosis [23]. This procoagulant condition significantly affects the veins, however, there is a large amount of evidence that indicates an increased risk of arterial thrombotic events in patients with COVID-19, especially for acute limb ischemia [24]. Galyfos et al. [25] performed a systematic review of data from multiple case studies to show that acute limb ischemia occurs more frequently in patients with COVID-19 and is associated with high mortality and amputation risk. Ischemic complications at the limb level were statistically significant in our study. Numerous retrospective studies have shown that the incidence of thrombotic events in SARS-CoV-2 patients ranges from 12% to 31%, as well as the fact that most are of venous origin. A study by Bozzani et al. [26] showed that arterial thromboembolic events are present in 4% of all thromboembolic complications. Al-Zoubi et al. [27] showed that the prevalence of acute limb ischemia is higher during SARS-CoV-2 infection than in the period before the pandemic. Of the seven patients observed in that study, two patients with asymptomatic SARS-CoV-2 infection underwent successful thrombectomy without mortality, while the remaining five who had severe infection and who were admitted in the intensive care unit had a lethal outcome within 24 hours of diagnosis [27]. In a large study conducted in the United States, Pharm et al. [23] showed that patients with COVID-19 and acute limb ischemia face worse clinical outcomes compared to patients with acute limb ischemia but without COVID-19. They concluded that COVID-19 can not only cause acute limb ischemia, but can also be responsible for a worse outcome of the disease [23]. The study of Bellosta et al. [28], which included 20 patients with acute limb ischemia, also confirmed a higher number of patients during SARS-CoV-2 infection than before the pandemic. Seventeen patients were treated surgically, revascularization was successful in 12 patients (70%), while 40% of patients had lethal outcome. Two patients underwent reintervention due to retrombosis within 48 hours. Bellosta et al. [28] showed that the failure rate of revascularization is almost 30%, as a result of hypercoagulable state, early recurrent thrombosis, poor clinical condition of patients and frequent postoperative complications. In addition, studies in the United States have shown that by increasing the rate of revascularization, amputation treatment is significantly less common in cases of critical limb ischemia. Unfortunately, in the case of patients with COVID-19, amputation is often the best option due to the severe general condition of the patients, late presentation to the health facility and rapid deterioration of the underlying disease [29]. Timely recognition of ischemic thrombotic events in patients with COVID-19 with intensive anticoagulant, thrombolytic treatment as well as a timely decision on revascularization treatment can reduce unwanted events in patients with acute limb ischemia.

CONCLUSION

Moderate and severe forms of SARS-CoV-2 infection are associated with an inflammatory response leading to an acute phase response and endothelial dysfunction, resulting in a procoagulant condition called COVID-19-associated coagulopathy. Incidence rates of thromboembolic complications in patients with SARS-CoV-2 infection are high despite pharmacological prophylaxis. Although most of the reports did not have a control group, as well as ours, the difference in incidence rates between those affected and those not affected is evident. Vulnerable groups, such as the elderly, pregnant women or people with multiple comorbidities, are at higher risk of hospitalization and even admission to the intensive care unit, which is a predisposition for the development of thromboembolic complications. The current consensus supports the use of anticoagulants in all hospitalized patients with SARS-CoV-2 infection who have moderate to severe disease, as well as in critically ill patients.

Conflict of interest: None declared.

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Тромбоемболијске компликације код оболелих од ковида 19 – искуства службе опште хирургије Клиничко-болничког центра „Земун“

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САЖЕТАК

Увод/Циљ Прошло је више од три године од откривања новог вирусног соја *SARS-CoV-2*, а вирус и даље представља изазов за све медицинске специјалности. Једна од најзначајнијих карактеристика је склоност ка развоју тромбоемболијских компликација, које су неретко леталне.
Циљ овог рада је приказ искуства Службе опште хирургије КБЦ Земун у хируршком лечењу оболелих од тромбоемболијских компликација.

Методе Истраживање је конципирано као ретроспективна студија која је спроведена у периоду од марта 2020. године до марта 2021. године. У студију су била укључена укупно 42 болесника и били су подељени у групу са дијагностикованом исхемијом танког и дебелог црева и групу са дијагностикованом акутном исхемијом екстремитета.

Резултати У обе групе доминантно је био заступљен мушки пол. Прву групу је чинило девет болесника. Сви су имали клинички налаз акутног абдомена или илеуса, док је њих седам имало и тешку клиничку слику обостране пнеумоније. У другој групи мањи број болесника је у почетку био кандидат за тромбектомију, док се код осталих приступило примарно ампутационом лечењу. Смртност од основне болести у обе групе је била висока.

Закључак Умерене и озбиљне форме инфекције *SARS-CoV-2* у спрези су са инфламаторним одговором који доводи до ендотелне дисфункције праћене високом стопом тромбоемболијских компликација упркос фармаколошкој профилакси. Тренутни консензус подржава примену антикоагуланаса код свих хоспитализованих болесника који имају умерену до тешку болест, као и код критично оболелих болесника.

Кључне речи: ковид 19; *SARS-CoV-2*; тромбоемболијске компликације; тромбоза

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Relationship between low vitamin D levels with Hashimoto thyroiditis

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SUMMARY

Introduction/Objective Vitamin D not only plays a role in calcium and phosphorus metabolism, but also has antiproliferative, prodifferentiation, anti-inflammatory and immunomodulatory effects.
The aim of this study was to investigate the association between vitamin D deficiency in individuals with autoimmune Hashimoto's thyroiditis.

Methods A total of 156 patients were enrolled and divided into two groups. First group included 108 patients with 25 (OH) D insufficiency, and second included 48 individuals with normal 25 (OH) D levels. All participants underwent a detailed clinical examination, laboratory tests for thyroid function [T3, fT4, TSH, thyroid antibodies (TPO-Ab, and TG-Ab)], as well as ultrasound scanning (thyroid volume and Doppler characteristics).

Results The patients with vitamin D insufficiency (n = 108 (69.2%)) were predominantly female and had a higher body mass index than the patients with normal vitamin D levels. The group with vitamin D insufficiency had statistically significantly higher TSH levels. The prevalence of positive thyroid antibodies was higher in the vitamin D insufficiency group, while thyroid volume, superior thyroid artery, and inferior thyroid arteries resistance index, as well as the prevalence of positive circular dichroism signals, were significantly higher in the vitamin D insufficiency group. Out of the 156 subjects, 44 were diagnosed with thyroiditis (28.2%). The mean serum level of 25 (OH) D was statistically notably lower in patients with thyroiditis (20.23 ± 8.10 ng/mL) than in the group without thyroiditis (25.44 ± 8.38 ng/mL), $p < 0.001$.

Conclusion There was an association between vitamin D insufficiency and hypothyroidism in subjects with Hashimoto's thyroiditis.

Keywords: vitamin D; insufficiency; Hashimoto's thyroiditis

INTRODUCTION

The vitamin D group consists of several related cholesterol-derived steroid compounds, the most important of which are vitamins D2 and D3. Vitamin D2 is a substituted part of vitamin D from foods and dietary supplements, while vitamin D3 is formed in the skin from 7-dehydrocholesterol under the influence of UVB from the solar spectrum. Thus, its synthesis is influenced by various factors such as skin pigmentation, lifestyle, etc. Vitamin D is synthesized as a biologically inactive precursor and exerts its physiological effects after two metabolic hydroxylation reactions [1, 2].

The main roles of vitamin D are the maintenance of calcium and phosphate homeostasis in the body as well as bone metabolism (deposition and resorption). In addition, vitamin D has been observed to play an important role in other diseases (autoimmune, malignancy, infectious and cardiovascular diseases) due to its binding to vitamin D receptor [3, 4].

Vitamin D supplementation plays a significant role in reducing inflammatory processes and suppressing the progression of autoimmune diseases in the treatment of obesity-related diseases (such as diabetes mellitus), in which obese people are frequently deficient in vitamin D [5–8].

Chronic lymphocytic thyroiditis (HT) is an autoimmune disease of the thyroid gland in which there is a gradual deterioration of the tissue of the gland itself. The incidence of HT is increasing in the world. In the early stages of thyroiditis, symptoms may be mild or even imperceptible, so the disease often goes undetected. The potential health, social, and/or economic benefits would likely be greater if diagnosis was not delayed. Diagnosis is based on laboratory indicators (hormone status and presence of thyroid antibodies) [9].

The relationship between vitamin D and autoimmune thyroid diseases has not been adequately elucidated. Therefore, several studies have been conducted to investigate the effects of serum vitamin D deficiency on autoimmune thyroid diseases and vitamin D supplementation in the prevention and treatment of these diseases, and conflicting results have been obtained [10, 11].

The results of some studies do not indicate an association between serum vitamin D deficiency and autoimmune thyroid disease [12, 13]. Other studies have found an association and have shown that low serum vitamin D levels in people with autoimmune thyroid disease lead to elevated TSH levels as well as increased anti-thyroid antibodies, goiter, and abnormal function [14, 15].

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The incidence of HT is increasing worldwide, and it is considered the most common autoimmune thyroid disease [16]. Given the multifactorial pathogenesis, a number of studies have been conducted linking genetic and other factors leading to the disease. Antiproliferative and immunomodulatory roles of vitamin D, as well as the presence of vitamin D receptor in most immune cells, are thought to play an important role in autoimmune thyroid diseases [17, 18].

The aim of this study was to analyze the relationship between vitamin D deficiency and thyroid function and its morphological features, anti-thyroid antibody levels, and the incidence of Hashimoto's thyroiditis.

METHODS

In this cross-sectional study, 156 medical records of patients who visited the Institute for Health Protection of Workers "Medical System Belgrade" in Belgrade as part of the annual systematic review from March 2019 to September 2020 were evaluated. The study was approved by the MSB Ethics Committee and was in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. A total of 156 patients were enrolled and divided into two groups. First group included 108 patients (69.2%) with 25 (OH) D insufficiency (< 30 ng/ml), and second included 48 individuals (30.8%) with normal 25 (OH) D levels (≥ (30 ng/ml) [4]. All participants underwent a detailed clinical examination, laboratory tests for thyroid function, as well as ultrasound scanning. Patients underwent testing for thyroid function T3, fT4, TSH, thyroid antibodies (TPO-Ab, and TG-Ab) and serum 25 (OH) D levels. In addition, all patients underwent thyroid ultrasonography to determine thyroid volume, Doppler pattern of signal intensity, and peak systolic velocity (PSV) and resistance index (RI) of the superior thyroid arteries (ATS) and inferior thyroid arteries (ATI).

The study included a total of 156 patients, 44 with HT (28.2%) and 112 without HT (71.8%), according to the presence of thyroid antibodies. The diagnosis of 44 patients with thyroiditis was based on TPO-Ab (> 100 mIU/L) and / or TG -Ab positivity (> 70 mIU/L) [4]. In addition, all subjects were divided into three groups according to thyroid status. The first group consisted of patients with overt hypothyroidism with serum TSH > 10 mIU/L and fT4 < 10.04 pmol/L or patients receiving levothyroxine regardless of their thyroid function status. The second group consisted of patients with subclinical hypothyroidism in whom serum levels of fT4 were between (10–24.97 pmol/L) and serum levels of TSH were between (4–10 mIU/L). The third group consisted of euthyroid patients with normal serum levels of fT4 and TSH (0.25–4.0 mIU/L).

Serum T3, fT4 and TPO Ab, TG Ab were tested by radioimmunoassay, while TSH were measured with a fluoroimmunometric assay (DELFIA). Electro-chemiluminescence binding assay (ECLIA) was used for 25 (OH) D level.

Thyroid ultrasound examinations were performed using a Toshiba aplio XG ultrasound scanner (Canon Medical Systems Corporation, Otawara, Tochigi, Japan) with a 12 MHz linear transducer.

Patients with metabolic bone disease, hyperparathyroidism, renal and liver disease, as well as patients taking medications that could affect vitamin D metabolism were excluded from the study.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY, USA) and MedCalc Version 11.4.2 (MedCalc Software Ltd., Ostend, Belgium). Comparison of categorical variables between groups was performed with the χ^2 test. Continuous variables are expressed as mean ± standard deviation. Student's t-test and single factorial ANOVA were used to compare continuous variables between two or more groups when normally distributed, as well as the Kruskal–Wallis test for ordinal data and the Mann–Whitney U test without normal distribution. Pearson's correlation analysis was performed to investigate the correlation between vitamin D and biochemical parameters. $p < 0.05$ was considered statistically significant for all tests.

RESULTS

The study included a total of 156 subjects [108 females (69.2%) and 48 males (30.8%)]. The mean age was 46.04 years, and the mean body mass index (BMI) was 26.2 kg/m^2. The mean serum level of 25 (OH) D was 23.97 ng/mL. The prevalence of vitamin D insufficiency was 63.5% respectively.

The patients with vitamin D insufficiency (n = 108) (69.2%) were predominantly female and had a higher BMI than the patients with normal vitamin D levels. The group with vitamin D insufficiency had statistically significantly higher TSH levels. The prevalence of positive thyroid antibodies was higher in the group with vitamin D insufficiency. Thyroid volume determined by ultrasound was statistically notably higher in the group with vitamin D insufficiency, as was the prevalence of Doppler signal positivity. The PSV of the ATS and ATI was significantly lower, while the RI of the ATS and ATI was significantly higher in the vitamin D insufficiency group compared with the control group.

There were no statistically significant differences in the concentrations of T3, fT4, TPO-Ab, TG-Ab, and age between the group with normal and insufficient vitamin D levels (Table 1).

Of 156 respondents, 44 (or 28.2%) had thyroiditis, while 112 (or 71.8%) did not have thyroiditis. The patients with thyroiditis were predominantly female and had a higher BMI. The mean serum 25 (OH) D level in patients with thyroiditis (20.23 ± 8.10 ng/ml) was statistically significantly lower compared with the group without thyroiditis (25.44 ± 8.38 ng/ml) $p < 0.001$. The level of fT4 was significantly lower in the thyroiditis group, while the concentrations of TSH, TPO-Ab, TG-Ab, were higher in the thyroiditis group, which was expected. Thyroid volume was statistically significantly higher in the thyroiditis group, as was the prevalence of Doppler signal positivity. The PSV of ATS and ATI, as well as the RI of ATS and ATI were

statistically significantly higher in the thyroiditis group than in the control group (Table 2, Figure 1).

Table 1. Laboratory and ultrasound characteristics of the thyroid gland in subjects with insufficiency and normal 25 (OH) D levels

Parameters	Insufficiency 25 (OH)D < (30 ng/ml) [n = 108]	Normal 25 (OH)D ≥ (30 ng/ml) [n = 48]	p-value
Age(years)	45.95 ± 9.89	46.23 ± 10.16	0.874
Female sex (n)	**85 (78.7%)**	**23 (47.9%)**	**< 0.001**
BMI (kg/m^2)	**27.3 ± 4.1**	**25.3 ± 3.3**	**0.002**
T3 (nmol/L)	1.79 ± 0.29	1.72 ± 0.56	0.431
fT4 (pmol/L)	13.56 ± 5.74	14.82 ± 3.88	0.827
TSH (μIU/ml)	**4.58 ± 3.88**	**3.05 ± 2.90**	**0.020**
TG-Ab (IU/ml)	99.3 ± 327.7	54.4 ± 107.1	0.113
TPO-Ab (IU/ml)	32.35 ± 87.52	41.01 ± 118.20	0.186
Prevalence of TPO-Ab or TG-Ab positivity(n)	**37 (34.3%)**	**7 (14.6%)**	0.02
Thyroid volume (ml)	9.97 ± 1.03	9.69 ± 0.94	0.028
Prevalence of Doppler signal positivity(n)	19 (17.6%)	7 (14.6%)	0.031
PSV ATS (cm/s)	30.42 ± 7.44	33.18 ± 6.62	0.022
PSV ATI (cm/s)	31.58 ± 6.93	32.84 ± 6.21	0.045
RI ATS (mean ± SD)	0.673 ± 0.05	0.612 ± 0.06	0.002
RI ATI (mean ± SD)	0.702 ± 0.07	0.643 ± 0.06	0.005

25 (OH)D – 25 hydroxyvitamin D; BMI – body mass index; T3 – triiodothyronine; T4 –thyroxine; fT4 – free thyroxine; TSH – thyroid-stimulating hormone; TG-Ab – thyroglobulin antibody; TPO-Ab – thyroid-peroxidase antibody; PSV ATS – peak systolic velocity-*arteria thyreoidea superior*; PSV ATI – peak systolic velocity *arteria thyreoidea inferior*; RI ATS – resistant index *arteria thyreoidea superior*; RI ATI – resistant index *arteria thyreoidea inferior*

Table 2. Laboratory and ultrasound characteristics of the thyroid gland in subjects with and without thyroiditis

Parameters	With thyroiditis n = 44	Without thyroiditis n = 112	p-value
Age (years)	46.29 ± 9.40	45.94 ± 10.19	0.840
Female sex (n)	**35 (79.5%)**	**73 (65.2%)**	**< 0.001**
BMI (kg/m^2)	**27.8 ± 3.5**	**24.3 ± 2.4**	**0.001**
25 (OH)D (ng/ml)	**20.23 ± 8.10**	**25.44 ± 8.38**	**< 0.001**
T3 (nmol/L)	1.81 ± 0.32	1.76 ± 0.41	0.509
fT4 (pmol/L)	**11.78 ± 6.23**	**14.79 ± 4.58**	**0.025**
TSH (μIU/ml)	**6.41 ± 4**	**3.20 ± 3.01**	**< 0.001**
TG-Ab (IU/ml)	**321.67 ± 524.23**	**15.69 ± 17.21**	< 0.001
TPO-Ab (IU/ml)	111.60 ± 159.96	4.43 ± 4.52	< 0.001
Thyroid volume (ml)	10.10 ± 1.02	9.65 ± 0.93	0.016
Prevalence of Doppler signal positivity (n)	19 (43.2%)	7 (6.2%)	< 0.001
PSV ATS (cm/s)	35.33 ± 8.21	30.15 ± 7.25	0.001
PSV ATI (cm/s)	36.29 ± 9.42	33.58 ± 8.69	0.02
RI ATS (mean ± SD)	0.828 ± 0.06	0.698 ± 0.06	0.001
RI ATI (mean ± SD)	0.794 ± 0.06	0.685 ± 0.05	0.001

25 (OH)D – 25 hydroxyvitamin D; BMI – body mass index; T3 – triiodothyronine; T4 – thyroxine; fT4 – free thyroxine; TSH – thyroid-stimulating hormone; TG-Ab – thyroglobulin antibody; TPO-Ab – thyroid-peroxidase antibody; PSV ATS – peak systolic velocity- *arteria thyreoidea superior*; PSV ATI – peak systolic velocity *arteria thyreoidea inferior*; RI ATS – resistant index *arteria thyreoidea superior*; RI ATI – resistant index *arteria thyreoidea inferior*

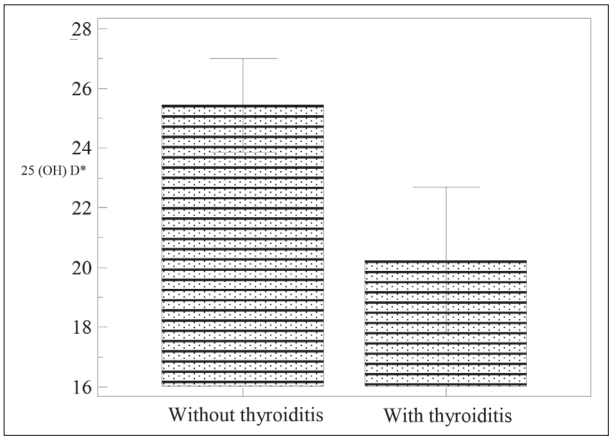

Figure 1. Concentrations of 25 (OH) D in subjects with and without thyroiditis;

*titer 25 (OH) D (ng/ml)

In terms of thyroid function, all subjects were divided into three groups. The first group consisted of patients with overt hypothyroidism, in whom serum levels of TSH > were 10 mIU/L and fT4 < were 10.04 pmol/L, or patients who received levothyroxine regardless of the status of thyroid function [40 patients (25.6%)]. The second group consisted of patients with subclinical hypothyroidism, in whom serum fT4 levels ranged from 10 to 24.97 pmol/L, and elevated serum TSH levels of 4–10 mIU/L (13 patients (8.3%)). The third group consisted of euthyroid subjects with normal serum fT4 and TSH levels (0.25–4 mIU/L) (103 subjects (66%)).

There was a statistically significant difference in 25 (OH) D levels between the group of euthyroid subjects (25.11 ng/ml) and the group with overt hypothyroidism (21.07 ng/ml) (p = 0.04). There was no statistically significant difference in the 25 (OH) D level between the group of euthyroid and subclinical hypothyroid patients (23.85 ng/ml) and between the subclinical hypothyroid patients and the patients with overt hypothyroidism (Table 3).

The mean thyroid volume was statistically significantly higher in the group of patients with overt hypothyroidism than in euthyroid patients, while the prevalence of Doppler signal positivity was higher in the groups with subclinical and overt hypothyroidism than in euthyroid patients. (Table 3, Figure 2)

Serum 25 (OH) D concentrations were significantly negatively correlated with serum TSH levels (r = - 0.284, p < 0.001), and BMI (r = - 0.228, p = 0.01), suggesting that lower 25 (OH) D concentration values were associated with subclinical, or overt hypothyroidism, as well as with obese people (Tables 1 and 3).

DISCUSSION

In this study, the vitamin D insufficiency group was predominantly female, with higher BMI, higher TSH levels. The 25 (OH) D level was significantly lower in the group with HT and in subjects with overt hypothyroidism compared

Table 3. Biochemical and ultrasound characteristics of the thyroid gland in subjects with different hormonal status

Parameters	25 (OH)D (ng/ml)[1]	Thyroid volume (ml)[2]	Prevalence of Doppler signal positivity (n)
Euthyroid status (n = 103)	25.11*	9.62*	11 (10.7%)*
Subclinical hypothyroidism (n = 13)	23.85	10.02	4 (30.8%)
Overt hypothyroidism (n = 40)	21.07*	10.09*	11 (27.5%)
*p-value	0.04	0.04	0.01

25 (OH)D – 25 hydroxyvitamin D;
[1]mean serum 25 (OH)D levels (ng/ml);
[2]ultrasound mean thyroid volume values

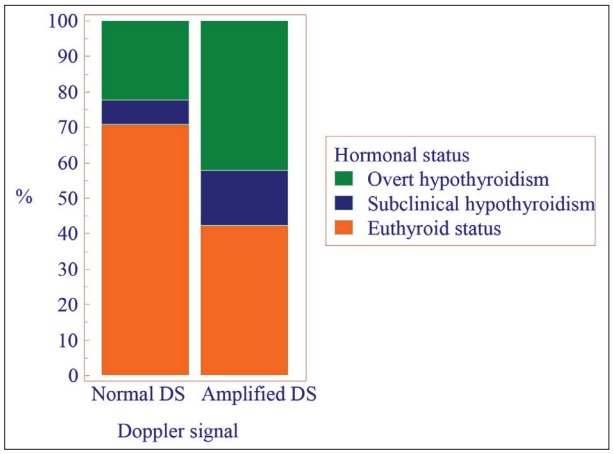

Figure 2. Doppler signal at different thyroid hormonal status

with the euthyroid subjects. We also obtained a higher prevalence of positivity of TPO-Ab and TG-Ab in the group with vitamin D insufficiency (p = 0.02), while the concentrations of TG-Ab and TPO-Ab showed no significant difference between the group with insufficiency and normal vitamin D levels. Some studies showed a negative correlation between vitamin D levels and TG -Ab concentrations in female subjects with HT, suggesting that vitamin D deficiency is higher in women with HT than in men, which is consistent with our findings [17, 19].

One of the first researchers to find an association between vitamin D and autoimmune thyroid disease was Kivity [20], and then further studies were conducted showing this association. Kivity et al. [20] showed that vitamin D deficiency was higher in respondents with HT than in those without HT. They also showed that vitamin D insufficiency correlated with the presence of thyroid antibodies. Some studies also show a negative correlation between the levels of TPO-Ab and TG-Ab and vitamin D insufficiency. In our study there was no statistically significant difference between thyroid antibodies titer and 25 (OH) D levels (TG Ab p = 0.113; TPO Ab p = 0.186) [21, 22].

Although we did not obtain a statistically significant difference between thyroid antibodies titer and 25 (OH) D levels, the prevalence of thyroid antibody positivity was higher in the vitamin D insufficiency group (p = 0.02), as in a study by Kim [4].

However, in the study by Yasmeh et al. [23], the results were different. They showed the association of normal and higher vitamin D levels in women with autoimmune thyroid disease compared to the control group. They also showed a positive correlation between vitamin D and TPO-Ab levels in men, which is not consistent with our results [23].

In our study, we obtained significantly higher TSH levels in the vitamin D insufficiency group compared to the group with normal vitamin D level (TSH = 4.58 ± 3.88 *vs*. TSH = 3.05 ± 2.90; p = 0.02), which is in agreement with the results of Chao et al. [15] and Sulejmanovic et al. [19].

The association between vitamin D insufficiency and HT has been demonstrated in many studies, but few indicate a higher prevalence of vitamin D deficiency in HT patients with overt hypothyroidism compared to subclinical hypothyroidism and euthyroid individuals [4, 24]. In our study, we found no statistically significant difference in vitamin D levels between overt hypothyroidism and subclinical hypothyroidism, but it existed between overt hypothyroidism and euthyroid individuals (p = 0.04), which is consistent with the study of Kim [4], which showed a statistically significant difference in vitamin D levels between overt hypothyroidism and euthyroid and subclinical hypothyroidism. It showed that patients with overt hypothyroidism and HT had lower vitamin D levels than patients without HT [4].

In contrast to these findings, some investigators found no association between vitamin D insufficiency and autoimmune thyroid disease and concluded that vitamin D insufficiency is not associated with the early stages of autoimmunity [13, 25].

It is not yet known whether vitamin D deficiency is a cause or a consequence of HT. Botelho et al. [26] showed that vitamin D levels were similar in patients with HT and without HT, and lower fT4 levels were considered a predictor of vitamin D deficiency for HT. In our study, we also showed lower fT4 levels in the vitamin D deficient group, but with no statistically significant difference (p = 0.827). Thyroid hormone levels play an important role in maintaining normal vitamin D levels. A positive correlation of fT4 with vitamin D suggests that levothyroxine substitution in HT is important for maintaining normal vitamin D levels and preventing serum insufficiency and deficiency [26]. Some studies also suggest that vitamin D supplementation lowers concentrations of TG-Ab and TPO-Ab, as well as TSH levels, especially in women with HT, who receive levothyroxine replacement therapy and have low serum vitamin D levels [24, 27].

In our study, we determined statistically significant differences in BMI in individuals with vitamin D insufficiency (p = 0.002, and in the group with thyroiditis p = 0.001). BMI was significantly higher in the group with vitamin D insufficiency than in the control group. In the study by De Pergola et al. [28] they pointed out the negative correlation between vitamin D and BMI and suggested that all obese people with vitamin D insufficiency should be screened for TPO-Ab and TG-Ab. Obese people with HT should also have their vitamin D levels checked [28].

Prolonged thyroiditis leads to increased vascularization of the parenchyma, formation of fibrous septa in the lobes, and a gradual decrease in thyroid volume [4, 12]. In our

study, patients with vitamin D insufficiency had lower flow rates and higher RI by ATS and ATI compared to the group with sufficient vitamin D.

Nalbant et al. [29] showed that the PSV of ATS and ATI was significantly higher in the group with sufficient vitamin D level than in the group with vitamin D insufficiency. There is a negative correlation between RI and vitamin D insufficiency, which is consistent with our results. They concluded that vitamin D deficiency leads to decreased blood supply to the thyroid gland as well as increased microvascular resistance in patients with HT [29].

In our study, the prevalence of circular dichroism positivity as well as thyroid volume is significantly higher in HT patients with vitamin D insufficiency. El Rawi et al. [30] compared ultrasound parameters of the thyroid gland in patients with HT and vitamin D insufficiency. They showed that vitamin D levels were lower in patients with HT with overt hypothyroidism and were inversely proportional to TSH, TPO-Ab and TG -Ab levels and thyroid volume. Low vitamin D levels are associated with increased vascularization, which is consistent with the results we obtained [30].

CONCLUSION

This study demonstrated a correlation between vitamin D insufficiency and hypothyroidism and an association with a positive prevalence of increased vascularization and greater thyroid volume in individuals with Hashimoto's thyroiditis. Further randomized controlled trials are needed to determine whether a causal relationship exists and to investigate the potential use of vitamin D in the treatment of autoimmune thyroid disease.

Conflict of interest: None declared.

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Повезаност нивоа витамина *D* са Хашимотовим тиреоидитисом

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САЖЕТАК

Увод/Циљ Осим улоге витамина *D* у метаболизму калцијума и фосфора, он остварује и антипролиферативне, диференцијалне, антиинфламаторне и имуномодулаторне ефекте. Циљ ове студије је био да се испита повезаност инсуфицијенције витамина *D* код особа са аутоимуним Хашимотовим тиреоидитисом.

Методе Испитивано је 156 болесника подељених у две групе. Прву групу чинило је 108 болесника са инсуфицијенцијом 25 (*OH*) *D*, а другу 48 особа са нормалним нивоом 25 (*OH*) *D*. Сви испитаници су подвргнути детаљном клиничком прегледу, лабораторијским тестовима функције штитасте жлезде [*T3*, *fT4*, *TSH*, тироидна антитела (*TPO-At*, і *TG-At*)], као и ултразвучном скенирању (запремина штитасте жлезде и карактеристике Доплерове дијагностике).

Резултати Испитаници са инсуфицијенцијом витамина *D* [*n* = 108 (69,2%)] били су претежно женског пола и имали су виши индекс телесне масе од оних са нормалним нивоом витамина *D*. Група са инсуфицијенцијом витамина *D* имала је статистички значајно виши ниво *TSH*. Преваленција позитивности аутоантитела на штитасту жлезду је била већа у групи са инсуфицијенцијом витамина *D*, док су волумени штитасте жлезде, индекси отпора горње тироидне артерије и доње тироидне артерије, као и преваленце позитивности сигнала циркуларног дихроизма, били статистички значајно већи у групи са инсуфицијенцијом витамина *D*. Међу 156 испитаника, њих 44 је имало дијагнозу тиреоидитиса (28,2%). Средњи нивои серумских 25 (*OH*) *D* код болесника са тиреоидитисом (20,23 ± 8,10 *ng/ml*) били су статистички значајно нижи у односу на групу без тиреоидитиса (25,44 ± 8,38 *ng/ml*), $p < 0,001$.

Закључак Постојала је повезаност између инсуфицијенције витамина *D* и хипотиреоидизма код особа са Хашимотовим тироидитисом.

Кључне речи: витамин *D*; инсуфицијенција; Хашимотов тиреоидитис

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

A retrospective analysis of different treatments of posterior acetabular wall fracture

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SUMMARY

Introduction/Objective The objective of the paper is an analysis of clinical outcomes of non-surgical conservative and operative management of patients with posterior acetabular wall fractures.

Methods We investigated 88 fractures of the acetabular joint, 31 of which were treated surgically and 57 non-surgically. Only screws or reconstruction plates and screws were used for surgical treatment and traction in patients who underwent nonsurgical treatment. The study period lasted at least three years. The measures used to assess the outcome of operative, surgical and non-operative, conservative approach were Merle d'Aubigné modified score, Harris hip score, and Matta's radiometric criteria.

Results Matta's evaluation criteria showed an excellent score of 40.4% in conservatively treated patients; 19.4% in patients who underwent surgery; a good score of 49.1% in conservatively treated patients; and 48.4% in patients who underwent surgery. Comparation between two patient groups differently treated, by Merle d'Aubigné tool, showed excellent results for 56.1% conservatively treated patients and 25.8% in those patients who underwent surgery, and good results in 29.8% conservatively treated patients and 38.7% in patients who underwent surgery. Harris hip score (excellent results were showed in 54.4% for non-operative-treated patients) also showed statistical significance, $p < 0.005$.

Conclusion Proper diagnostics and a proper definitive diagnosis can help avoid surgical treatment if the fracture cannot be treated surgically, making the postoperative period more comfortable for the patient.

Keywords: acetabulum; fracture; non-operative treatment; operative treatment

INTRODUCTION

Acetabular fractures have always been difficult for orthopedic surgeons to treat, as many postoperative complications may occur. Fractures of the posterior wall of the acetabulum are the most common among acetabular fractures and instability of the hip itself may depend on the size of a fragment. Standard protocol implies, after non-operative or operative treatment, immobilization for an average of at least 12 weeks [1, 2, 3]. In a situation of acetabular fracture with hip luxation and the absence of luxated fracture fragments, closed reposition could be managed, followed by traction during the next two months for acetabular relief [4]. Operative treatment includes reposition of the fragments with osteosynthesis by screws and plate [5, 6]. The most common approach used in operative treatment is Kocher–Langenbeck approach. Postoperatively, physical therapy is recommended. After operative treatment, it is recommended to avoid the loading of the injured hip at least up to 12 weeks [7]. Varying results by different authors have been published about the outcomes in the case of operative treatment. Closed reduction in short-term anesthesia can be made in the case of acetabular fracture with dislocation of the joint, and the absence of displacement of bone fragments, followed by application of traction up to two months for acetabular relief [4]. In the case of operative treatment that includes repositioning of fragments, their osteosynthesis with screw or plate with screws, the most commonly used is the Kocher–Langenbeck approach. More papers present operative treatment as a better solution than the non-operative one [8–11]. When the remaining intact part of the acetabulum is sufficient to keep the femoral head in a normal position with the roof of the acetabulum, non-operative treatment is indicated. There is no standard protocol regarding the use of solely screws or screws with plates in operative treatment [5, 6]. Most of the clinicians use the Harris hip score (HHS) and the Merle d'Aubigné and Postel method in the assessments of functional results [12].

Overall rise in high-energy trauma has resulted in an increase in acetabular fractures in Serbia.

The aim of this retrospective study was to analyze and correlate functional results and scores of non-operative, conservative management of patients with fractures of posterior acetabular wall with operative management of fractures of posterior acetabular wall, at the Orthopaedic Department of the University Clinical Centre of Serbia.

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METHODS

Our investigation included 81 patients with posterior wall acetabular fractures out of which 31 underwent operative treatment at the Orthopaedic Department Emergency Centre, University Clinical Centre of Serbia, Belgrade, Serbia. Conservative, non-operative management took 57 patients. The study was approved by the Ethics Committee of the University Clinical Centre of Serbia, Belgrade, Serbia (approval number 29/V-15).

The inclusion criteria for both groups of this study were as follows:

1. Injury of the posterior wall of the acetabulum;
2. Follow-up of at least three years;
3. No other surgical interventions on the injured hip.

Exclusion criteria for both examined groups were as follows:

1. Inadequate patient's history;
2. Insufficient follow-up period of the patient;
3. Patients who were treated in other hospitals.

The inclusion criteria for operative group of this study were as follows:

1. Unstable hip joint after repositions;
2. Fragment dislocation bigger than 3 mm;
3. Not a demanding patient, with no high expectations.

All of the patients were evaluated with three-dimensional computed tomography (CT) besides conventional, golden standard, X-ray examination, in order to define the type of fracture, bone fragment size, fragment quantity, and dislocation severity.

After patients' physical condition was determined as stable, those indicated for operative treatment underwent operative treatment. Closed reduction of the hip dislocation was performed under general anesthesia. Hip was flexed to 90°, then rotated internally for 20°, and, finally, maximally adducted in order to establish stability. One of the indications for surgery was re-dislocated hip fracture when more than 50°. We used Kocher–Langenbeck exposure with special attention to the sciatic nerve, which we preserved and protected from possible injuries. There were two types of fixations that we used. First, we used multiple screws in the case of comminute fractures, with a bone fragment large enough to accommodate at least two screws. In that case, the main fracture was on the superior-posterior side of the acetabulum. Secondly, we used reconstruction plating in cases of very severe comminute fracture, in which case the main fracture was determined at the middle-inferior side of the acetabulum. The X-ray established the reposition of the fragments and reduction after the operative procedure was done. The immobilization period was four weeks. Partial weight-bearing was suggested afterwards, with a recommendation for a gradual progression to total-body weight-bearing 12 weeks after surgery was performed.

Those patients who were not indicated to be treated operatively stayed at the hospital for a short follow-up and additional diagnostics. Those who did not have hip luxation were discharged from the hospital. Traction was also used as a non-operative treatment.

Modified Merle d'Aubigné and Postel method, HHS, and radiological grading criteria by Matta were the tools that we used to analyze and estimate hip function during regular medical check-ups. Modified Merle d'Aubigné and Postel method include verification of different ranges of movement manifested and scored as the percentage normal hip score, measured by evaluating the total range of the movements (flexion–extension, abduction, adduction, external rotation, and internal rotation for the injured hip) in degrees, divided by the total score of the normal, healthy hip. The overall clinical score is formed as a sum of pain values, walking, and range of movements. Post-operative follow-up is very often evaluated by HHS, referring to greater dysfunction if the score is higher (total score of 70 – poor results, 70–80 – good, moderate results, 90–100 is an excellent result in postoperative follow-up).

RESULTS

In the group of operatively treated patients, there were 28 male (90.3%) and three female (9.7%) patients. In the group of non-operatively treated patients, there were 51 male (89.5%) and six female (10.5%) patients.

Core mechanism of the injury was traffic accident and the percentage was 56.8%. The left hip was injured in 46 patients (52.3%), and associated hip luxation was present in 77 patients (87.5%). There was also associated injury to another system observed. Conjoint injuries were present in two cases (2.3%), who had sciatic injury, eight (9.1%) had head injury, and seven (8%) had chest injury. Fragment displacement of less than 3 mm, which was evaluated by preoperative CT, was seen in 51.1% of patients, and more than 3 mm in 48.9% of patients. Fractures were fixed with screws alone in 21 patients (23.9%), and with screws and plates in 10 patients (11.4%) (Table 1).

Table 1. Comparing the type of treatment with other parameters

Type of treatment *vs.*	p
Sex	0.900
Injury	**0.037**
Hip	0.422
Conjoint with hip luxation	**0.001**
Other conjoint	0.503
Type of injury	0.125
Early complications	0.213
CT/RTG post-operative evaluation	**0.000**
Late complications	0.096
Ossification	**0.008**
Traction	0.967
Matti	**0.049**
Merle d'Aubigné – Postel score	**0.023**
Harris hip score	**0.030**

Post-operative CT showed anatomical reposition in 48 patients (54.5%), fragments luxation less than 3 mm in 34 patients (38.6%), and more than 3 mm in six patients (6.8%). Avascular necrosis as a post-operative complication

was observed in four patients (4.5%), and post-traumatic arthrosis in 84 patients (95.5%). Ossification was found in 54 patients (61.4%). Results of different treatment approaches were estimated by different specific tools very sensitive to this orthopedic pathology. If we analyze Merle d'Aubigné values, the percentage results were 45.5% (excellent), 33% (good), 11.4% (fair), and 10.2% (poor). Observing and estimating HHS, the results were 44.3% (excellent), 34.1% (good), 11.4% (fair), and 10.2% (poor). The Matta grading scale percentage of excellent, good, fair, and poor was 33%, 48.9%, 9.1%, and 9.1%, respectively (Table 2).

Table 2. Level of efficiency of different treatments used by three scales

Type of treatment	Good %	Poor %	Total %	Test and p-value
Operatively	67.7	22.3	100	*Matta2*
Non-operatively	89.5	10.5	100	**0.012**
Operatively	64.5	35.5	100	*Merle2*
Non-operatively	86	14	100	**0.019**
Operatively	64.5	35.5	100	*Harris2*
Non-operatively	86	14	100	**0.019**

On comparing the methods of treatment of the operative and the non-operative groups of patients, we found statistical significance of p = 0.037.

Statistical significance was shown when a comparison was made between the operative and the non-operative groups of patients in relation to the methods of treatment and conjointment with the hip luxation (p = 0.001) (Table 2).

Statistical significance was also shown when using Pearson's χ^2-compared methods of treatment and level of ossification (p = 0.008).

Our results showed excellent scores of 40.4% in the group of conservatively treated, non-operative patients, and 19.4% in the group of patients who were treated operatively, referring to Matta values analysis. Good results were estimated at 49.1% for the conservatively managed group of patients and at 48.4% for the patients who underwent surgery. In analysis of modified Merle d'Aubigné scores, statistical parameters that manifested significance (p < 0.005) were excellent results in 56.1% of the conservatively treated and in 25.8% of those who underwent surgery. We found statistical significance in results of HHS; there were excellent results of 54.4% for non-operatively treated patients. Pearson's χ^2 showed statistical significance for the association methods of treatment and Matta radiographic grading (p = 0.012).

Table 3. Receiver operating characteristic curve results for the duration of not supporting the injured leg after the surgery

Test result variable(s)		Duration of not supporting		P/N ratio
Area	Asymptotic sig.	Asymptotic 95% confidence interval		
		Lower bound	Upper bound	Cut-off point
0.767	0.000	0.662	0.872	63 days

Using the receiver operating characteristic (ROC) curve, we found high statistical significance for the duration of not supporting the injured leg after the surgery (p = 0.000).

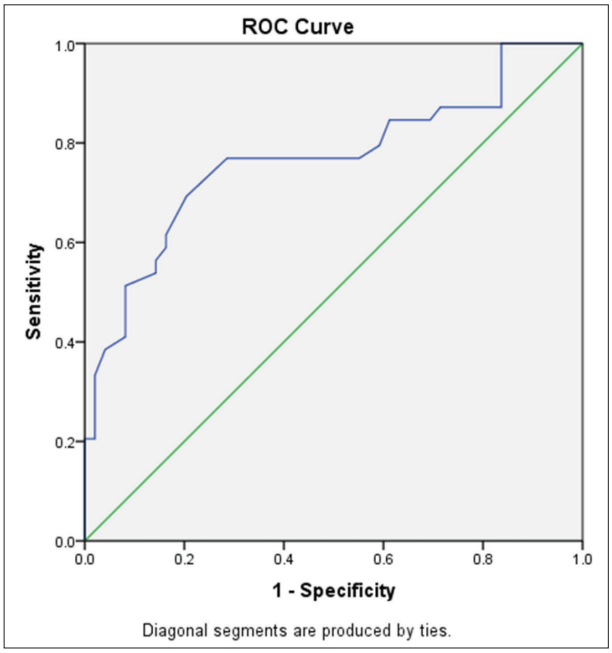

Figure 1. Sensitivity and specificity for the treatment and duration of support

The cut-off point was 63 days given by the P/N ratio (Table 3) and area under the ROC curve is 0.767 (95% confidence interval: 0.662, 0.872).

High sensitivity and specificity were shown using the ROC curve for the treatment and duration of support to the injured leg after the surgery (Figure 1).

DISCUSSION

Acetabular fractures present a complex situation in which operative treatment is recommended unless the medical indication for nonoperative, conservative treatment is met and if it is not, the final decision depends on the patients' comorbidities and their expectations after treatment. There is also one more variable in this equation related to medical technical support and the surgeon's experience according to which the decision is going to be made. In each way chosen, the treatment should be based on early mobilization in order to avoid postoperative complications. Acetabular fractures generally remain an enigma for orthopedic surgeons, especially for those coming from developing countries. The posterior wall of the acetabulum presents very specific anatomical substrate and its fractures and classification can be very difficult to observe, partially due to poor technical support [13]. Previous investigations showed that even when a satisfying management of the posterior acetabular wall fractures was performed, not all of them presented efficient clinical and functional result [13, 14]. The emphasis of this result was osteonecrosis manifestation and difficulties in managing the reconstruction of heavy comminated fractures [14, 15, 16]. Our research focused on the analysis of conservative-treatment results and correlate them to operative-treatment results. According to our results analysis, in the case of Matta radiographic grading,

we had 81.9% good-to-excellent clinical result when the patients were conservatively treated, in the case of HHS we had 78.4%, and in the case of Merle d'Aubigné we had 75.5% good-to-excellent clinical results [17]. Results of clinical investigation performed by Matta et al. [18] showed poor results, and only 15 patients had good-to-excellent results. Possible causes were irregular congruence of articulation surfaces, patient's age and injury to the femoral neurovascular bundle. Previous studies suggest that postoperative outcomes were better in younger- than in older-age patients, as they had greater percentage of postoperative complications and therefore physical therapy went poorly. Moreover, adjacent conditions such as obesity, diabetes, and heart disease present important risk factors that may predispose the direction of postoperative follow-up. Present adjacent arthritis presents a condition which leads to non-satisfying overall functional results if the operative technique includes internal fixation. The mental status of the patient is of great importance as it may impact the determination to be activated physically and a will to overcome bad painful periods of the postoperative period.

The follow-up period was not less than three years and included contacts with the patients through regular medical controls and check-ups. Patients followed for less than three years with a poor clinical result were not excluded from the study.

As previously mentioned, there are many factors that make a great impact on treatment plan of posterior wall acetabular fractures, such as medical equipment and technical support, which is always lacking, especially in developing countries. We might consider the above mentioned as a limitation of our study. Anatomical reposition can be a very demanding and important predicting factor related to postoperative outcomes. Previous experimental studies showed that proper anatomical reposition with internal fixation does not intentionally improve posterior acetabular wall fracture specifically. Our study results analysis support previous study conclusions of great importance of anatomically correct reposition in a fast overall restitution of a patient's health. Time management is of great importance if we want satisfying clinical results; therefore, less than 12 hours from the initial differential diagnosis would be borderline time to start a specific treatment [19, 20, 21].

Clinically excellent or very good functional results of fracture treatment generally remain stable over time, but when arthritis is present, the results which were satisfying may decrease or deteriorate [22]. Previous investigations defined core risk factors for disappointing results regardless of the treatment going in the non-operative or the operative direction. These factors were postponement of more than 12 hours before the reduction of a hip fragment dislocation, age of 55 years and older, femoral head osteonecrosis, and intra-articular comminution [22, 23, 24]. Femoral head osteonecrosis is not present as a complication in every patient if a delayed reduction management of a hip dislocation is done, or if an early reduction does not induce its presentation. Previous evidence points to the fact that any unnecessary delay of treatment of any kind should be evaded.

CONCLUSION

Our study suggests that non-operative treatment with early movement activation, weight-bearing, may avoid serious complications that can be related to surgical management.

Conflict of interest: None declared.

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Ретроспективна анализа различитих начина лечења прелома задњег зида ацетабулума

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САЖЕТАК

Увод/Циљ Циљ рада је процена исхода неоперативно и оперативно лечених болесника са преломима задњег зида ацетабулума.

Методе Процењено је укупно 88 прелома ацетабулума, 31 оперативно и 57 неоперативно лечених. У оперативном лечењу коришћени су или само шрафови или реконструктивне плоче и шрафови. Тракција као метода коришћена је код болесника који су лечени неоперативно. Период праћења је био најмање три године. Инструменти коришћени за процену исхода оперативног и неоперативног лечења били су модификовани скор Мерл д'Обиње (*Merle d'Aubigne*), Харисов скор кука и радиолошки критеријуми за оцењивање по Мати (*Matta*).

Резултати Имали смо статистичку значајност $p < 0,005$ и одличне резултате са 40,4% у неоперативној групи и 19,4% у оперативној групи болесника користећи Мата евалуацију; добре резултате са 49,1% за неоперативну групу и 48,4% за оперативну групу. Помоћу модификованог инструмента Мерл Д'обиње поређење две групе, неоперативне и оперативне, показало је одличне резултате: 56,1% за неоперативно лечене болеснике и 25,8% за оперативно лечене болеснике. Добри резултати су били код 29,8% неоперативних и код 38,7% оперативно лечених болесника. Када смо повезали неоперативне и оперативне болеснике, пронашли смо статистичку значајност $p < 0,005$ у случају Харисовог скора кука; одлични резултати су били код 54,4% неоперативно лечених болесника.

Закључак Адекватну дијагностику и тачну коначну дијагнозу треба поставити на начин да се избегне оперативно лечење уколико се прелом може лечити неоперативно.

Кључне речи: ацетабулум; прелом; неоперативно лечење; оперативно лечење

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Concentrated triamcinolone acetonide suprachoroidally administered for the treatment of diabetic macular oedema

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SUMMARY

Introduction/Objective Diabetic macular oedema is the accumulation of fluid in the macular tissue leading to its thickening. The aim of the study was to evaluate the efficacy of concentrated triamcinolone acetonide 10 mg / 0.1 ml injection into the suprachoroidal space in patients with diabetic macular oedema and decreased visual acuity.

Methods In 12 eyes with diabetic macular oedema, without any prior treatment, using a small-diameter 26G needle, an injection of 10 mg / 0.1 ml triamcinolone acetonide was applied into the suprachoroidal space in the superotemporal quadrant of the eye 4 mm from the limbus. Prior to the injection, as well as one, three, six, nine, and 12 months after the injection, visual acuity and intraocular pressure were measured, and central subfield thickness was recorded using optical coherence tomography.

Results After one, three, six, and nine post-injection months there was a statistically significant reduction in central subfield thickness (315.92 μm, 257.66 μm, 281.08 μm and 295.51 μm, respectively) compared to the baseline of 447.67 μm. At the end of the 12th month an increase in central subfield thickness was observed again (392.16 μm). Visual acuity improved significantly from the baseline (0.32) during the first three months (0.61) and remained stable until the end of the nineth month (0.51), but at the end of 12 months it decreased again (0.39). No significant intraocular pressure elevation and cataract development were observed in either eye during the entire follow-up period.

Conclusion A single dose of 10 mg / 0.1 ml triamcinolone acetonide injected in suprachoroidal space can significantly stabilize diabetic macular oedema and maintain satisfactory visual acuity for up to nine months.

Keywords: diabetic macular oedema; triamcinolone acetonide; suprachoroidal injection

INTRODUCTION

In patients with diabetes mellitus, especially in type 2, the visual loss is mainly caused by the development of diabetic macular oedema (DMO). Nowadays, anti-vascular endothelial growth factor (anti-VEGF) agents, intravitreally applied, are the most effective treatment for DMO, especially for the eyes in which the central part of the macula is affected by oedema [1]. The time-limited effect of these drugs, the need for frequent repeated intravitreal injections, as well as possible adverse events related to the intravitreal application itself make it difficult to maintain such treatment for a long period of time.

Numerous inflammatory mediators have been implemented in the development of diabetic retinopathy, so it can be considered a form of chronic inflammation [2]. For this reason, corticosteroids are important drugs for the treatment of DMO patients, but mostly as a second-line option. Intravitreal injection of triamcinolone acetonide (TA) has been shown to be very effective in reducing DMO and improving visual acuity (VA); however, its use has also been associated with frequent adverse ocular effects, such as the increased intraocular pressure (IOP) and cataract progression [3, 4].

In order to achieve higher therapeutic doses in the target layers of the eye, i.e., in the retina, retinal pigment epithelium, and choriocapillaris, administration of drugs in the suprachoroidal space (SCS) may represent a new path of their application. The SCS is a virtual potential space between the choroid and sclera that may expand and become real in various pathological conditions such as suprachoroidal hemorrhage, choroidal detachment, and uveal effusion syndrome, but also by applying therapeutic fluids or suspensions to it. The animal studies have shown that SCS expansion is volume-dependent; larger volumes lead to greater expansion of this space. Also, these studies have shown that this space can receive up to 1 ml of fluid, which is a much larger volume than the volume needed to achieve the therapeutic level of common drugs that are used for the treatment of retinal diseases [5].

Suprachoroidal injection of TA represents a relatively new approach for the treatment of various retinal diseases. Numerous pre-clinical

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and clinical trials have confirmed the high efficacy of TA used in this way in the treatment of DMO and macular oedema in retinal vein occlusion and noninfectious uveitis [6–9]. It has been noted that the concentration of TA in the posterior eye tissues is 10 times higher than in the anterior segment of the eye, so the occurrence of side effects such as cataracts and IOP elevation is significantly lower [10]. Pharmacokinetic studies have confirmed a longer duration of activity of TA applied in this way to macular oedema and a longer stabilization of VA, which requires their less frequent application.

The SCS injection can be performed by using the standard small-gauge needles (26G, 27G) or specially designed micro needles (30G) and in both cases these needles penetrate through the sclera only 1 mm in length reaching the SCS [11]. In that way, the risk of injury to intraocular structures, retinal tear, retinal detachment, vitreous hemorrhage, and endophthalmitis, is much lower compared to intravitreal injections since the needle does not penetrate through the retina and vitreous cavity.

So far, several studies have mainly examined the efficacy and safety of suprachoroidal application of 4 mg / 0.1 ml TA in the treatment of DMO [9]. Our study evaluated the efficacy and length of therapeutic effect of concentrated 10 mg / 0.1 ml TA injected into the SCS on DMO, VA, IOP, cataract development, as well as the safety profile of this treatment.

METHODS

The study was conducted at the Clinic of Ophthalmology, University Clinical Center of Kragujevac, Serbia, in a period from June 2020 to August 2021. This was a prospective, observational, interventional, non-randomized follow-up study of 12 diabetic patients with clinically significant DMO and consequently decreased VA. This study was approved by the Medical Ethics Committee of the Kragujevac University Clinical Center. The technique, purpose, possible complications of the procedure were explained to all the patients included in the study, who were also informed about the fact that it is an off-label use of TA. After that, at the beginning of the investigation, the written informed consent from all patients was obtained.

The main inclusion criterion was the presence of clinically significant macular oedema (CSMO). It is defined by one or more statements: retinal thickening in the area within 500 μm from the center of the fovea; hard exudates in the area within 500 μm from the fovea combined with adjacent retinal thickening; retinal thickening size of one optic disc diameter (1500 μm) which is at least in part within the one disc diameter from the foveal center [12]. CSMO is confirmed by the biomicroscopic fundus examination, fluorescein angiography, and optical coherence tomography (OCT) scan, with a concomitant decrease in VA ≤ 0.5 Snellen lines. The study included only eyes that had not previously undergone any laser treatment or intravitreal application of anti-VEGF drugs. Only the eyes with transparent ocular media were included in this study. Eyes with glaucoma, pre-existing other ocular diseases or previous ocular surgery were excluded.

Full ophthalmologic examination, including VA measurement, IOP measurement, biomicroscopy of ocular media, fundus biomicroscopy with Goldmann three-mirror contact lens and Volk 78 lenses and spectral domain OCT (SD-OCT) scanning was performed in all the patients before suprachoroidal injection of TA and at each follow-up examination after one, six, nine, and 12 months. On the first post-injection day, only a biomicroscopic examination of the anterior ocular segment and measurement of IOP were performed, while during the subsequent control examinations complete ophthalmological examinations were performed as described above. It was decided that anti-glaucoma drugs should be prescribed only in the case of an IOP increase by more than 5 mmHg compared to pre-injection values. A fixed combination of dorzolamide hydrochloride-timolol maleate (Cosopt, MSD, Haarlem, The Netherlands) was chosen as the initial antiglaucomatous drug.

All the analyzed eyes had CSMO, confirmed and documented by fundus photography and fluorescein angiography (Carl Zeiss, Meditec, Inc., Dublin, CA, USA). SD-OCT examination was performed before the SCS TA injection and then after one, six, nine, and 12 months using SD-OCT (Optopol REVO NX 130 SD OCT, OPTOPOL Technology, Zawiercie, Poland). The central subfield thickness (CST) was measured and as its thickening ≥ 305 μm for males and ≥ 290 μm for females was considered pathological according to the OCT 3 definition [13].

Suprachoroidal injection of TA was performed in the operating room in sterile conditions, under local anesthesia. For TA injection, preservative-free 40 mg / 1 ml Kenalog was used (Kenalog, Bristol Myers Squibb, Athens, Greece). Since 0.1 ml of the original Kenalog solution contains 4 mg of triamcinolone, in order to achieve a higher concentration of the drug, we applied the technique of triple sedimentation, described by Jonas et al. [3]. The entire volume of the 1 ml Kenalog bottle was aspirated into a 1-ml tuberculin syringe. The syringe was vertically positioned on the operating table for at least 15 minutes, because of sedimentation. Then, upper 0.8 ml were eliminated out of the syringe and only the 0.2 ml sedimentary part of the crystal was left in the syringe. Ringer's solution was used to refill the 1 ml syringe, and then the syringe was repositioned in the vertical position for 5 minutes for additional sedimentation. This procedure of removing upper 0.8 ml of the suspension, refilling with Ringer's solution and re-sedimenting was repeated twice. In the end, upper 0.9 ml was eliminated out of the syringe while the remaining 0.1 ml, containing about 10 mg of TA, was injected into the SCS.

For suprachoroidal TA injection we used a standard 1-ml tuberculin syringe with a 26G needle, 0.45 mm in diameter and 12 mm in length (Chirana, Stara Tura, Slovakia). In order to ensure adequate penetration into the SPC, the preparation of this needle was performed as follows. The needle was passed through the lumen of the plastic sheath of the intravenous cannula 24G with an outer

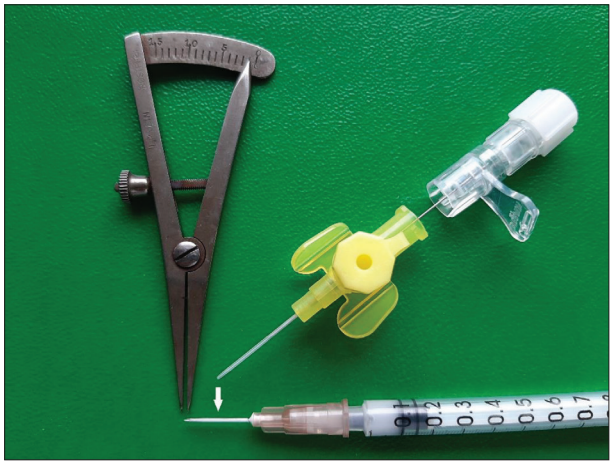

Figure 1. The preparation of small-gauge needles (26G) for suprachoroidal injection

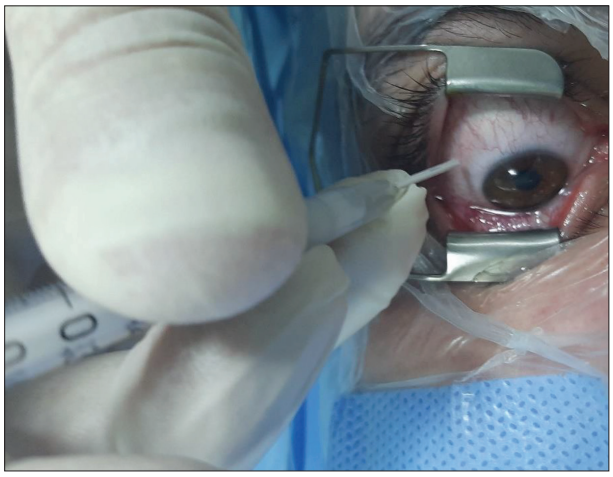

Figure 2. The suprachoroidal space application of 10 mg / 0.1 ml triamcinolone acetonide in the superotemporal quadrant 4 mm from the limbus

diameter of 0.7 mm (B Braun, Melsungen, Germany). This plastic sheath of the branula was cut to an approximate length of 11 mm so that only the tip of the needle up to the bevelled edge was exposed, only 0.9–1 mm. Thus, only the terminal tip of the needle was available for manipulation, which was only long enough to penetrate through the scleral thickness and reach the SPC. All these measurements were performed using a sterile caliper. Figure 1 shows the preparation of a small-gauge needle (26G) for suprachoroidal injection.

Before the intervention, the eye was cleaned with a solution of 5% povidone iodine. In the inferotemporal quadrant, 1% lidocaine was injected subconjunctivally. The lid speculum was placed and patients were instructed to look down and toward their nose. In the superotemporal quadrant, a distance of 4 mm from the limbus was measured with a caliper and injection of TA was applied at that point. The needle was inserted perpendicular to the sclera wherein the bevel of the needle was pointed to the opposite side of the limbus towards the posterior part of the eyeball. In this way, the diffusion of the drug posteriorly to the macular area is ensured. The TA suspension was injected slowly and during the entire time of administration, it was checked whether there was any backflow from the injection site. If this was observed, additional pressure was applied with the needle to create a small hole in the sclera to ensure sufficient penetration through the scleral thickness. After the injection is completed, the tip of the needle is slowly pulled out of the injection site that is gently pressed with a cotton swab to prevent spillage of the suspension. Figure 2 shows the SCS application of 10 mg / 0.1 ml TA in the superotemporal quadrant 4 mm from the limbus. Immediately after the intervention, the presence of cortisone crystals in the vitreal cavity was checked with an indirect ophthalmoscope, which would indicate an accidental unplanned intravitreal placement of TA. At the end of the procedure, tobramycin 0.3%-dexamethasone 0.1% ointment was instilled. Ofloxacine 0.3% drops were applied topically five times a day as the prophylactic treatment for five days.

In analyzing statistical data, IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA) was used. The Kruskal–Wallis test was used for testing the changes in macular thickness and VA during the follow-up period. The value of $p < 0.05$ was considered to be statistically significant.

RESULTS

The current study included 12 eyes of 12 diabetic patients. Seven (58.3%) patients were female and five (41.7%) were

Table 1. The mean values of central subfield thickness, visual acuity, and intraocular pressure before suprachoroidal space injection of 10 mg / 0.1 ml triamcinolone acetonide and during the follow-up period after one, three, six, nine, and 12 post-injection months

Parameter	Baseline	> 1 month	> 3 months	> 6 months	> 9 months	> 12 months
CST µm	447.67 ± 117.48 (315–802)	315.92 ± 45.49 (301–452)	257.66 ± 46.79 (241–403)	281.08 ± 43.11 (264–438)	295.51 ± 38.62 (265–452)	392.16 ± 57.27 (307–547)
p	–	0.017*	0.000*	0.005*	0.012*	0.058
VA (Snellen)	0.32 ± 0.15 (0.08–0.4)	0.49 ± 0.27 (0.2–0.7)	0.61 ± 0.28 (0.3–0.8)	0.56 ± 0.25 (0.3–0.7)	0.51 ± 0.2 (0.2–0.6)	0.37 ± 0.19 (0.1–0.5)
p	–	0.017*	0.000*	0.011*	0.019*	0.055
IOP mmHg	15.67 ± 2.25 (12–20)	19.42 ± 2.64 (15–22)	18.08 ± 2.05 (15–21)	17.08 ± 2.02 (14–21)	16.42 ± 1.68 (14–21)	15.92 ± 1.97 (14–20)
p	–	0.048*	0.085	0.132	0.256	0.423

CST – central subfield thickness, VA – visual acuity, IOP – intraocular pressure;
p – values compared to baseline
*statistical significance

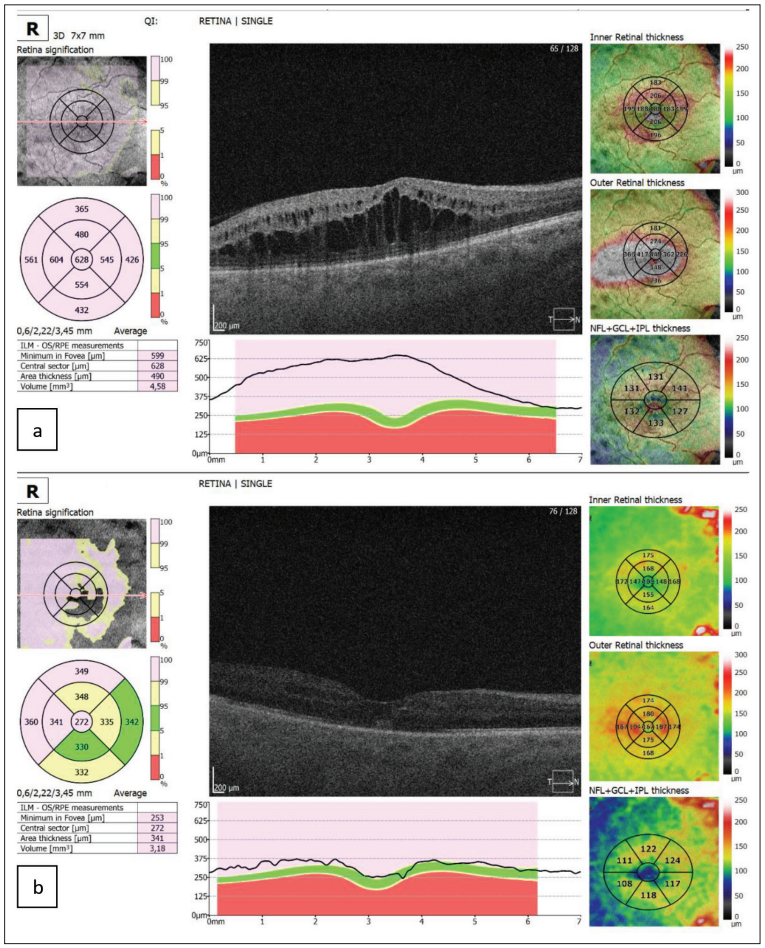

Figure 3. a – Clinically significant macular oedema with very increased central subfield thickness (628 µm) before suprachoroidal space injection; b – significant resolution of oedema in the central foveal zone (272 µm) even six months after injection

male. The mean age of patients was 65.42 ± 5.82 years (53–73 years) and all had type 2 diabetes mellitus. The average duration of diabetes mellitus in the examined patients was 17.42 ± 2.87 years. CSMO which involves central subfield of macula was confirmed in the right eye in seven and in the left eye in five patients. All examined eyes were phakic without or with very incipient cataract. In all the eyes, the initial value of IOP was lower than 22 mmHg. No laser treatment or intravitreal administration of anti-VEGF agents were performed in any of the examined eyes until the moment of SCS injection of TA.

Table 1 shows the mean values of CST, VA, and IOP before SCS injection of 10 mg / 0.1 ml TA and during the follow-up period after one, three, six, nine, and 12 post-injection months.

The mean pre-injection value of CST was 447.67 ± 117.48 µm (321–696 µm), the average VA was 0.32 ± 0.15 (0.08–0.5), and the mean IOP was 15.67 ± 2.35 mmHg (12–20 mmHg).

OCT measurements at the end of the first post-injection month showed a statistically significant reduction in CST 315.92 ± 45.49 µm compared to pre-injection values of 447.67 ± 117.48 µm (p = 0.017). CST was especially statistically reduced at the end of the third post-injection month compared to baseline (257.66 ± 46.79 µm, p = 0.000), and remained stable at the end of the sixth (281.08 ± 43.11 µm, p < 0.001) and ninth month (295.51 ± 38.62 µm, p = 0.012). Figure 3a shows CSMO with very increased CST (628 µm) before the SCS injection, while Figure 3b shows the significant resolution of oedema in the central foveal zone (272 µm) even six months after the injection. At the end of the 12th month, an increase in the CST was observed (392.16 ± 57.27 µm), and no longer differed statistically from the initial thickness (p = 0.058).

VA improved significantly at the end of the first month in relation to the initial values (0.49 ± 0.27, p = 0.018), and at the end of the third post-injection month this difference was the most pronounced (0.61 ± 0.28, p = 0.000). During the sixth and ninth month, VA remained stable (0.56 ± 0.25, p = 0.011; 0.51 ± 0.20, p = 0.019), but at the end of the monitoring period, its decrease was noticed and there was no longer a significant difference from baseline (0.39 ± 0.19, p = 0.055).

At the end of the first post-injection month, a moderate statistically significant increase in IOP in relation to the initial values was observed (19.42 ± 2.64 mmHg, p = 0.048), but neither eye required the use of anti-glaucoma therapy. During the entire remaining follow-up period there was no significant difference in the level of IOP compared to baseline (after three months 18.08 ± 2.05 mmHg, p = 0.085; after six months 17.08 ± 2.02 mmHg, p = 0.132; after nine months 16.42 ± 1.68 mmHg, p = 0.256; after 12 months 15. 92 ± 1.97 mmHg, p = 0.423).

No significant cataract development occurred in either eye during the follow-up period. The subconjunctival hemorrhage at the injection site is the only side effect during this intervention and was observed in five eyes. Three patients felt mild pain during the injection, most likely due to expansion of the SCS. Immediately after the given injection, by indirect ophthalmoscopy, we did not notice in any of the eyes inadvertently intravitreal penetration of TA and subretinal or choroidal hemorrhages, but in two eyes dilation of vascular vessels at the injection site was observed. In our study, during the follow-up period, no eye had choroidal hemorrhage, retinal or choroidal detachment or endophthalmitis.

DISCUSSION

Although intravitreal drug administration, especially of anti-VEGF agents, is currently the major mode in the treatment of retinal diseases, it has recently been shown that drug administration to the SCS may represent a new route for drug administration to the posterior ocular tissue [5, 6]. Nowadays, the advanced OCT technology using

the ultra-high-resolution OCT (UHR-OCT), that has far deeper scanning penetration of the posterior eye segment, the SCS can be identified as hyporeflective band between the outer border of the choroid and the sclera [14].

Clinical trials have shown promising results in the application of TA via this route in reducing macular oedema in patients with various retinal diseases [7, 8, 9, 15, 16, 17]. Our results are in complete agreement with the findings of other researchers that this type of treatment of DMO is very effective. However, the design of these studies differed somewhat. Some of them used the SCS TA injection as mono-therapy and some combined it with simultaneous SCS application of anti-VEGF drugs [9, 16, 17]. Some studies have used the SCS TA injection in patients with no previous therapeutic exposure (primary naïve patients), and others in patients with persistent retinal thickening despite anti-VEGF therapy [9, 16]. As reported in previous studies, a single SCS injection of 4 mg / 0.1 ml TA is highly effective in reducing DMO for up to six months; at six months after SCS TA injection, the mean CST in the HULK trial was about 22%, while in the study by Yousef et al. [17] it was 36.6% lower than the initial values [16]. In our work, at the end of the sixth post-injection month, we noticed that CST was about 35% lower than the pre-injection values. Similar to the reduction in CSFT, both of these studies showed that there was a significant improvement in VA after injection: after 6 months in the HULK trial, the mean best-corrected visual acuity gain was +1.7 Snellen lines, while in the study by Yousef et al. [17], the mean best-corrected visual acuity gain was +2.0 Snellen lines [16]. In our study, this increase in VA after six months was about +2.4 Snellen lines.

The length of therapeutic effect of the SCS injected with 4 mg / 0.1 ml TA has not yet been determined. The conclusions of different studies are very different from each other. In the HULK trial, patients received the mean of 2.6 SCS TA injections during the six months of follow-up, i.e., every 2.5 months [16]. The MAGNOLIA study reported that approximately 50% of patients did not require additional treatment until nine months after the last SCS TA injection [7]. The PEACHTREE study that followed patients for 16 weeks after the SCS TA injection found that after four months, only 13.5% of them required repeated treatment [15]. All the above studies used a dose of 4 mg / 0.1 ml TA. The results of our study indicate that with a higher dose (10 mg / 0.1 ml TA), DMO can be successfully regulated with a single injection even for up to nine months.

Fluid from SCS can be cleared via physiological pathways by passive diffusion through the scleral canals around the vortex veins or through fenestrated choroidal capillaries. However, the particles of a suspension cannot be cleared by diffusion before they degrade [18]. Since experimental works have shown that large molecules can be retained in the SCS for a longer period of time due to slow clearance, this leads to the conclusion that the liquids in the form of a suspension are a better option for sustained drug delivery than solutions. Since TA particles have an average size of 11.8–18.8 μm, and their aggregates can be as large as 100–200 μm, the clearance rate of TA crystals is very slow [19]. Slow clearance of TA suspension can sustain the release of the drug over a long period of time, enabling high therapeutic concentrations within the retina, retinal pigment epithelium, and choroid.

All the previous studies had in common that they all used the same dose of 4 mg / 0.1 ml TA for the SCS injection and all showed that DMO could be successfully regulated for up to six months. In our study we used a 2.5-times higher concentration of TA (10 mg / 0.1 ml) and our results indicate that DMO can be successfully controlled with this dose for up to nine months. It was only after nine months that we noticed the recurrence of oedema, followed by a consecutive decrease in VA which would require a repeated injection.

Two most common side effects of intravitreal injection of TA are the increase of IOP and cataract development. In the report by the Diabetic Retinopathy Clinical Research (DRCR) network, the use of intravitreal triamcinolone acetonide 4 mg was associated with 40–50% incidence of IOP elevation, and 51–59% incidence of cataract [4]. As reported by previous studies, the SCS of TA injection significantly less often leads to these complications. This can be explained by the fact that the anterior propagation of the TA is restricted by the scleral spur, so the structures in the anterior part of the eye, especially the crystalline lens and trabecular meshwork, are spared from high drug exposure. In the PEACHTREE study, IOP elevation was recorded in 11.5%, in the TANZANITE study in 8.7%, and in the TYBEE study in only 8.3% of the eyes [8, 9, 15]. Also, the incidence of cataract is significantly lower compared to intravitreal use of TA: in the PEACHTREE study cataract development was recorded in 11.5%, while in the TANZANITE study in only 4.4% of the eyes [8, 15]. Some studies did not show an IOP elevation and cataract development at all during the follow-up period [17]. In our study, a slight increase in IOP was observed at the end of the first post-injection month, but the IOP values by the end of the monitoring period did not differ statistically from the initial values.

We did not observe significant side effects in any of the analyzed eyes, either during the SCS TA injection or during the entire follow-up period. Our results support the fact that such a high concentration of TA is well tolerated and safe for diabetics. Although our study had a small number of eyes analyzed, due to the delicacy of the design and examination procedures, its results led us to the conclusion that only one concentrated (10 mg / 0.1 ml) TA SCS injection can stabilize macular oedema very effectively for nine months and maintain satisfactory VA. According to the newest data, our results confirm that a high concentration of SCS-applied TA can stabilize DMO over a much longer period compared to lower doses, without any additional side effects [20]. The main limitation of our study was the small number of eyes analyzed to draw a reliable conclusion that a concentrated dose of 10 mg / 0.1 ml TA is effective over a long period of time in the majority of eyes with clinically significant diabetic macular edema, and the fact that we were not able to use the UHR-OCT instrument for evaluation of the SCS after injection.

CONCLUSION

Suprachoroidal injection of TA provides high therapeutic drug concentrations in the target tissues i.e., the retina, retinal pigment epithelium, and choriocapillaris. In the treatment of DMO, the SCS application of TA leads to significant reduction of oedema and significant improvement of VA. Slow clearance of TA suspension can allow the sustained release of the drug over a long period of time. The single dose of 10 mg / 0.1 ml TA injected into the SCS can significantly stabilize macular oedema and maintain satisfactory VA for up to nine months. Since the propagation of TA applied in this way to the anterior ocular structures is very limited compared to intravitreal application of TA, the incidence of IOP elevation and the cataract development is much lower. A greater number of participants, a longer period of monitoring, and the use of an UHR-OCT instrument to assess the SCS after injection are necessary to conclude the benefit of the suprachoroidal-applied high-dose TA in the treatment of DMO.

Conflict of interest: None declared.

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Супрахороидално апликован концентровани триамцинолон-ацетонид у лечењу дијабетичког макуларног едема

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САЖЕТАК

Увод/Циљ Дијабетички макуларни едем је абнормално накупљање течности у макуларном ткиву које доводи до његовог задебљања.

Циљ студије је био да се процени ефикасност инјекције концентрованог триамцинолон-ацетонида од 10 *mg* / 0,1 *ml* у супрахороидални простор код болесника са дијабетичким макуларним едемом и сниженом видном оштрином.

Методе Код 12 очију са дијабетичким макуларним едемом, које до тада нису имале никакав претходни третман, употребом игле малог пречника (26Г) апликована је инјекција од 10 *mg* / 0,1 *ml* триамцинолон-ацетонида у супрахороидални простор у суперотемпоралном квадранту ока, 4 *mm* од лимбуса. Пре инјекције, као и један месец, три, шест, девет и 12 месеци после инјекције, проверавани су видна оштрина и интраокуларни притисак, а централна фовеална дебљина је мерена помоћу оптичке кохерентне томографије.

Резултати Један месец, три, шест и девет месеци после инјекције дошло је до статистички значајног смањења централне фовеалне дебљине (315,92 *μm*, 257,66 *μm*, 281,08 *μm* и 295,51 *μm* респективно) у односу на њену почетну вредност од 447,67 *μm*. Крајем 12. месеца поново је примећен пораст централне фовеалне дебљине до 392,16 *μm*. Видна оштрина се значајно побољшала у односу на почетну вредност (0,32) током прва три месеца (0,61) и остала је стабилна до краја деветог месеца (0,51), али се на крају 12. месеца поново смањила (0,39). Током читавог периода праћења ни код једног ока нису примећени значајно повишење интраокуларног притиска и развој катаракте.

Закључак Једна доза од 10 *mg* / 0,1 *ml* триамцинолон-ацетонида убризгана у супрахороидални простор може значајно стабилизовати дијабетички макуларни едем и одржати задовољавајућу видну оштрину до девет месеци.

Кључне речи: дијабетички макуларни едем; триамцинолон-ацетонид; супрахороидална инјекција

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Risk factors for depression in glaucoma patients

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SUMMARY

Introduction/Objective Glaucoma diagnosis often induces fear of vision loss and blindness, as well as concerns related to the lifelong use of eye drops and financial expenses, which can lead to certain emotional disorders, depression and anxiety in particular.
As these psychological disturbances usually coexist with physical disorders, the aim of the present study was to assess the risk factors for depression in patients with glaucoma.

Methods This cross-sectional study involved 132 consecutive glaucoma patients that were seen between September 2018 and December 2019 at the Glaucoma Department of Clinic for Eye Diseases, University Clinical Centre of Serbia, in Belgrade. All participants completed the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale to assess depression and anxiety, respectively.

Results The mean age of glaucoma patients was 65.67 ± 8.63 years, whereby the mean age in the group with depression/anxiety was 65.74 ± 7.6 / 64.67 ± 5.51. Prevalence of cardiovascular diseases and previous surgery was statistically significantly greater among glaucoma patients exhibiting depression relative to those that did not report any depressive symptoms (42.6% *vs*. 15.4%, 66.7% *vs*. 34.6%, respectively). On the other hand, these two groups were indistinguishable with respect to the evaluated ophthalmological parameters and the number of eye drops used to treat glaucoma.

Conclusion Our analyses revealed that low economic status, poor health, prevalence of cardiovascular diseases, history of surgeries, and non-beneficial lifestyle habits such as coffee consumption are the main risk factors for depression. However, none of the investigated clinical ophthalmological characteristics emerged as the risk factors for depression.

Keywords: glaucoma; depression; anxiety; rating scale

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide and is, by its very nature, a chronic disease [1]. Upon receiving glaucoma diagnosis, most patients experience fear of vision loss and blindness, while also being concerned with the prospect of lifelong use of eye drops and associated material expenses. Moreover, they anticipate deterioration in their quality of life due to restrictions imposed on the range of physical activities they will be able to perform. In some cases, these issues are compounded by inadequate communication or poor understanding of medical terms, which can lead to certain emotional disorders, depression and anxiety in particular [2]. Anxiety and depression are two common forms of psychological disturbances that usually coexist with physical disorders. Thus, it is not surprising that patients with glaucoma have been found to be at an increased risk of developing depression and/or anxiety following their diagnosis [3, 4, 5], as these conditions adversely affect the quality of life in patients with glaucoma [6]. Likewise, presence of depressive symptoms has been identified as an obstacle to glaucoma treatment adherence [7]. Hence, glaucoma patients need to be provided appropriate psychological care in order to improve their quality of life and compliance with medical advice. In order to detect, prevent, and treat the emotional problems that develop in patients with glaucoma, it is important to understand the risk factors for these psychological disturbances.

In the present study, the Hamilton Depression Rating Scale (HDRS) [8] was employed to assess depression in patients with glaucoma, while anxiety was assessed using the Hamilton Anxiety Rating Scale (HARS) [9]. HDRS is the most widely used clinician-administered depression assessment scale. The original version containing 17 items (HDRS17) was subsequently revised, leading to a 21-item version (HDRS21) which has become the gold standard for the assessment of depression in clinical practice.

In this study, we aimed to assess the risk factors for depression in patients with glaucoma.

METHODS

Study population

This cross-sectional study involved 132 consecutive glaucoma patients that were seen between September 2018 and December 2019

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at the Glaucoma Department of Clinic for Eye Diseases, University Clinical Centre of Serbia in Belgrade. Only individuals aged 40 years or older who have been receiving glaucoma treatment for at least six months were eligible for inclusion. Patients with primary open-angle glaucoma (POAG), normal tension glaucoma (NTG), primary angle-closure glaucoma (PACG) and secondary glaucoma which are not the result of any ocular or systemic disease, such as pseudoexfoliative glaucoma (XFG) and pigmentary glaucoma, were included in our research.

Exclusion criteria were: (1) presence of severe psychiatric illness (psychosis); (2) experience of a personal trauma such as death of a loved one, job loss in the last year, or recent divorce; (3) secondary glaucoma as a consequence of some other ocular/systemic disease; (4) current use of any medication that may result in a psychiatric disorder or cognitive impairment which could affect the psychological assessment, such as systemic use of β-blockers; and (5) presence of some other ocular disease that has led to a significant decrease in vision.

All subjects that met the study inclusion criteria received a detailed explanation of the study purpose and the nature of their involvement, and those that agreed to take part in the investigation signed an informed consent form, in accordance with the principles embodied in the Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of the University Clinical Center of Serbia, Belgrade.

Questionnaire

The data collection instruments employed in the present study included questionnaires eliciting relevant sociodemographic information, presence of any comorbidities and their characteristics, as well as the Serbian versions of the HDRS and HARS instruments for psychiatric evaluation.

The consultation started with a face-to-face interview conducted by the ophthalmologist, guided by a structured questionnaire probing into the patient's demographic data and medical history. Demographic data included age and gender, educational attainment, place of residence, employment status, marital status, self-reported economic situation, family history of glaucoma, and family history of psychiatric diseases. Information pertaining to systemic diseases, malignancies and previous surgeries was obtained through a review of patient's medical records and was verified/updated during the individual interview. All patients had their body weight and body height measured, allowing their body mass index (BMI) to be calculated.

Patients were also asked to respond to questions regarding pertinent lifestyle factors, namely smoking, alcohol and coffee consumption, and physical activity level.

The HDRS was used to assess depression, whereas anxiety was evaluated via the HARS. The original HDRS and HARS instruments were translated into Serbian language as well as back-translated to English to ensure that the original meaning was retained.

The HDRS comprises 21 items with the following scores, which determine the severity of depression:

< 8 – depression is not present
8–16 – mild depression
17–24 – moderate depression
> 24 – severe depression

The HARS consists of 14 items with the following scores, which determine the anxiety level:

< 14 – absence of anxiety
14–27 – mild anxiety
28–41 – moderate anxiety
42–56 – severe anxiety

Eye examinations

Ocular examination in all patients was performed by one ophthalmologist and included visual acuity (VA), slit-lamp biomicroscopy, gonioscopy, intraocular pressure (IOP) measurement (using Goldmann applanation tonometry) and fundus examination. A visual field test was performed using the Threshold C 24-2 Swedish Interactive Testing Algorithm standard program with Humphrey Visual Field Analyzer II (Carl Zeiss, Oberkochen, Germany). VA was measured by Snellen chart standing six meters away and was recorded as the logarithm of the minimum angle of resolution (logMAR). Indices of glaucoma severity were expressed numerically as vertical cup-to-disk ratio (VCDR), along with the staging of visual filed defects using Hodapp Classification, as well as visual field mean deviation (MD).

Statistical analysis

Categorical data were presented as absolute and relative values. Numerical variables were described using arithmetic mean with standard deviation or median with range (from minimum to maximum), depending on the data distribution. Distribution normality was evaluated by mathematical (Shapiro–Wilk and Kolmogorov–Smirnov tests, skewness and kurtosis, and coefficient of variation) and graphical (histogram, box-plot) methods. Study groups defined as glaucoma patients with (HDRS ≥ 8) and without (HARS < 8) depression were compared with respect to categorical variables using χ^2 test if the numerical criteria were met, and Fisher's exact test otherwise. For comparisons involving numerical variables, Student's t-test for independent samples or Mann–Whitey U test was adopted, depending on the data distribution. In order to evaluate factors that are potentially associated with the presence of depression among glaucoma patients, univariate and multivariate logistic regression modeling was used, reporting OR, 95% CI OR and p-value. All statistical analyses were performed in IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp, Armonk, NY, USA) whereby $p < 0.05$ was considered to denote statistical significance.

RESULTS

The study sample comprised 132 glaucoma patients with an average age of 65.67 ± 8.63 years, whereby the

mean age in the group with/without depression was 65.74 ± 7.61 / 65.62 ± 9.36, while in the anxiety group was 64.67 ± 5.51. Their median HDRS and HARS scores were 6.5 (0–22) and 4 (0–17), respectively for all glaucoma patients. Depression was identified in 54 (41%) glaucoma patients (HDRS ≥ 8), while only 11 (8%) individuals experienced anxiety (HARS ≥ 14), as shown in Table 1. Thus, due to the small number of patients with anxiety, the sample was segregated into those with and without depression for further analyses. The demographic characteristics of glaucoma patients with and without depression are presented in Table 2.

Table 1. Frequency of depression and anxiety in glaucoma patients

Depression/Anxiety	Depression n* (%)	Anxiety n* (%)
No symptoms	78 (60)	121 (92)
Mild	43 (32)	11 (8)
Moderate	10 (8)	0 (0)
Severe	1 (0)	0 (0)

Table 2. Socioeconomic characteristics of glaucoma patients with and without depression

Characteristics	Depression (n* = 54)	Without depression (n* = 78)	p*
Age (years), mean ± sd	65.74 ± 7.61	65.62 ± 9.36	0.953€
Male gender, n (%)	23 (42.6)	38 (48.7)	0.550£
BMI, mean ± SD	26.04 ± 3.34	27.80 ± 4.41	0.063€
Educational level, n (%)			0.500£
Secondary or lower	38 (70.4)	61 (78.2)	
Tertiary or higher	16 (29.6)	17 (21.8)	
Place of residence, n (%)			0.149£
urban	36 (66.7)	40 (51.3)	
rural	18 (33.3)	38 (48.7)	
Employment status, n (%)			0.225£
employed	5 (9.3)	16 (20.5)	
unemployed/retired	49 (90.7)	62 (79.5)	
Marital status, n (%)			0.054£
with partner	36 (66.7)	65 (83.3)	
without partner	18 (33.3)	13 (16.7)	
Self-reported economic situation, n (%)			0.023£
unsatisfying	33 (61.1)	2 (2.6)	
satisfying	21 (38.9)	76 (97.4)	

*for the 0.05 level of significance according to the Student's t-test (denoted by €) and χ^2 test (indicated by £)

Comorbidities of glaucoma patients identified in the subgroup exhibiting depression and the subgroup without depression are presented in Table 3.

Lifestyle habits and physical activity levels of glaucoma patients with and without depression are presented in Table 4.

Ophthalmological characteristics, type of glaucoma, and therapy received by two groups of glaucoma patients, with and without depression are presented in Table 5.

Table 3. Comorbidities of glaucoma patients in the subgroup exhibiting depression and the subgroup without depression

Comorbidity	Depression (n* = 54)	Without depression (n* = 78)	p*
DM status, n (%)	11 (20.4)	20 (25.6)	0.461£
DM therapy, n (%)			0.122£
oral	14 (25.9)	7 (9)	
insulin	34 (63)	62 (79.5)	
without therapy	6 (11.1)	9 (11.5)	
Cardiovascular diseases, n (%)	23 (42.6)	12 (15.4)	0.010£
SH, n (%)	39 (72.2)	53 (67.9)	0.846£
ACD, n (%)	3 (5.6)	0 (0)	0.163¥
Malignancies, n (%)	0 (0)	3 (3.8)	0.511¥
Previous surgery, n (%)	36 (66.7)	27 (34.6)	0.003£
Self-reported health status			0.020£
satisfying	31 (57.4)	75 (96.2)	
unsatisfying	23 (42.6)	3 (3.8)	

*for the 0.05 level of significance according to the Mann–Whitney U test §, χ^2 test £, and Fisher's exact test ¥;
DM – diabetes mellitus; SH – systemic hypertension; ACD – acute cerebrovascular disease

Table 4. The lifestyle habits and physical activity levels of glaucoma patients in the subgroup exhibiting depression and the subgroup without depression

Lifestyle factors	Depression (n* = 54)	Without depression (n* = 78)	p*
Smoking status, n (%)			0.595£
smoker	28 (51.9)	45 (57.7)	
non-smoker	26 (48.1)	33 (42.3)	
Alcohol consumption, n (%)	16 (29.6)	26 (33.3)	0.692£
Coffee consumption, n (%)	50 (92.6)	64 (82.1)	0.052£
Cups of coffee per day, Median (min–max)	3 (1–7)	2 (1–4)	0.038§
Physical activity, n (%)	20 (37)	24 (30.8)	0.617£
FHG, n (%)	21 (38.9)	22 (28.2)	0.370£
FHPD, n (%)	2 (3.7)	0 (0)	0.408¥

*for the 0.05 level of significance according to the Mann–Whitney U test § and χ^2 test £;
FHG – family history of glaucoma; FHPD – family history of psychiatric diseases

The results of univariate and multivariate logistic regression modeling with presence of depression as the dependent outcome are presented in Table 6.

DISCUSSION

As glaucoma is a chronic disease, it has been the focus of many studies exploring depression, which indicate that prevalence is high in individuals suffering from glaucoma, ranging from 10.9% to 24.7%, respectively, depending on the geographical region and investigated cohort [4, 10, 11]. For example, approximately 10% of glaucoma patients in America [4] and Japan [3] suffer from depression, whereas 12.1% prevalence was reported for Hungary [12] and 19.09% for Australia [13], and in Turkey the depression occurrence among glaucoma patients ranges from 24.66% [14] to 57% [6]. Depression was also found to affect 32.1% of patients with severe glaucomatous disease [13].

Table 5. Ophthalmological characteristics, type of glaucoma and therapy of glaucoma patients with and without depression

Characteristic	Depression (n* = 54)	Without depression (n* = 78)	p*
VA(LogMAR), median (min–max)			
Better eye	0 (0–2)	0 (0–1)	0.950§
Worse eye	0.15 (0–1.5)	0.15 (0–2)	0.543§
MD (dB), median (min–max)			
Better eye	-2.98 (-30.31 to 0.73)	-3.46 (-26.85 to -0.39)	0.550§
Worse eye	-7.60 (-27.91 to -0.75)	-11.78 (-28.80 to -1.32)	0.205§
Hodapp, better eye, n (%)			0.705£
early	35 (64.8)	57 (73.1)	
moderate	7 (13)	7 (9)	
advanced	12 (22.2)	14 (17.9)	
Hodapp, worse eye, n (%)			0.624£
early	22 (40.7)	25 (32.1)	
moderate	11 (20.4)	17 (21.8)	
advanced	21 (38.9)	36 (46.1)	
VCDR, median (min–max)			
Better eye	0.65 (0.2–1)	0.45 (0.3–1)	0.286§
Worse eye	0.80 (0–1)	0.88 (0–1)	0.683§
IOP (mmHg), mean ± SD	20 ± 8	18 ± 7	0.546§
Number of eye drop types used (min–max)	2 (0–3)	2 (1–4)	0.592§
Use of β-blockers, n (%)	38 (70.4)	73 (93.6)	0.009£
β-blocker use duration (y), median (min–max)	4 (0.2–15)	3 (0.1–30)	0.456§
Use of OCAI, n (%)	7 (12.9)	4 (5.1)	0.199£
History of glaucoma surgery, n (%)	10 (18.5)	14 (17.9)	0.862£
History of LI, n (%)	9 (16.7)	14 (17.9)	0.851£
Glaucoma type, n (%)			0.778£
secondary	16 (29.6)	26 (33.3)	
POAG and NTG	29 (53.7)	37 (47.5)	
PACG	9 (16.7)	15 (19.2)	

for the 0.05 level of significance according to the Mann–Whitney U test § and χ^2 test £; n – number of patients; VA – visual acuity; IOP – intraocular pressure; MD – mean deviation; VCDR – vertical cup-to-disk ratio; y – years; OCAI – oral carbonic anhydrase inhibitors; LI – laser intervention; POAG – primary open-angle glaucoma; NTG – normal tension glaucoma; PACG – primary angle-closure glaucoma

Extant research also indicates that patients with glaucoma are at a significantly higher risk of developing depression compared with those that do not suffer from this condition [15]. This finding has prompted investigations into the risk factors that predispose glaucoma patients toward depression and anxiety. The aim of the present study was thus to contribute to this body of literature by identifying the main risk factors for depression in patients with glaucoma in our country. As far as we know, this was the first study in Serbia that examined risk factors for depression in glaucoma patients. However, due to the small number of patients that exhibited anxiety, it was not possible to establish its potential links with the examined sociodemographic and clinical characteristics.

Depression is a highly prevalent disease, projected to be one of the three main disease burdens by 2030 worldwide [16]. As previously noted, the main reason for depression among glaucoma patients is the chronic nature of this disease that leads to vision loss. Furthermore, depression has been found to be associated with patients' perception of vision; however, in contrast to subjective measures of visual perception, objective measures of function such as VA or visual field results have not been linked to depression [13]. In 2022, Wu et al. [17] reported that patients' self-reported vision-related quality of life (VR-QoL) played a much more important role in the emergence of psychiatric illnesses compared to objective visual function indices, such as MD and VA. In the present study, none of the objective measures of glaucoma severity or visual function – including VA, VCDR, staging of visual filed defects using Hodapp Classification and MD – were found to be significant predictors of depression while subjective measures of visual perception were not considered in our investigation. Similarly, both Wang et al. [4] and Wilson et al. [10] noted that objective measures of disease and visual function (such as VA, VCDR, and visual field defects) were not associated with depression among subjects with glaucoma, whereas most self-reported measures of visual disability were linked to depression. These findings suggest that objective measures of glaucoma severity may not be as important to the mental health of glaucoma patients as their perception of illness and disability. In 2019, Wu et al. [18] concluded that the deterioration of vision impairment and visual field defects, in addition to increased recognition of psychological

Table 6. Factors associated with depression according to univariate and multivariate logistic regression analysis

Factor	Univariate logistic regression			Multivariate logistic regression[a]		
	OR	95% CI OR	p	OR	95% CI OR	p
Self-reported economic situation	0.280	0.09–0.87	0.027	0.030	0.01–0.31	**0.003**
Cardiovascular diseases	0.255	0.09–0.75	0.013	0.191	0.03–1.32	0.094
Previous surgery	0.238	0.09–0.63	0.004	0.177	0.04–0.84	**0.029**
Self-reported health state	4.870	1.18–20.17	0.029	2.230	0.25–19.64	0.470
Use of β-blocker eye drops	5.727	1.41–23.34	0.015	17.397	1.84–164.28	**0.013**
HARS score	1.708	1.29–2.25	< 0.001	2.277	1.42–3.64	**0.001**

[a]adjusted for age and gender
HARS – Hamilton anxiety rating scale

disturbances, significantly reduces the VR-QoL of glaucoma patients. This view concurs with the opinion shared by many authors that depression severity is closely linked to the degree of visual impairment as a result of glaucoma [13, 15, 19]. The reason for this positive correlation is patients' concern regarding the potential future worsening of the visual functions [20]. Consequently, the more severe patients' glaucoma is, the more likely they are to be depressed, which is consistent with the conclusions reached by Shin et al. [2]. Faster visual loss progression was also recognized by other authors as the potential risk factor for depression in patients with glaucoma [21]. Extant research also indicates that patients that have suffered damage to the visual field but do not experience further progression tend to tolerate their condition much better than patients in whom visual field continues to worsen.

While some authors reported associations between the use of topical β-blockers and depression, others do not recognize this as a factor for the onset of depression [10, 22]. In the present study, topical β-blocker application was not identified as a factor in the development of depression. In fact, our analyses indicate that those who did not take β-blockers had a greater chance of developing depression.

In the pertinent literature, depression is typically viewed as a consequence of being diagnosed with a chronic disease [2]. As glaucoma is a chronic disease, its duration, its effect on VA, need for repeated application of eye drops, and number of previous glaucoma operations and laser interventions are expected to contribute to the onset of depression. However, in our cohort, neither the history of glaucoma surgery and laser interventions, nor the number of drops required, were the risk factors for depression.

Controversies exist regarding the variations in depression prevalence between different glaucoma types. In the present study, no such difference was found between POAG, PACG and secondary glaucoma, which is in accordance with the results reported by Zhang et al. [23], although the percentage of patients with POAG who had depression was the highest. On the other hand, Mabuchi et al. [3] demonstrated a link between POAG and prevalence of depression and anxiety. Conversely, Kong et al. [24] established significantly higher depression levels in PACG patients relative to POAG patients and controls.

Following their evaluation of the link between depression and pseudoexfoliation, Cumurcu at al. [14] reported that the HDRS scores were significantly higher in the XFG group compared with the POAG and the control group. These authors further noted that in each of the three examined groups, there was no correlation between the HDRS scores and any of the following parameters: duration of glaucoma, medical treatment, VA, IOP, perimetric stage, cup-disc ratio and number of glaucoma operations.

In our cohort, age and gender did not affect the likelihood of depression, countering the findings reported by Wilson et al. [10]. On the other hand, these authors did reach similar conclusions as those derived from our work with respect to VA, changes in the visual field, and β-blocker use, as neither emerged as a risk factor for depression, although these authors gathered their data using The Center for Epidemiologic Studies Depression Scale (CES-D), Composite International Diagnostic Interview, and Short Form (CIDI-SF) questionnaires. It is also worth noting that, Chen et al. [15], indicating that older age and female glaucoma patients were at a greater risk of developing depression. These authors further noted that lower income was a significant risk factor for developing depression [15]. Our investigation led to a similar conclusion, as over 60% of analyzed glaucoma patients who showed symptoms of depression reported that they were dissatisfied with their economic situation compared to 3.8% who did not have symptoms of depression, while 97.4% were satisfied with their financial status and had no symptoms of depression. Our analyses of the relationship between depression and marital status similarly indicate that depression is more frequent in those without a partner, concurring with the results reported by Tastan et al. [6].

These findings could potentially indicate that absence of financial or emotional support may predispose people to depression which implies that economic burden and living alone may increase the risk of depression among glaucoma patients. Therefore, familial and social support are highly important for their psychological health.

Furthermore, depression is associated with unhealthy lifestyle behaviors, including smoking, drinking, and sedentary lifestyle [25]. According to the findings yielded by the present study, coffee consumption and self-reported dissatisfaction with one's health status were predictors for the onset of depression. On the other hand, BMI did not emerge as a statistically significant factor, but its greater values tended to be associated with lower depression scores.

In addition, presence of cardiovascular diseases significantly increased the risk for depression, concurring with the findings reported by other authors [26]. Available evidence further indicates that receiving a chronic disease diagnosis can prompt an onset of depression due to functional limitations, social isolation, loss of relationships, guilty feelings and anxiety about the future [11]. In our cohort, history of surgical interventions was also a significant predictor for the onset of depression.

It is also worth noting the anecdotal as well as empirical evidence [27] indicates that the recent COVID-19 pandemic has increased the frequency of depression and anxiety in most communities. However, as the present study was conducted before its onset, we can rule out COVID-19 infection as a possible risk factor for depression and/or anxiety.

When interpreting the results yielded by our investigation, it is important to note some study limitations, one of which is a small sample size especially those with anxiety. Moreover, we relied solely on the data gathered through self-report questionnaires when assessing our patients' depression and anxiety symptoms rather than considering a clinical diagnosis. However, the same approach has been adopted in a considerable body of research [3, 6, 10, 13, 14].

CONCLUSION

In conclusion, our analyses revealed that low economic status, poor health, presence of comorbidities such as cardiovascular diseases, history of surgeries, and non-beneficial lifestyle habits such as coffee consumption are the main risk factors for depression in glaucoma patients. However, none of the investigated clinical ophthalmological characteristics emerged as the risk factors for depression. In addition, owing to the small number of subjects in whom anxiety was identified through self-reported questionnaires, it was not possible to establish any associations of demographic and clinical characteristics with anxiety. Further research into emotional disorders involving larger glaucoma patient cohorts is thus warranted. Nonetheless, the overarching message arising from this study is that, when treating glaucoma, ophthalmologists need to focus not only on the medical aspects of this condition, but must also provide psychological support to their patients.

Conflicts of interest: None declared.

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Фактори ризика за депресију код болесника са глаукомом

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САЖЕТАК

Увод/Циљ Дијагноза глаукома веома често је повезана са страхом од губитка вида и слепила, са једне стране, те доживотним коришћењем капи и материјалним издацима, са друге стране, што све заједно може да доведе до одређених емоционалних поремећаја, од којих су најчешћи депресивност и анксиозност.

Циљ овог рада био је испитати факторе ризика за депресију код болесника са глаукомом.

Методе Студија је спроведена на Клиници за очне болести Универзитетског клиничког центра Србије у Београду, у периоду од септембра 2018. године до децембра 2019. године. Користили смо Хамилтонову скалу за процену депресивности и Хамилтонову скалу за процену анксиозности.

Резултати Просечна старост свих болесника била је 65,67 ± 8,63 година, док је у групи са депресијом/анксиозношћу била 65,74 ± 7,6 / 64,67 ± 5,51. Присуство кардиоваскуларних болести и број претходних операција било је статистички учесталије код болесника који су имали симптоме депресије у односу на оне без њих (42,6% наспрам 15,4%, 66,7% наспрам 34,6%). Испитиване офталмолошке клиничке карактеристике и број капи које су болесници користили нису били фактори ризика за симптоме депресије.

Закључак У нашој студији општи предиктори за депресију били су лоша економска ситуација, лоше здравствено стање, коморбидитети као што је присуство кардиоваскуларних болести, број претходних операција, затим лоше животне навике, као што је превелико конзумирање кафе. Ниједна од испитиваних офталмолошких клиничких карактеристика није била фактор ризика за депресивност.

Кључне речи: глауком; депресија; анксиозност; скале испитивања

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Characteristics of patients with diagnosed chronic fungal rhinosinusitis surgically treated in the past five years

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SUMMARY

Introduction/Objective Fungal rhinosinusitis comprises of a wide range of immune-pathological responses, including invasive, chronic, granulomatous, and allergic diseases.
Aim of this study was to determine total number of patients, their characteristics, frequency of symptoms, the manner of disease manifestation and the success of therapy.

Methods Study included 21 patients with fungal rhinosinusitis diagnosis made according to the 2020 EPOS guidelines.

Results Based on the visual analogue scale, feeling of localized pressure, i.e., facial pain, was dominant with a score of 9.57 ± 0.98, followed by the secretion from the nose with 8.14 ± 1.62, problems with breathing through the nose with 6.67 ± 3.25, and reduction the sense of smell with 2.14 ± 3.00. The t-test showed a statistically significant difference between mucosal changes on the diseased and healthy sides of the patient's face ($p < 0.0001$). Only one sinus was affected intraoperatively in 18 (85.71%) patients. The most commonly affected sinus was the maxillary one, in 13 (54.17%) patients, followed by the sphenoid sinus in five (20.83%) patients. *Aspergillus* was proven as the couse of rhinosinusitis in 12 (57.14%) patients.

Conclusion The dominant symptom of patients with fungal rhinosinusitis was localized pain/pressure in the area of the affected sinus. Endoscopically, on the side of the affected sinus, the pathological mucosa with thick, pithy, mucous secretion dominated. The maxillar sinus was primarily unilaterally affected, in more than half of the patients. *Aspergillus* has been proven to be the most common cause of rhinosinusitis.

Keywords: fungal rhinosinusitis; chronic rhinosinusitis; headache; facial pain/pressure; nasal discharge; nasal obstruction

INTRODUCTION

Fungal rhinosinusitis (FRS) comprises of a wide range of immunopathological responses, including invasive, chronic, granulomatous, and allergic diseases. They differ in clinical picture, histological phenomena, and biological significance [1, 2].

During the course of the disease, we distinguish between the acute form, which lasts up to four weeks, and the chronic form, with the duration of the symptoms longer than 12 weeks. Acute rhinosinusitis is well categorized. Controversy exists around the concept of chronic rhinosinusitis (CRS), i.e., the role of fungi in this condition. Based on histopathological findings, FRS can be broadly divided into two categories: invasive and noninvasive. The noninvasive form of FRS behaves clinically like chronic bacterial rhinosinusitis. Three noninvasive FRS have been described: saprophytic fungal infection, fungal ball (fungus ball or sinus mycetoma), and fungal-associated eosinophilic rhinosinusitis, including allergic fungal rhinosinusitis (AFRS). Invasive forms of FRS, in which the infection results in a mass that behaves like a malignant neoplasm, eroding the bones and spreading to the adjacent tissue, are the following: acute (fulminant) invasive, granulomatous invasive, and chronic invasive types. The granulomatous invasive type is mainly described in chronic cases of FRS from Sudan, India, and Pakistan, where patients are immunocompetent, almost exclusively identified with *Aspergillus flavus* and presented as non-seated granulomas, almost all of which have proptosis in clinical manifestations. These cases differ from chronic invasive FRS, which has a chronic course, often in subtly immunocompromised patients, such as those with diabetes mellitus and/or treated with corticosteroids, with a dense accumulation of hyphae attacking the tissue, sometimes associated with orbital apex syndrome [1, 2, 3].

AFRS is a type of chronic rhinosinusitis, as a reaction of hypersensitivity to fungi that colonize the sinus. It mainly affects young, atopic, immunocompetent patients, who often have nasal polyps and asthma. It is characterized by eosinophilic inflammation of the mucous membrane and thick mucin, the consistency of peanut or cheese butter, brownish to black, rich in eosinophils. Bent and Kuhn criteria are used to diagnose AFRS: nasal polyps, the presence of fungi in a microscopic finding or culture of sinus contents, eosinophilic mucin without

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fungal invasion of the sinus tissue, type 1 hypersensitivity to fungi, proven by skin or *in vitro* tests, and a characteristic CT finding (computed tomography of the paranasal sinuses – sinus expansion or heterogeneous shading). The therapy is surgical: all fungal material and nasal polyps are removed. Postoperative nasal lavage with salt water and intranasal corticosteroids improves the likelihood of long-term cure.

Fungus ball or sinus mycetoma is a dense accumulation of hyphae inside one or more sinuses, usually maxillary, without tissue invasion. Clinical signs and symptoms are nonspecific or absent, so the diagnosis of fungus ball is made mostly by chance, radiologically. Like AFSR, it can be associated with the presence of nasal polyps. The therapy is surgical: all fungal material is removed. There is no need for drug therapy postoperatively [2–6].

The aim of this research was to determine the total number of patients with FRS, their distribution by sex, age, to identify the leading symptom, most common localization, endoscopic and radiological characteristics, the extent of the disease and the success of therapy.

METHODS

In this prospective-retrospective study during the previous five years, among 557 operatively treated patients with diagnosed CRS, FRS was microbiologically and pathohistologically verified in 21 patients. They were operatively treated at the Clinic for Ear, Throat and Nose Diseases of the Clinical Centre of Vojvodina, Novi Sad, Serbia. Fungal rhinosinusitis diagnosis was made according to the 2020 EPOS guidelines [1]. Patients' data were collected from the medical histories (sex, age, diabetes mellitus, use of corticosteroids, lifestyle, smoking, chemical contaminants, chronical inflammations, allergens). Diagnostic protocol included the VAS (visual analogue scale), intraoperative nose swab, endoscopic intraoperative finding, CT finding, laboratory test (eosinophils in nasal secretions, total immunoglobulin E (IgE), and complete blood count). The patients assessed their symptoms intensity on the VAS from 0 to 10, with 0 indicating no trouble and 10 indicating the maximum intensity of symptoms. The VAS assessed the following: nasal breathing, nasal secretions, secretions flowing through the posterior wall of the pharynx, decreased sense of smell, and pressure or pain in the affected sinus.

Endoscopic examination of the nose assessed the appearance of the mucosa (0 – mucosa without changes, 1 – there is mild edema, 2 – polypoid degeneration), the presence of secretion (0 – none, 1 – a small amount of clear secretion, 2 – thick and/or mucopurulent secretion), the presence of polyps (none, first degree, second degree, third degree), and deviation and deformities of the nasal septum.

The study was carried out according to the principles of the Helsinki Declaration and it was approved by the local ethics committee, decision number 00-15/1700. All the patients were fully informed on the study itself and they signed their consent to participate. Numerical data are presented as measures of central tendency (mean, median), the measures of variability (standard deviation, minimum, maximum), and categorical data are presented as frequencies and percentages. Statistical analysis was performed using IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among 557 operatively treated patients diagnosed with CRS, during five years, 21 (3.8%) patients had microbiologically and pathohistologically verified FRS. CRS with polyposis was found in nine (42.9%) patients. There were 11 (52.4%) female patients, as opposed to 10 (47.6%) male patients. The average age was 45.33 ± 16.51 years (18–75 years).

Of the associated diseases, allergies were present in 14 (66.67%) patients, headache in six (28.57%) patients, hypertension in six (28.57%) patients, asthma in five (23.8%) patients, cardiovascular disease in three (14.29%) patients, diabetes in two (9.52%) patients, hearing impairment in two (9.52%) patients, and hemophilia, urticaria, gastric ulcer and hypocroticism in one (4.78%) patient. Patients were predominantly allergic to inhaled allergens – in nine (42.9%) patients, while drug allergy was reported by seven (33.3%) patients, and food allergy by one (4.8%). The most common inhaled allergens are mites, in five (15.5%) cases, followed by weed pollen in four (12.1%) cases, house dust in three (9.1%) cases, mold/mildew/fungi in three (9.1%) cases, grass pollen in three (9.1%), tree pollen in one (3%) case.

In the laboratory findings, we were interested in the following data: eosinophils in nasal secretions, total IgE, and complete blood count. Eosinophilic granulocytes were found in nasal secretions in 12 (57.14%) patients. Total IgE was elevated in nine (42.85%) patients and decreased in two (9.52%) patients. Blood of seven (33.33%) patients showed eosinophilia, in one (4.76%) patient anti-*Aspergillus* antibodies were isolated, and the remaining 13 (61.9%) patients did not show peculiarities in the blood.

Based on the visual analogue scale, feeling of localized pressure, i.e., facial pain, was dominant with a score of 9.57 ± 0.98, followed by the secretion from the nose with 8.14 ± 1.62, problems with breathing through the nose with 6.67 ± 3.25, and reduction of the sense of smell with 2.14 ± 3.00 (Figure 1).

The appearance of the mucosa on the patient's side was evaluated by endoscopic examination in all patients with a grade of 2 (mean value: 2 ± 0). Nasal secretion was evaluated with 1 in four (19.05%) patients, with 2 in 17 (80.95%) patients (mean: 1.81 ± 0.4). The presence of polyps was evaluated with 0 in 12 (57.14%) patients, the first degree of polyposis was found in two (9.52%), the second degree in five (23.81%), and the third degree was found in two (9.52%) patients (mean: 0.86 ± 1.11). Deviation and deformities of the nasal septum were present in 12 (57.14%) patients. Using the obtained results, we compared the diseased and the healthy side of the patient. The obtained results are shown in Table 1.

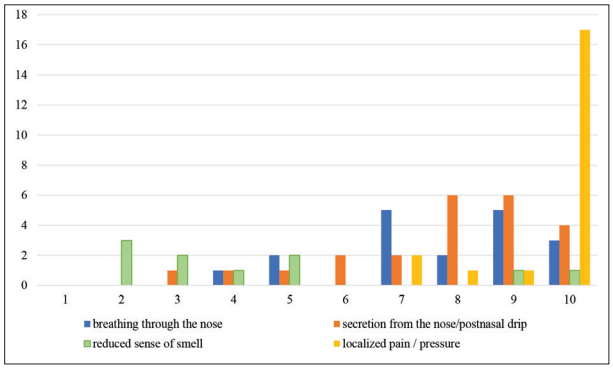

Figure 1. Visual analog scale score of nasal symptoms (nasal block, secretion/postnasal drip, hyposmia/anosmia, local pressure of the sinuses)

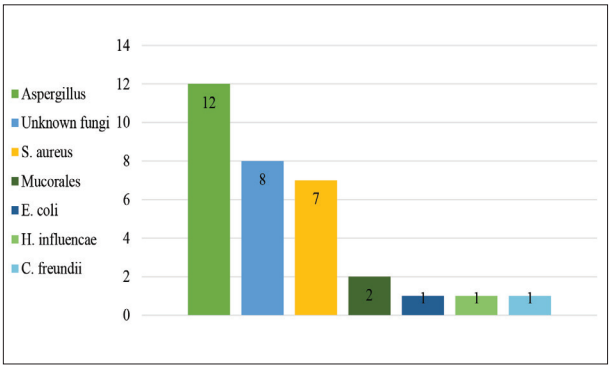

Figure 2. Pathogenic microorganisms isolated in nasal swab/material from the affected sinuses

Table 1. Endoscopic analyses of the nose

Parameter	Mucosa	Nasal secretion	Polyp	Nasal deviation	
				Yes	No
Diseased side (M ± SD)	2 ± 0**	1.81 ± 0.4**	0.86 ± 1.11	12 (57.14%)	9 (42.86%)
Healthy side (M ± SD)	0.76 ± 0.83**	0.33 ± 0.67**	0.33 ± 0.8	4 (19.05%)	17 (80.95%)

M – middle value; SD – standard deviation;
*p < 0.05;
**p < 0.001

Table 2. Analyses of the CT scan of the paranasal sinuses

Sinus	Maxillar	Ant. ethmoidal	Post. ethmoidal	Sphenoidal	Frontal	Osteomeatal complex
Diseased side (M ± SD)	1.33 ± 0.91**	1.43 ± 0.81**	0.9 ± 0.77*	0.62 ± 0.92*	0.67 ± 0.58*	1.48 ± 0.87**
Healthy side (M ± SD)	0.24 ± 0.54**	0.19 ± 0.51**	0.19 ± 0.51*	0.14 ± 0.48*	0.09 ± 0.3*	0.24 ± 0.54**

M – middle value; SD – standard deviation;
*p < 0.05;
**p < 0.001

The t-test showed there is a statistically significant difference between mucosal changes on the diseased and healthy sides of the patient's face ($p < 0.0001$). There is a statistically significant difference between the amount and properties of secretions on the diseased and healthy side of the patient's face ($p < 0.0001$). Also, there is no statistically significant difference in the presence of nasal polyps on the diseased and healthy side of the patient's face ($p = 0.0835$).

Binomial test showed that there is no statistically significant difference in whether or not there is a deviation on the affected side ($p = 0.664$).

Intraoperative in 18 (85.71%) patients only one sinus was affected, in the remaining 3 (14.29%) two sinuses were affected. The most commonly affected sinus was the maxillary sinus, in 13 (54.17%) patients, followed by the sphenoid sinus in five (20.83%) patients, the posterior ethmoid in three (12.5%) patients, the anterior ethmoid sinus in two (8.33 %) patients, and the frontal sinus was affected in only one (4.17%) patient (Table 2).

Nasal swab or analysis of the material obtained from the affected sinus showed the presence of fungi in all the patients. *Aspergillus* was proven in 12 (57.14%) patients, and mucormycosis (a fungus of the order Mucorales) was diagnosed in one (4.76%) patient. Fungal material was found in eight (38.1%) patients, and was not examined in more detail. In addition to fungi, we also isolated the following: *Staphylococcus aureus* in 33.33% (seven patients), *Escherichia coli* 9.25% (two patients), *Haemophilus influenzae* and *Citrobacter freundii* 4.76% each (one patient) (Figure 2).

Using the t-test, we determined whether there was a statistically significant difference in the changes on the CT finding on the healthy and sick side of the patient's face. There is a statistically significant difference of the shading of the maxillary sinus on the diseased *vs.* the healthy side of the patient's face ($p < 0.0001$) (Table 2).

There is a statistically significant difference between the shading of the anterior ethmoid and of the posterior ethmoid sinus on the diseased and the healthy side of the patient's face ($p < 0.0001$). There is a statistically significant difference between the shading of the sphenoid sinus on the diseased and the healthy side of the patient's face ($p = 0.0403$). There is a statistically significant difference between the shading of the frontal sinus on the diseased and the healthy side of the patient's face ($p = 0.0002$). There is a statistically significant difference between the shading of the osteomeatal complex on the diseased and the healthy side of the patient's face ($p < 0.0001$).

DISCUSSION

The incidence of chronic rhinosinusitis in European countries has been continuously growing over the years. There

is an increasing presence of non-invasive fungi, i.e., "fungus ball" in the intraoperative finding in affected sinuses, patients undergoing surgical treatment. This phenomenon is explained by the increased and uncontrolled use of antibiotics, immunosuppressive therapy and changes in life habits (primarily increased stay in air-conditioned rooms and vehicles). While some authors cite the use of more advanced diagnostic methods as a reason for detecting fungi in the sinuses [6].

The study analyzed 557 patients diagnosed with CRS, surgically treated at the Clinic for Ear, Throat and Nose Diseases of the Clinical Centre of Vojvodina, Novi Sad, Serbia. In 21 (3.77%) patients the presence of non-invasive fungi in the affected sinus was proven intraoperatively, and of that number, 12 (57.14%) had CRS without polyposis and nine (42.86%) had nasal polyps [7]. Of the 21 patients examined, 11 (52.4%) were female and 10 (47.6%) were male. A higher incidence of the female sex in FRS is also found in other papers [7, 8]. Cho et al. [9] and Jiang et al. [10] also note that the disease is more common in middle-aged women, for no apparent reason. The average age of our respondents was 45.33 years, which is in line with the literature – the disease is characteristic of adult patients, while it is rarely found in children and adolescents [7].

The most common comorbidities in the study were allergies (66.67%). Of these, inhaled allergens (42.9%), drug allergies (33.3%) and nutritional allergens (4.78%) were noted. Of other diseases, headache was present in 28.6%, hypertension in 28.6%, lower respiratory tract disease in 23.8%, and bronchial asthma in 19% of the patients. Tyler et al. [11]. report allergic rhinitis in 48% of their patients, bronchial asthma in 33.8%, hypertension in 25.8% of patients, and aspirin intolerance in 22.5%. Diabetes mellitus was found in our patients in only two (9.5%) cases. In the study by Tyler et al. [11] it was also among the less common comorbidities (3.2%). Diabetes mellitus, as well as other immunodeficiency conditions, is characteristic of invasive forms of fungal rhinosinusitis, such as acute necrotizing and chronic invasive fungal rhinosinusitis [12].

In relation to sinus involvement, the changes can be unilateral and bilateral. All patients in our study had changes exclusively unilaterally, which is in line with most studies, which more often find that only one side of the face is affected [7, 8]. The maxillary sinus was most commonly affected, in 13 (54.67%) patients. The sphenoid sinus was the second most affected, in five (20.83%) patients. Although such epidemiology is confirmed by other studies, they state that the increased frequency of jaw sinus disease is associated with dental procedures performed on the upper jaw [7, 8, 12, 13, 14]. In our study, we had no data on previous dental interventions. Other sinuses were less frequently affected by fungal infection: the posterior ethmoid three (12.5%) times, the anterior ethmoid two (8.33%) times, and the frontal ethmoid only once (4.17%).

The microbiological findings of the examined patients showed the presence of fungi in all (100%) the patients. *Aspergillus* is the most common isolated fungus, in as many as 12 (57.14%) patients, which is in line with other studies [10, 11, 15, 16]. In eight (38.1%) specimens in which fungal material was found, the type of fungus was not defined, and fungi from the order Mucorales, which cause mucormycosis, were found once (4.7%). The presence of *Staphylococcus aureus* in the findings of seven (33.33%) patients is interesting. Tyler et al. [11] and Singh [12] found frequent infections with this bacterium. *Escherichia coli* was isolated in two (9.5%) patients, *Haemophilus influenzae* and *Citrobacter freundii* in one (4.8%).

The dominant problem in the VAS, in all the patients, was the characteristic localized pain, i.e., facial pressure, with an average score of 9.57. The second most severe symptom was nasal discharge or discharge down the throat, with an average score of 8.14. Nasal congestion was reported by 18 (85.7%) patients with a mean score of 6.6. Mild odor disorder with a mean score value of only 2.14 was registered in only 10 (47.62%) patients. These findings differ from the claims of Fadda et al. [7], according to which the most common symptom of the maxillary sinus involvement is nasal congestion (76.9%), followed by rhinorrhea (61.5%), with facial pain in the third place (46.1%). Compared to the same paper, when the sphenoid sinus is affected, our findings are similar given that the most common symptom for their patients is facial pain (77.8%), followed by rhinorrhea (66.7%), and cacosmia (33%), while only 11% of the patients complained of nasal congestion. Comparing the endoscopic findings of the healthy and diseased (fungal infiltrate-affected) sides of the nose, the t-test showed a statistically significant difference in the appearance of the mucosa ($p < 0.0001$). There is a significant difference in the quality and quantity of nasal secretions ($p < 0.0001$). The presence of polyps was not shown to be a statistically significant characteristic of chronic fungal rhinosinusitis ($p = 0.0835$), nor was the existence of nasal septal deviation or deformity ($p = 0.664$). In a study by Tyler et al. [11], diagnostic nasal endoscopy showed polypoidal changes in 71 patients (37.3%), blackish debris in 14 patients (7.4%), and mucopurulent discharge in middle meatus in 49 cases (25.8%) out of 81 cases of fungal sinusitis. A CT scan of paranasal sinus cavities was done for all the cases and sinus involvement. Using the t-test and comparing the score of the diseased and of the healthy side of the nasal cavity and the patient's sinuses, a statistically significant difference in the appearance of all sinuses was proved. For the maxillary, anterior ethmoid, and frontal sinuses, and the osteomeatal complex, statistically extremely significant differences were shown between shading on the healthy and the diseased sides ($p < 0.0001$). These findings correspond to the published data [15, 16]. In a study by Fadda et al. [14], unilateral involvement was seen in 83.3% of cases and 33.3% cases of fungal rhinosinusitis show features of dense metal deposits and 30.9% of cases show bony erosion.

CONCLUSION

The dominant symptom of patients with fungal rhinosinusitis in the study was localized pain/pressure in the area of the affected sinus, followed by secretion/discharge of nasal

secretions, and nasal congestion. Nasal endoscopy in all the patients was dominated on the side of the pathologically fungally altered sinus by pathological mucosa with thick, pithy, mucous secretion. Intraoperative findings revealed unilateral involvement of the affected sinus in all the patients, primarily the maxillary sinus, which was affected in more than half of the patients. *Aspergillus* has been proven to be the most common cause of the disease.

Conflict of interest: None declared.

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Карактеристике болесника са дијагнозом хроничног гљивичног риносинузитиса хируршки лечених у протеклих пет година

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САЖЕТАК

Увод/Циљ Гљивични риносинузитис обухвата широк спектар имунопатолошких одговора, укључујући инвазивне, хроничне, грануломатозне и алергијске болести носа и параназалних шупљина.

Циљ овог истраживања био је да се утврди укупан број болесника, њихове карактеристике, учесталост симптома, начин манифестовања болести и успех терапије.

Методе У нашу студију је укључен 21 болесник са микробиолошки и патохистолошки верификованим гљивичним риносинузитисом.

Резултати На основу визуелне аналогне скале болови у лицу били су доминантни са оценом 9,57 ± 0,98, секреција из носа са оценом 8,14 ± 1,62, проблем дисања на нос са 6,67 ± 3,25, док је смањење чула мириса било са оценом 2,14 ± 3,00. *T*-тест је показао да постоји статистички значајна разлика између промена слузокоже на болесној и здравој страни лица болесника ($p < 0,0001$). Интраоперативно је код 18 (85,71%) болесника захваћен само један синус, и то најчешће максиларни у 13 (54,17%) случајева, потом сфеноидни синус у пет (20,83%) случајева, задњи етмоид у три (12,5%) случаја, предњи етмоид у два (8,33%) случаја и фронтални синус само код једног (4,17%) болесника. *Aspergillus* је дијагностикован код 12 (57,14%) болесника, а мукор микоза (гљива реда *Mucorales*) код једног (4,76%) болесника.

Закључак Доминантан симптом болесника са гљивичним риносинузитисом је локализован бол/притисак у пределу захваћеног синуса. Ендоскопски, на страни захваћеног синуса, доминирала је патолошка слузница са густим, пихтијастим, мукозним секретом. Првенствено је унилатерално захваћен вилични синус, код више од половине болесника. *Aspergillus* је доказан као најчешћи узрочник риносинузитиса.

Кључне речи: гљивични риносинузитис, хронични риносинузитис; главобоља; бол/притисак у лицу; секреција из носа; опструкција носа; поремећаји мириса; визуелна аналогна скала

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effects of cardiac rehabilitation on quality of life and exercise capacity in patients with coronary artery disease – do women benefit equally?

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SUMMARY

Introduction/Objective This paper aimed to examine whether women and men benefit equally from comprehensive cardiac rehabilitation (CR) in terms of quality of life (QOL), and exercise tolerance in patients with coronary artery disease (CAD).

Methods The study involved 1603 CAD patients, 1231 (76.8%) men and 372 (23.2%) women, who were referred to a three-week CR program. All patients were tested for physical strain at the beginning and at the end of CR. The QOL was assessed at the beginning and at the end of CR by validated questionnaire Short-Form 36.

Results Improvements in physical strain tolerance were more pronounced in women compared to men (18.46% *vs*. 14.23% for level, and 19.1% *vs*. 16.34% for the duration of the test). Also, CR has led to the improvement of the QOL in both men and women. However, women had greater improvement than men in all parameters - physical functioning: 26.85% *vs*. 10.12%, limitations due to physical health: 76.39% *vs*. 28.11%, limitations due to+ emotional problems: 23.12% *vs*. 21.07%, energy/fatigue: 13.33% *vs*. 6.77%, emotional well-being: 11.19% *vs*. 6.77%, social functioning 14.48% *vs*. 4.96%, body pain 15.76% *vs*. 10.16%, general health 10.53% *vs*. 7.38%, and health change 24.06% *vs*. 12.69%.

Conclusion Women generally less participate in CR than men. Results indicated that CR improves exercise capacity and QOL in CAD patients, in both men and women. However, these positive changes were more pronounced in women. This is why CR needs improvement in the referral and participation of women.

Keywords: coronary artery disease; cardiac rehabilitation; quality of life; physical strain tolerance; gender differences

INTRODUCTION

With 17.9 million deaths per year, cardiovascular diseases (CVDs) are the leading cause of death in the world [1]. Coronary artery disease (CAD) remains the most lethal CVD in countries with all income groups as seven million people die annually due to ischemic heart disease (IHD) [2]. However, it seems that the mortality rate caused by IHD is declining over time [2]. This is probably the consequence of new diagnostic and therapeutic possibilities.

Although men have a higher incidence of CAD, the mortality rate from acute cardiovascular events is higher in women and they tend to have a worse prognosis compared to men [3]. This is probably due to the gender-related disparities in the diagnostic and therapeutic approach. Namely, women are less likely to be referred to coronary angiography or interventional procedure compared to men [4]. This is of great importance as 1/3 of female patients die due to CAD. Also, it is widely believed that premenopausal women are less likely to suffer from CAD. However, the presence of IHD among young women is increasing. This is probably the consequence of unfavorable lifestyle changes.

A well-organized cardiac rehabilitation (CR) includes exercise training, adequate patient education, management of modifiable cardiovascular risk factors, psychosocial support and dietary advice [5]. As such, CR improves the quality of life (QOL) and physical strain tolerance, leads to weight loss, and tobacco cessation, has an anti-inflammatory effect, reduces the blood pressure (BP) values, and, what is most important, reduces cardiovascular and overall morbidity and mortality [6, 7]. This is why CR is recommended by major medical societies worldwide [8, 9]. However, the utilization rate for CR is still very low [10]. Furthermore, although beneficial effects of CR are proven in both gender, women participate in CR programs in a significantly lower percentage than men [11, 12].

The aim of our paper was to examine whether women and men benefit equally from comprehensive CR in terms of QOL and exercise tolerance in patients with CAD.

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METHODS

The study involved 1603 patients, 1231 (76.8%) men and 372 (23.2%) women. The average age of the subjects was 59.99 ± 9.58 years. All participants were referred to the CR at the Institute for Treatment and Rehabilitation Niška Banja after surviving myocardial infarction (MI), percutaneous coronary intervention (PCI) or surgical myocardial revascularization. During a three-week program of cardiovascular rehabilitation, patients were subjected to dosed and personalized aerobic physical training which included aerobic exercises, bicycle riding and walking 45 minutes per session, two sessions on a daily basis. The training was dosed according to the way revascularization was done [for example, patients with coronary artery bypass grafting (CABG) did not perform chest exercises], the condition of the locomotor system (some patients did not ride a bicycle due to problems with their knees), and the completeness of revascularization (patients with uncompleted revascularization underwent low intense training). Also, all patients were tested for physical strain at the beginning and the end of CR. The tests were done on a treadmill (Full Vision Drive Inc., Newton, KS, USA) according to the Bruce protocol. After the first exercise stress test (EST), training was modified according to the results achieved. Tests were limited by submaximal heart rate [(SHR) – calculated as 85% from the 220-age equation], symptoms and signs like chest pain, lack of air, dizziness, etc., a sudden increase of systolic BP to values ≥ 220 mmHg, or decrease in systolic BP > 10 mmHg, complex heart rhythm disorders, and/or ischemic changes on the electrocardiogram which were defined as horizontal and/or down-sloping ST depression ≥ 1 mm.

Psychological dimensions and the QOL were assessed at the beginning and at the end of CR by validated questionnaire Short-Form 36 Health Status Survey (SF-36). All data were analyzed based on gender.

The study was approved by the ethical committee of the Niška Banja Institute for Treatment and Rehabilitation. Decision number is 29074.

Statistics

Qualitative data were expressed as frequencies and percentages while quantitative data are presented as mean ± standard deviations. Normality of distribution was tested by Kolmogorov–Smirnov test. Normally distributed data were compared by Student's t test, while the Mann–Whitney test and Wilcoxon test were used for abnormally distributed data. For the comparison of frequencies, the χ^2 test was used. Statistical significance was accepted for $p < 0.05$. Data were analyzed using SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY, USA) software.

RESULTS

The age structure of patients differed significantly between genders as men were younger than women (59.68 ± 9.66 *vs.* 61.02 ± 9.25, t = 2.352, p = 0.019). MI was more common in women ($\chi^2 = 5.493$; p = 0.019). On the other hand, CABG was more common in men ($\chi^2 = 16.110$; p < 0.001). There was no difference in the incidence of PCI in relation to gender (Table 1).

Table 1. Distribution of myocardial infarction, percutaneous coronary intervention and coronary artery bypass grafting among genders

Distribution	Male n (%)	Female n (%)	χ^2	p
Myocardial infarction	971 (78.9)	314 (84.4)	5.493	0.019
Coronary artery bypass grafting	541 (43.9)	20 (32.3)	16.110	< 0.001
Percutaneous coronary intervention	686 (55.7)	213 (57.3)	0.272	0.602

The incidence of arterial hypertension was higher in women compared to men ($\chi^2 = 4.399$; p = 0.036). Other risk factors for CVDs (hyperlipidemia, diabetes mellitus, smoking status, heredity) did not differ between the groups (Table 2).

Table 2. Risk factors for cardiovascular diseases

Parameters	Male n (%)	Female n (%)	χ^2	p
Hyperlipidemia	1088 (88.4)	337 (90.6)	1.411	0.235
Arterial hypertension	1023 (83.1)	326 (87.6)	4.399	0.036
Diabetes mellitus	308 (25)	99 (26.6)	0.382	0.536
Smoking	686 (55.7)	195 (52.4)	1.263	0.261
Heredity	543 (44.1)	157 (42.3)	0.372	0.542

At the beginning and at the end of CR EST was performed. The differences between the first EST (EST1) and the second EST (EST2) are shown in Table 3. On the EST2 patients achieved a higher level of strain (Z = 16.872; p < 0.001), and the EST2 lasted longer (Z = 20.944; p < 0.001) compared to the EST1 (Table 3). Also, more patients achieved SHR on EST2 ($\chi^2 = 429{,}46$; p < 0.001).

The differences in strain tolerance on EST1 between men and women are shown in Table 4. Tests lasted longer in men (Z = 8.171; p < 0.001) and men achieved a higher level of strain compared to women (Z = 5.059; p < 0.001). Also, the double product (DP) which was defined as systolic BP x heart rate, was higher in men before (Z = 3.160; p = 0.002), and after EST1 (Z = 2.154; p = 0.031). The incidence of chest pain, ST segment depression and SHR did not differ between the genders.

EST2 was performed after a three-week rehabilitation program. The average strain level was significantly higher among men (Z = 7.366; p < 0.001), as well as the duration of the test (Z = 8.023; p < 0.001). There were no significant differences in DP before the EST2. However, the DP after the test was significantly higher in men (Z = 3.248; p = 0.001). The incidence of chest pain, ST depression and SHR did not differ between genders (Table 5).

At the end of CR, we compared the results of EST1 and EST2 in order to determine if there were differences in the effects of CR on the tolerance of physical strain in relation to the gender.

Table 3. Comparison between the first and the second exercise stress test (EST) in all patients

Parameters	EST1	EST2	Z/χ^2	p
EST level	2.29 ± 0.93	2.63 ± 0.96	16.872	< 0.001[1]
EST duration (min)	5.40 ± 2.66	6.33 ± 2.68	20.944	< 0.001[1]
Double product before	9819.28 ± 4923.61	9696.32 ± 2068.11	1.351	0.177[1]
Double product after	21427.07 ± 7583.58	21874.49 ± 3770.19	7.194	< 0.001[1]
ST depression	171 (10.7)	222 (13.9)	541.48	< 0.001[2]
Submaximal heart rate	835 (52.2)	1060 (66.5)	429.46	< 0.001[2]
Chest pain	25 (1.6)	15 (0.9)	33.29	< 0.001[2]

Z – Wilcoxon test, χ^2 – Chi squared test

Table 4. The first exercise stress test

Parameters	Male n (%)	Female n (%)	Z/χ^2	p
EST level	2.39 ± 0.93	1.95 ± 0.87	5.059	< 0.001
EST duration (min)	5.69 ± 2.67	4.45 ± 2.39	8.171	< 0.001
Double product before	9780.48 ± 5475.77	9931.12 ± 2226.04	3.160	0.002
Double product after	21609.99 ± 8380.37	20792.49 ± 3785.42	2.154	0.031
ST depression	137 (11.1)	34 (9.2)	1.110	0.291
Submaximal heart rate	653 (53.1)	182 (49.3)	1.614	0.204
Chest pain	18 (1.5)	7 (1.7)	0.345	0.557

Z – Mann–Whitney U test; EST – exercise stress test

Table 5. The second exercise stress test

Parameters	Male n (%)	Female n (%)	Z/χ^2	p
EST2 level	2.73 ± 0.94	2.31 ± 0.88	7.366	< 0.001
EST2 duration (min)	6.62 ± 2.69	5.30 ± 2.45	8.023	< 0.001
Double product before	9675.60 ± 2102.82	9765.20 ± 1949.45	1.162	0.245
Double product after	22045.47 ± 3767.56	21304.05 ± 3727.65	3.248	0.001
ST depression	176 (14.4)	46 (12.5)	0.813	0.367
Submaximal heart rate	824 (67.2)	236 (64.1)	1.205	0.272
Chest pain	11 (0.9)	4 (1.1)	0.109	0.741

Z – Mann–Whitney U test; EST – exercise stress test

Table 6. Comparison between the first and the second exercise stress test (EST) in men

Parameters	EST1	EST2	Z/χ^2	p	%
EST level	2.39 ± 0.93	2.73 ± 0.94	14.482	< 0.001	14.23
EST duration (min)	5.69 ± 2.67	6.62 ± 2.69	17.952	< 0.001	16.34
Double product before	9780.48 ± 5475.77	9675.60 ± 2102.82	2.251	0.024	-1.07
Double product after	21609.99 ± 8380.37	22045.47 ± 3767.56	6.737	0.031	2.02
ST depression	137 (11.1)	176 (14.4)	399.317	< 0.001	28.47
Submaximal heart rate	653 (53.1)	824 (67.2)	323.160	< 0.001	26.19
Chest pain	18 (1.5)	11 (0.9)	51.045	< 0.001	-38.89

Z – Wilcoxon test

The average strain level in men was significantly higher in EST2 (Z = 14.482; p < 0.001). Also, the duration of the test was significantly longer in the second test (Z = 2.251; p = 0.024). DP before the test was significantly lower on EST2 (Z = 2.251; p = 0.024), but DP after the test was significantly higher in EST2 (Z = 6.737; p = 0.031). The percentage of male patients with ST depression (χ^2 = 323.160; p < 0.001) and SHR (χ^2 = 105.652; p < 0.001) were more frequent on EST2. On the other hand, the percentage of male patients with chest pain was significantly lower in the second EST (χ^2 = 51.045; p < 0.001) (Table 6).

The average strain level in women was significantly higher in the second test (Z = 8.712; p < 0.001). Likewise, the EST2 lasted significantly longer than EST1 (Z = 10.865; p < 0.001). The DP before the test did not differ substantially between EST1 and EST2. However, the DP after the EST2 was higher compared to EST1 (Z = 2.602; p = 0.009). In the second test, the percentage of female patients with ST depression (Z = 145.635; p < 0.001) and SHR (Z = 105.652; p < 0.001) was higher. The percentage of female patients experiencing chest discomfort, on the other hand, did not differ between the tests (Table 7).

Thus, a three-week program of CR has led to the improvement of the physical strain tolerance in both men and women. Namely, in both groups of patients, EST2 lasted significantly longer than EST1, and the patients achieved a higher level of loading in the second test. Moreover, these improvements were more pronounced in women compared to men (18.46% *vs.* 14.23% for level, and 19.1% *vs.* 16.34% for the duration of EST) (Tables 5 and 6).

The effects of CR on the QOL in 360 patients (299 men and 61 women) with CAD were assessed by validated questionnaire Short-Form 36 Health Status Survey (SF-36). In Table 8 the comparison of mean scores for SF-36 subscales in all examined patients before and after CR is shown. All parameters were improved after CR: physical functioning (Z = 8.804; p < 0.001), limitations due to physical health (Z = 5.227; p < 0.001), limitations due to emotional problems (Z = 4.322; p < 0.001), energy/fatigue (Z = 7.803; p < 0.001), emotional well-being (Z = 7.731; p < 0.001), social functioning (Z = 4.541; p < 0.001), pain (Z = 6.867; p < 0.001), general health (Z = 6.417; p < 0.001) and health change (Z = 5.839; p < 0.001).

Table 9 shows the comparison of mean scores for SF-36 subscales in male patients before and after CVR. All parameters were improved after CR: physical functioning (Z = 7.171; p < 0.001), limitations due to physical health (Z = 4.539; p < 0.001), limitations due to emotional problems (Z = 3.796; p < 0.001), energy/fatigue (Z = 7.146; p < 0.001), emotional well-being (Z = 6.683; p < 0.001), social functioning (Z = 3.478; p < 0.001), pain (Z = 5.771; p < 0.001), general health (Z = 5.491; p < 0.001) and health change (Z = 4.977; p < 0.001).

Table 10 shows the comparison of mean scores for SF-36 subscales in female patients before and after CR. All parameters except limitations due to emotional problems were improved after CR: physical functioning (Z = 5.248; p < 0.001), limitations due to physical health (Z = 2.660; p = 0.008), energy/fatigue (Z = 3.113; p = 0.002), emotional well-being (Z = 3.888; p < 0.001), social func-

Table 7. Comparison between the first and the second exercise stress test (EST) in women

Parameters	EST1	EST2	Z/χ^2	p	%
EST level	1.95 ± 0.87	2.31 ± 0.88	8.712	< 0.001	18.46
EST duration (min)	4.45 ± 2.39	5.30 ± 2.45	10.865	< 0.001	19.1
Double product before	9931.12 ± 2226.04	9765.20 ± 1949.45	1.335	0.182	-1.67
Double product after	20792.49 ± 3785.42	21304.05 ± 3727.65	2.602	0.009	2.46
ST depression	34 (9.2)	46 (12.5)	145.635	< 0.001	35.29
Submaximal heart rate	182 (49.3)	236 (64.1)	105.652	< 0.001	29.67
Chest pain	7 (1.7)	4 (1.1)	0.078	0.779	-42.86

Z – Wilcoxon test

Table 8. The comparison of mean scores for Short-Form 36 Health Status Survey subscales in all patients before and after cardiovascular rehabilitation

Parameters	Before rehabilitation	After rehabilitation	Z	p
Physical functioning	61.60 ± 24.23	69.27 ± 23.66	8.804	< 0.001
Limitations due to physical health	28.16 ± 37.13	37.37 ± 40.12	5.227	< 0.001
Limitations due to emotional problems	37.64 ± 39.09	45.70 ± 40.07	4.322	< 0.001
Energy/fatigue	59.12 ± 20.74	65.29 ± 21.52	7.803	< 0.001
Emotional well-being	68.63 ± 21.97	73.79 ± 22.28	7.731	< 0.001
Social functioning	67.96 ± 24.05	72.32 ± 24.31	4.541	< 0.001
Pain	62.43 ± 25.05	69.34 ± 24.69	6.867	< 0.001
General health	53.82 ± 17.34	58.08 ± 18.96	6.417	< 0.001
Health change	51.04 ± 37.26	58.38 ± 35.77	5.839	< 0.001

Z – Wilcoxon test

Table 9. The comparison of mean scores for Short-Form 36 Health Status Survey subscales in male patients before and after cardiovascular rehabilitation

Parameters	Before rehabilitation	After rehabilitation	Z	p	%
Physical functioning	64.42 ± 23.99	70.94 ± 23.94	7.171	< 0.001	10.12
Limitations due to physical health	30.98 ± 38.29	39.69 ± 40.66	4.539	< 0.001	28.11
Limitations due to emotional problems	38.34 ± 39.18	46.42 ± 40.44	3.796	< 0.001	21.07
Energy/fatigue	60.31 ± 21.21	66.28 ± 21.68	7.146	< 0.001	9.9
Emotional well-being	69.24 ± 22.13	73.93 ± 22.92	6.683	< 0.001	6.77
Social functioning	69.98 ± 23.94	73.45 ± 24.08	3.478	< 0.001	4.96
Pain	63.56 ± 25.19	70.02 ± 25.03	5.771	< 0.001	10.16
General health	54.37 ± 17.99	58.38 ± 19.29	5.491	< 0.001	7.38
Health change	52.80 ± 37.46	59.50 ± 35.61	4.977	< 0.001	12.69

Z – Wilcoxon test

Table 10. The comparison of mean scores for Short-Form 36 Health Status Survey subscales in female patients before and after cardiovascular rehabilitation

Parameters	Before rehabilitation	After rehabilitation	Z	p	%
Physical functioning	48.49 ± 20.92	61.51 ± 20.77	5.248	< 0.001	26.85
Limitations due to physical health	15.08 ± 27.88	26.60 ± 35.87	2.660	0.008	76.39
Limitations due to emotional problems	34.39 ± 38.79	42.34 ± 38.45	1.899	0.058	23.12
Energy/fatigue	53.57 ± 17.49	60.71 ± 20.29	3.113	0.002	13.33
Emotional well-being	65.78 ± 21.14	73.14 ± 19.20	3.888	< 0.001	11.19
Social functioning	58.58 ± 22.44	67.06 ± 24.83	3.189	0.001	14.48
Pain	57.18 ± 23.86	66.19 ± 22.94	3.934	< 0.001	15.76
General health	51.27 ± 13.79	56.67 ± 17.44	3.408	0.001	10.53
Health change	42.86 ± 35.48	53.17 ± 36.34	3.084	0.002	24.06

Z – Wilcoxon test

tioning (Z = 3.189; p = 0.001), pain (Z = 3.934; p < 0.001), general health (Z =53.408; p = 0.001) and health change (Z = 3.084; p = 0.002).

A three-week program of CR has led to the improvement of the QOL in both men and women. Namely, in both groups of patients, almost all examined parameters were better after CR (Tables 8 and 9). However, compared to the baseline, and based on gender, women had greater improvement than men in all parameters - physical functioning: 26.85% *vs.* 10.12%, limitations due to physical health: 76.39% *vs.* 28.11%, limitations due to emotional problems: 23.12% *vs.* 21.07%, energy/fatigue: 13.33% *vs.* 6.77%, emotional well-being: 11.19% *vs.* 6.77%, social functioning 14.48% *vs.* 4.96%, body pain 15.76% *vs.* 10.16%, general health 10.53% *vs.* 7.38%, and health change 24.06% *vs.* 12.69%.

DISCUSSION

A well-designed CR has multiple positive effects. It leads to better control of cardiovascular risk factors, increases exercise tolerance, enhances the QOL, and reduces rehospitalization for cardiac causes [13, 14, 15]. The positive effects of CR are shown in all CAD patients, regardless of ejection fraction [16]. This is why the current European Society of Cardiology Guidelines for cardiovascular prevention strongly advises CR in CAD patients giving it an IA recommendation [17]. However, despite these positive effects of CR, it remains underutilized [18].

In our study, a three-week CR led to a significant improvement in physical strain tolerance in CAD patients. Namely, all patients achieved a higher level on the EST2. Also, the EST2 lasted significantly longer compared to EST1. This well-known beneficial effect of exercise training on physical strain tolerance is documented in previous studies [6, 11, 16].

When comparisons between gender were made, the results showed better strain tolerance in men compared to women at the beginning and et the end of CR (Tables 3 and 4). This is in concordance with previous studies which showed that exercise capacity in male

patients is higher than in female patients [19, 20]. However, in our study, a three-week CR led to improved exercise capacity in both men and women. Namely, the average strain level in men and women was significantly higher and the duration of the test was significantly longer in the EST2. Moreover, these improvements were more pronounced in women compared to men (18.46% *vs*. 14.23% for level, and 19.1% *vs*. 16.34% for the duration of EST) (Tables 5 and 6). These data suggest that women have greater benefits from CR programs compared to men. Moreover, women who participate in CR may have a greater mortality reduction compared to men [21]. However, the referral rate and attendance to CR remain lower in women than in men [22, 23]. The main reasons why women participate less in CR compared to men are lack of family and social support, and the unawareness of medical personnel about the importance of CR [24]. Our study once again showed that women generally less participate in CR than men.

CR, an essential secondary prevention tool once limited to physical activity programs only, has evolved towards the ongoing and preventive improvement of not only physical but the emotional well-being of an individual who has suffered a cardiovascular event [25, 26]. Numerous studies have discussed the bidirectional link between cardiovascular events and the emotional status of the patient [27]. However, unlike the rehabilitation benefit to physical health, research on post-rehabilitation emotional health is scarce, especially in gender-related circumstances. Moreover, on the contrary to a proven effect of CV rehabilitation on reduction of future CV events through physical activity, promotion of healthy and active lifestyle and its implementation is underutilized, especially in women [11, 12, 28], in spite of proven better functional improvement and reduction in mortality of greater magnitude when compared to men.

Given the fact that women are as twice as more prone to anxiety and depression when compared to males, due to the protective role of testosterone [28], lesser adherent to CV rehabilitation in whom they benefit greater than men [29], and without gender preference in CVD prevalence, we wanted to explore whether women benefit equally from CR, and are they on the long run, in what may be called "double jeopardy" [27]? We evaluated the impact cardiovascular rehabilitation had on the quality of mental life in the mixed-gender patient group after a cardiovascular event, using the SF-36 questionnaire.

In our study patients who completed CR reported higher levels of mental QOL and lower levels of anxiety and depression in both gender groups. These findings are consistent with Francis et al. [29], inputs on health-related QOL (HRQOL) in patients of similar (same) settings. In the male group levels of vitality, physical functioning, bodily pain, general health perceptions, physical, emotional, and social role functioning, and mental health were reported higher after the completion of rehabilitation. What is notable is that the female group is less large in a sample compared to men, but within the group women statistically benefited both physical and emotional role functioning as well in bodily pain occurrence. Literature data regarding this matter, both in worlds and especially domestic studies are scarce to compare with [28].

No matter the sample sizes of both groups positive feedback considering mental health was achieved, and this could be due to already reported dynamic relationship between one's emotional valance and physical condition and their positive interrelation [30]. This study indicates that CR in patients with CAD sets a strong relationship between improved physical QOL and mental well-being of individuals who suffered a CV event. Yet, constant failure to refer women in a timely manner to rehabilitation is a matter of great concern for both physical and mentally related QOL within women.

Study limitations

There are several limitations:

1. We did not perform echocardiographic examinations. Left ventricular ejection fraction (LVEF) may play a key role in dosing and conducting CR. However, in our previous paper, we showed that CR leads to a better strain tolerance, regardless of the LVEF [19].
2. EST were performed and not cardiopulmonary tests. We analyzed the influence of EST on strain tolerance by measuring time and levels. Some parameters like MET or VO2 max are lacking.
3. Our study included the CR program that lasted for three weeks and most Guidelines and papers suggest 4–8 weeks of CR.

CONCLUSION

CR led to a significant improvement in exercise capacity in men as well as in women. Also, results indicated that CR improves QOL in CAD patients, in both men and women. However, these positive changes in QOL were more pronounced in women. This is why CR needs improvement in the referral and participation of women.

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Ефекти кардиоваскуларне рехабилитације на толеранцију физичког напора и на квалитет живота код болесника са коронарном артеријском болешћу – да ли жене имају подједнаку корист?

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САЖЕТАК

Увод/Циљ Циљ рада је био испитати да ли жене и мушкарци оболели од коронарне артеријске болести имају подједнаку корист од кардиоваскуларне рехабилитације (КВР) у смислу квалитета живота и толеранције физичког напора.

Методе Студија је укључивала 1603 болесника са коронарном артеријском болешћу, 1231 (76,8%) мушкараца и 372 (23,2%) жене, који су упућени на тронедељну КВР. Сви болесници су тестирани на физички напор на почетку и на крају КВР. Квалитет живота је процењен на почетку и на крају КВР валидираним упитником *Short-Form* 36. Сви подаци су анализирани у односу на пол.

Резултати КВР је довела до побољшања толеранције физичког напора и код мушкараца и код жена. Побољшање је било израженије код жена у поређењу са мушкарцима (18,46% наспрам 14,23% за ниво оптерећења и 19,1% наспрам 16,34% за дужину трајања теста). Такође, КВР је довела до побољшања квалитета живота и мушкараца и жена. Међутим, жене су имале већи напредак у поређењу са мушкарцима у свим испитиваним параметрима – физичко функционисање: 26,85% наспрам 10,12%; ограничења због физичког здравља: 76,39% наспрам 28,11%; ограничења због емоционалних проблема: 23,12% наспрам 21,07%; енергија/умор: 13,33% наспрам 6,77%; емоционално благостање: 11,19% наспрам 6,77%; социјално функционисање: 14,48% наспрам 4,96%; бол у телу: 15,76% наспрам 10,16%; опште здравље: 10,53% наспрам 7,38%; здравствена промена: 24,06% наспрам 12,69%.

Закључак Жене мање учествују у КВР него мушкарци. Резултати су показали да КВР побољшава толеранцију физичког напора и квалитет живота и код мушкараца и код жена са коронарном артеријском болешћу. Међутим, ове позитивне промене су биле израженије код жена. Због тога КВР треба унапредити упућивањем и учешћем жена.

Кључне речи: коронарна артеријска болест; кардиоваскуларна рехабилитација; квалитет живота; толеранција физичког напора; полне разлике

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Relationship between work-related outcomes of healthcare professionals in transfusion medicine units

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SUMMARY

Introduction/Objective Professional burnout has sparked academic interest as one of the phenomena with the most serious implications for healthcare employees' well-being. As burnout becomes an increasingly common issue in medical practice, more extensive research on its predictors is needed.
This study aimed to examine whether and how job satisfaction and work-related burnout affect personal burnout.

Methods A structured questionnaire was used to collect primary data. The sample consists of 218 employees from transfusion medicine units located in five cities in the central part of Serbia. Descriptive statistical analysis, correlation, and hierarchical regression were applied.

Results We found the personal burnout is negatively affected by job satisfaction, predominantly by working conditions (β = -0,141, t = -2,780, $p < 0.01$), and positively impacted to work-related burnout (β = 0,690, t = 13,409, $p < 0.001$) indicated that workload has strong impact on personal life quality of healthcare professionals employed in blood banks.

Conclusion This research contributes to more comprehensive understanding of personal burnout factors. The findings of this study can be used to develop strategies to promote employee well-being and prevent burnout in different manifestations.

Keywords: job satisfaction; work-related burnout; personal burnout; blood bank

INTRODUCTION

Burnout might lead to severe consequences that affect not only work attitudes, but also the overall quality of healthcare provided to patients. High levels of burnout cause a rise in sickness absence from work and society, as well as substantial repercussions on nursing performance [1]. Due to its multifaceted nature, burnout management requires a systematic approach and prompt action. According to Stašević-Karličić et al. [2], healthcare professionals who are susceptible to burnout symptoms need to receive special psychological support. Therefore, to avoid burnout and develop effective prevention strategies, it is necessary to investigate its various forms as well as the relationship with the potential antecedents. In the Copenhagen Burnout Inventory (CBI) instrument, Kristensen et al. [3] assess the assignment of fatigue and exhaustion to specific domains of an individual's life, namely personal, work-related, and client-related burnout. While personal burnout refers to general exhaustion, work-related burnout is closely associated with the job itself and its occurrence is triggered by work environment determinants.

Over the last few decades, there has been recorded presence of burnout syndrome in medical practice. Moreover, Berat et al. [4] highlight the higher prevalence of work-related burnout among employees in the Republic of Serbia compared to previous research findings measuring this construct in other countries. However, prior studies were particularly concerned with examining the prevalence of work-related and personal burnout in various occupations. None of them explores the CBI inter-scale cause-effect relationships, therefore it is still uncertain which form of burnout occurs first. Besides, the number of studies that assessed employee satisfaction and burnout in the work and personal domain, specifically in the healthcare industry, is limited. To address the identified research gap, this study will look into the impact of job satisfaction and work-related burnout on personal burnout.

Job satisfaction and burnout

Assessing work satisfaction among medical professionals is a necessary step in the process of continuously raising the standard of healthcare [5]. A significant number of research have examined job satisfaction and burnout in the healthcare area. According to Tsigilis and Koustelios [6], both investigated conceptions describe affective reactions to working environments, are multidimensional, and despite some degree of overlap, they are distinct ideas. Job

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satisfaction and burnout are constructs that influence one another. Burnout has been linked to lower levels of both job and personal satisfaction, according to Hombrados-Mendieta and Cosano-Rivas [7]. The combined effects of working at highly loaded hospitals, low wages, long working hours, and occupational burnout lead to lower levels of job satisfaction [8]. Furthermore, work-related burnout is discovered to be a statistically significant negative predictor of job satisfaction in the study by Ślusarz et al. [9], whereas job satisfaction has a feedback effect, reducing the symptoms of burnout in nurses working in neurology and neurosurgery departments.

Because of the aforementioned, further research is required to understand the nature of the connection between burnout and satisfaction and to establish its causality [6]. In the study of Figueiredo-Ferraz et al. [10], a direct two-way association between nurse burnout and satisfaction was also found. However, several studies find that satisfaction is a requirement for the decrease in burnout symptoms among medical professionals, which embodies the prevention of severe implications like incorrect diagnoses, inaccurate assessments, career interruption, and early retirement, that potentially harm both employees and patients [11]. Because of this, job satisfaction is not considered a result of burnout in this study but rather a predictor.

Healthcare professionals' performance can be greatly influenced by their satisfaction level and burnout symptoms. These two factors interact to affect nurse productivity, patient care quality, and nurse retention in the workplace [12]. Their capacity to predict employee behavior illustrates how important the integrated analysis of satisfaction and burnout is. In previous studies, these constructs have been associated with employee retention. Unlike most other professions, the medical industry is characterized by emotional labor that lowers employee satisfaction, leads to burnout, and ultimately implies the intention to quit the job [13, 14].

The connection between satisfaction and burnout syndrome has been empirically proven multiple times. Song et al. [11] showed that job satisfaction is a direct negative predictor of job burnout among medical workers in mental hospitals. Furthermore, job satisfaction, along with nurses' demographic characteristics, their involvement in management, and working in multiple institutions, is a significant antecedent of burnout in Portuguese hospitals [14]. The same authors concluded that job satisfaction reduces emotional exhaustion, as one of the burnout manifestations. Furthermore, Tremolada et al. [15] found a significant association between job satisfaction and burnout in a sample of health professionals in apheresis units. In addition, their research revealed high values for all burnout indicators.

Job satisfaction and personal burnout

The cause-effect relationship between job satisfaction and burnout using the CBI approach is almost completely unaddressed. There are only a few studies in the literature that have linked employee satisfaction in various sectors to these types of burnout. Lee and Lin [16] found that overall satisfaction correlates with a burnout in personal and work domains in the sample of Taiwanese clinical nurses. According to a study by Payne et al. [17] that involved a sample of staff members affiliated with psychiatric nursing, low levels of job satisfaction are substantially correlated with higher rates of burnout, including personal, work-related, and client-related burnout. Based on the Project on Burnout, Motivation and Job Satisfaction study, Kristensen et al. [3] tested the validity of the CBI instrument and found a significant relationship between job satisfaction and all forms of burnout, including personal burnout. According to Berat et al. [4], relationships with colleagues, the nature of work, and communication, are negatively connected to work-related burnout in a sample of employees in the Republic of Serbia working in a variety of occupations.

Work-related burnout and personal burnout

Personal burnout differs from work-related burnout since it represents general tiredness and people's attribution of burnout in their personal life [18]. However, there is no empirical evidence in the extant literature concerning the pattern and sequence in which different forms of burnout arise. Work-related and personal burnout are both inversely correlated with job satisfaction among American nurses, according to Montgomery et al. [19], and there is a substantial relationship between these two components of the burnout scale. Work-related burnout is positively associated with personal burnout among social workers [3]. It positively correlates with burnout in the personal domain in a study conducted on a sample of teachers in Italian schools by Fiorilli et al. [20]. Sestili et al. [21] identified a significant positive relationship between work-related and personal burnout among academics in medicine and pharmacy. A very strong positive intercorrelation between work-related and personal burnout was also established in the research of Walters et al. [22] and Lapa et al. [23] in a group of social workers and physicians of different specialties in Portugal, respectively.

METHODS

A cross-sectional study was performed within the hospital blood banks at stationary health institutions in five cities in the central part of Serbia. The questionnaire forms were distributed to employees and 218 of them were returned fully completed. The academic purpose of the study was explicitly disclosed to all participants and their anonymity was ensured. In light of the foregoing, respondents inserted the completed questionnaire in the special envelope and only the research team had access to the data. Regarding gender, 66.5% of the sample is female. The majority of respondents were between the ages of 46 and 55, followed by those under the age of 35, while 23.8% of respondents were aged 55 and over. The most numerous groups in the sample are respondents with a high school degree (155),

followed by specialists, subspecialties, and primarii (54). Respondents with master's and Ph.D. degrees make up 2.3% of the sample, while the smallest group of respondents have a primary school degree. Employees with more than 20 years of work experience exceed those with less than five years of experience, who are almost equally present in the sample as respondents with 11–20 years of experience. The smallest percentage has 6–11 years of service in the current institution.

Measurements

In addition to the demographic data section, the questionnaire had three other segments. The first two measure the independent variables, while the last section consists of items for assessing the dependent construct. Using previously established and multiple times tested scales in previous research provided high reliability of the measures in our study. All the items were translated from English and adjusted to the Serbian setting. The participants scored every question on a five-point Likert scale, ranging from "strongly disagree", marked by 1, to "strongly agree" indicated by 5.

The first subscale includes eight statements used to estimate job satisfaction. These were derived from the Job Satisfaction Survey developed by Spector [24] and proved suitable for human service research. These statements analyze the nature of work, operating conditions, and communication. The nature of work was measured with two items, for instance, "My job is enjoyable." The operating conditions subscale contained three negatively worded items. One of the items in this measure, for example, states "My efforts to do a good job are seldom blocked by red tape." Communication was also measured with three items, while some of them were negatively keyed; for instance, "Work assignments are not fully explained." The Cronbach's α value for job satisfaction was 0.75, which indicated satisfactory internal consistency of the items.

We used the CBI [3] to assess burnout levels and constitute the other two subscales. This instrument has been validated in a variety of occupations, including the medical field. Three questions designed to assess work-related burnout were placed in the first subscale and included "Are you exhausted in the morning at the thought of another day at work?", and "Do you feel that every working hour is tiring for you?" The last section refers to personal burnout. It also consists of three questions, such as "How often are you emotionally exhausted?" and "How often do you feel worn out?" The Cronbach's α for work-related and personal burnout was 0.86 and 0.88, respectively, showing excellent reliability for both subscales.

Using the SPSS Statistics for Windows, Version 26.0. (IBM Corp., Armonk, NY, USA) we performed several statistical analyses, beginning with descriptive statistics and correlation. Job satisfaction, work-related, and personal burnout constituted a hierarchical regression model in this research. Sex, age, education, and length of service of participants, were chosen as control variables.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

According to the results of descriptive statistics, respondents indicated moderately high levels of job satisfaction. Mean values were highest for the statements "I like doing the things I do at work" (M = 4.16) and "My efforts to do a good job are seldom blocked by red tape" (M = 3.86). Within the scale that measured burnout, we found the highest mean value for the question "Do you have enough energy for family and friends during leisure time?" (M = 3.19) with the major standard deviation (SD = 1.46). Within items that measured job satisfaction, the highest heterogeneity of responses was recorded for the question "Many of our rules and procedures make doing a good job difficult" (SD = 1.32) (Table 1).

As presented in Table 1, the strongest positive connection was identified between work-related and personal burnout (r = 0.742). Among job satisfaction dimensions, we found a moderately strong positive correlation between the nature of work and operating conditions (r = 0.489). According to the results, work-related and personal burnout negatively correlate with operating conditions.

Table 1. Correlation analysis of personal burnout, job satisfaction, work-related burnout, and control variables (n = 218)

	Variables	1	2	3	4	5	6	7	8	9
1	Sex									
2	Age	0.134*								
3	Education	0.070	0.041							
4	Years within organization	0.083	0.751**	-0.087						
5	Nature of work	-0.095	-0.054	0.104	-0.073					
6	Operating conditions	0.046	-0.131	-0.004	-0.155*	-0.025				
7	Communication	0.086	-0.042	0.065	-0.108	0.489**	0.190**			
8	Work-related burnout	-0.034	0.243**	-0.012	0.264**	0.008	-0.442**	-0.152*		
9	Personal burnout	-0.122	0.198**	-0.161*	0.256**	-0.133	-0.433**	-0.243**	0.742**	

Note: *p < 0.05, **p < 0.01, ***p < 0.001

Table 2. Hierarchical multiple regression analyses for job satisfaction and work-related burnout of personal burnout

Constructs	R^2	R^2 change	F	Standardized coefficient β	t	Tolerance	VIF
Block 1: Control variables	0.085		4.963***				
Sex				0.054	1.173	0.921	1.085
Age				0.031	0.444	0.405	2.469
Education				0.097	2.126*	0.932	1.073
Years within organization				0.055	0.785	0.397	2.519
Block 2: Job satisfaction	0.245	0.159	9.713***				
Nature of work				0.103	2.038*	0.764	1.309
Operating conditions				-0.141	-2.780**	0.760	1.316
Communication				-0.001	-0.025	0.714	1.401
Block 3: Work-related burnout	0.594	0.349	38.211***	0.690	13.409***	0.733	1.363

Note: *p < 0.05, **p < 0.01, ***p < 0.001
VIF – variance inflation factor

Concerning the connection between burnout and the control variables, it was either statistically insignificant or significant, but very mild.

As reported in Table 2, control variables were responsible for an 8.5% variance in personal burnout. Nature of work, operating conditions, and communication were entered in the second set and accounted for an additional 15.9% variance in personal burnout. The nature of work significantly affects personal burnout at the level $p < 0.05$. The operating conditions are a negative predictor of work-related burnout and this result is significant at the level $p < 0.001$ Lastly, work-related burnout accounted for an additional 34.9% variance. The result implies that among the variables that have been observed, work-related burnout has the strongest influence on burnout in the personal domain. The three sets accounted for 59.4% of the variance in personal burnout. A considerable F change after the inclusion of two sets of variables indicates that adding job satisfaction and work-related burnout significantly increases model prediction.

DISCUSSION

The results of the study showed that job satisfaction has a statistically significant impact on the level of personal burnout in transfusion units. Observed dimensions of satisfaction – nature of work, working conditions, and communication, are inversely connected with burnout, which partially supports the conclusion made by Berat et al. [4]. Among the studies that used the same burnout measurement, the result is also consistent with the conclusions of the research by Payne et al. [17] and partially corresponds to the results generated by Kristensen et al. [3]. Additionally, the obtained finding is consistent with the research of Berthelsen et al. [25], as well as with the one conducted by Piko [26], showing that job satisfaction is a negative predictor of all dimensions of burnout among Hungarian healthcare staff. The reported result partially contradicts the study by Tsigilis and Koustelios [6], which found a weak or very weak association between certain dimensions of satisfaction and emotional exhaustion, depersonalization, and personal achievement.

The observed partial instead of complete agreement with previous research is a result of the use of different measuring instruments that assessed burnout levels, as well as the variety of professions in which the relationship between satisfaction and burnout was studied. The same constructs are structured differently in these studies as a result of the use of various measuring tools, which restricts the ability to compare relevant findings. The research conducted revealed that a high level of job satisfaction lowers the likelihood of experiencing generic or personal burnout. In other words, the development of positive work attitudes among employees functions as a mechanism for preventing or minimizing personal burnout syndrome, which enhances employees' health and might even inspire improved performance [27]. At the same time, the analysis showed that the strongest negative effect on personal burnout is achieved by satisfaction with operating conditions. The degree to which an employee evaluates working conditions, including policies and procedures, can prevent burnout.

Another significant factor of personal burnout among employees in transfusion departments identified in this research is work-related burnout. The two forms of burnout are linked, according to several prior studies, however, these analyses are correlational in nature, making it challenging to establish a causal connection between the investigated constructs. In this regard, the result obtained is quite consistent with the work of Kristensen et al. [3], Fiorilli et al. [20], Sestili et al. [21], Walters et al. [22], and Lapa et al. [23]. Additionally, it supports the findings of Molinero-Ruiz et al. [18], who examined the reliability of the CBI using a sample of workers from the Spanish educational, healthcare, social work centers, and industry sector and found a high correlation between personal and work-related burnout. The result also agrees with the finding of the study by Thrush et al. [28] who showed a very strong correlation between work-related and personal burnout. Nevertheless, it partially conflicts with the findings of a study by Youssef et al. [29] which examines the validity of the Arabic version of the CBI instrument on a sample of community pharmacists and found a very poor link between work-related and personal burnout.

The findings indicate that tiredness, a lack of time for friends and family, frustrations, and effort related to the

work itself all lead to the emergence of personal burnout, which manifests as persistent fatigue, emotional and physical exhaustion, and a sense of weakness. According to this research, the form of burnout that occurs as a result of the job features increases the risk of developing a set of symptoms known as personal burnout, which decides an individual's overall quality of life.

CONCLUSION

Designing preventive strategies for burnout requires an understanding of the elements that contribute to its development. Managers and staff members need to become aware of the risk of burnout, which may eventually result in their intention to quit their job, which has several detrimental effects on the entire institution. Burnout should be addressed collaboratively by all organization members, and its suppression needs to be a group effort rather than an individual concern. It is recommended that managers change the way things are done to decrease paperwork and work volume. Additionally, they should look for approaches to influence how staff members view their job so that they like it, take pride in it, and have a passion for what they do. Efforts should be made to enhance group communication. In this regard, managers should attempt to make the organization's goals more explicit while involving staff in significant decisions. Besides, they need to make sure that work tasks are understood by everyone in the organization for higher levels of satisfaction. Greater satisfaction would be ensured by the enhancement of these components, which eventually results in less burnout.

Conflict of interest: None declared.

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Однос између различитих исхода посла здравствених радника у јединицама за трансфузију крви

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САЖЕТАК

Увод/Циљ Као један од феномена са озбиљним последицама на понашање и добробит здравствених радника, професионално сагоревање пробудило је заинтересованост савремених истраживача. Како овај синдром постаје све чешћа појава у медицинској пракси, јавила се потреба за опсежнијим испитивањем његових предиктора.

Циљ ове студије је да испита да ли и на који начин задовољство и сагоревање повезано са послом утичу на личне факторе сагоревања.

Методе Примарни подаци прикупљени су техником структурираног упитника. Истраживачки узорак обухватио је 218 испитаника запослених у јединицама за трансфузију крви у централној Србији. За потребе анализе података примењене су дескриптивна статистика, корелација и хијерархијска регресија.

Резултати Студија је показала да је задовољство послом негативан предиктор личних фактора сагоревања, првенствено радни услови (β = -0,141, t = -2,780, p < 0,01), док сагоревање повезано са послом има статистички значајан позитиван утицај на личне факторе сагоревања (β = 0,690, t = 13,409, p < 0,001) указујући да оптерећење послом може имати снажан утицај на квалитет живота здравствених радника запослених у јединицама за трансфузију крви.

Закључак Спроведено истраживање доприноси подробнијем разумевању детерминанти анализираног конструкта. Резултати ове студије обезбеђују смернице менаџерима за развој стратегија за повећање добробити запослених и превенцију различитих облика сагоревања код здравствених радника.

Кључне речи: задовољство послом; сагоревање повезано са послом; лични фактори сагоревања; банка крви

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PRELIMINARY COMMUNICATION / ПРЕТХОДНО САОПШТЕЊЕ

Otorhinolaryngological symptoms in hospitalized patients with COVID-19 – single-medical-center study in Serbia

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SUMMARY

Introduction/Objective The infectious condition named coronavirus disease 2019 (COVID-19) was caused by coronavirus2 (SARS-Cov-2). Patients with COVID-19 disease may have symptoms which can range from mild to severe clinical condition.

The aim of this study was to observe and analyze the presence of otorhinolaryngology symptoms in hospitalized patients with moderate to severe COVID-19 disease.

Methods The descriptive clinical study analyzed data from medical records in 230 hospitalized patients with moderate to severe COVID-19 pneumonia at Zvezdara Clinical Hospital Center, Belgrade, Serbia. Otorhinolaryngology symptoms as well as generalized COVID-19 related symptoms were analyzed from medical records during the year 2021. SARS-CoV-2 virus infection was previously confirmed in all patients with positive polymerase chain reaction test and/or rapid antigen test.

Results The mean age of 230 patients included in this study was 64 years. The most common general symptoms were cough 72%, fever 52%, dyspnea 46%, malaise 46% while to a lesser extent were observed myalgia 19%, vomitus 3%, and diarrhea 3%. The distribution of otorhinolaryngological symptoms showed that the most frequent symptom was anosmia 22%, while the throat pain was present in 20% and ageusia in 19% of patients. The otorhinolaryngological symptoms which were present in lower frequencies were headache in 16% of patients, tinnitus in 6%, vertigo in 5%, and hearing loss in 3% of patients. Comorbidities were observed more often in patients older than 50 years. Hypertension was the most common chronic disease in 60%, followed by diabetes in 23%, chronic obstructive pulmonary disease in 7%, malignancy in 7%, hypothyroidism in 6%, and renal disease in 4% of patients.

Conclusion Otorhinolaryngological conditions that should be the subject of further post COVID survey are prolonged anosmia, ageusia or hypogeusia, auditory dysfunction and vertiginous complaints.

Keywords: COVID-19; otorhinolaryngology symptoms; SARS-CoV-2 virus

INTRODUCTION

Coronaviruses can cause respiratory and gastrointestinal mucosa dysfunction as well as neurological and hepatic dysfunction in animals and humans [1, 2]. Viral invasion of the respiratory mucosa can cause symptoms of the upper respiratory airways. Recent studies showed that SARS-CoV-2 virus infection named as COVID-19 disease could cause fever, cough, dyspnea, and fatigue but as well otorhinolaryngological symptoms as pharyngodynia, nasal congestion, rhinorrhea and headache [3, 4]. The loss of smell (anosmia) and altered function of taste (dysgeusia) or loss of taste (ageusia) were the most prominent otorhinolaryngological symptoms frequently reported with heterogenous frequencies. In mild to moderate COVID-19 infection patients reported olfactory dysfunction in more than 85% while gustatory dysfunction was reported in more than 88% of patients [4]. In recent meta-analysis the rate of gustatory dysfunctions ranged from 5.6% to 62.7% while for olfactory disfunction varied from3.2% to 98.3% [5]. American Academy of Otolaryngology-Head and Neck Surgery proposed symptoms as anosmia and dysgeusia as symptoms for screening procedure for possible COVID-19 disease [5]. Anosmia can occur as an early symptom before other COVID-19 symptoms [6]. Besides this most frequent otorhinolaryngology disorders, less frequently were reported tinnitus, vertigo, as well as hearing loss [7]. The entry mechanism of SARS-CoV-2 virus was described as binding of the viral S protein to the angiotensin-converting enzyme 2 (ACE2) receptor. Spike proteins on the surface of SARS-CoV-2 virus binds to ACE2 receptors on the surface of the target cell. The entry of the virus in the host cell is enabled by serine protease type II (TMPRSS2) which binds and cleaves the ACE2 receptors which are highly expressed in the nasal and bronchial mucosa. Recent studies suggested that olfactory dysfunction as a consequence of SARS-CoV-2 virus infection was caused by non-neuronal cell-specific mechanism operating within the olfactory epithelium [8, 9].

Considering the route of SARS-CoV-2 virus transmission, otorhinolaryngology examination was not a part of clinical routine for hospitalized patients, first of all because of the high

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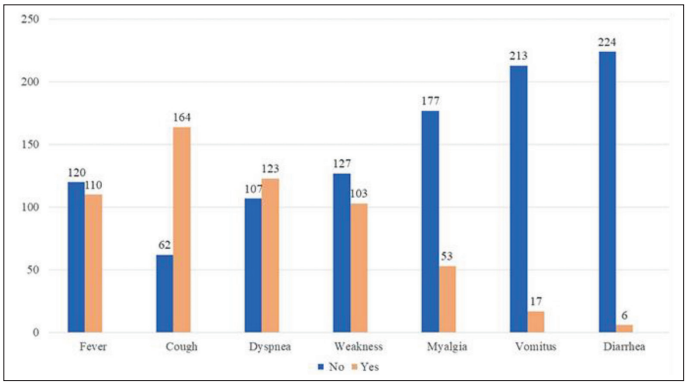

Figure 1. Distribution of the general symptoms in COVID-19 hospitalized patients

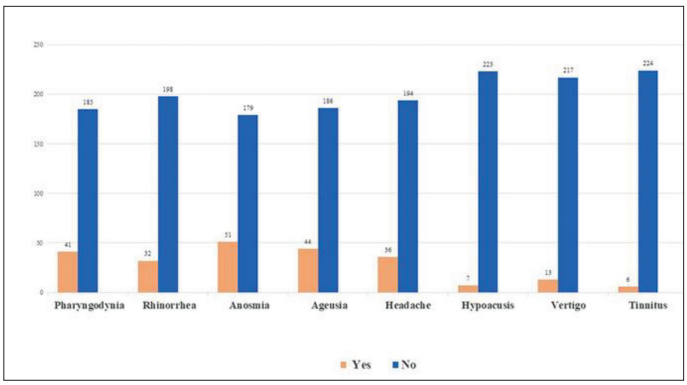

Figure 2. Distribution of otorhinolaryngology symptoms in hospitalized COVID-19 patients

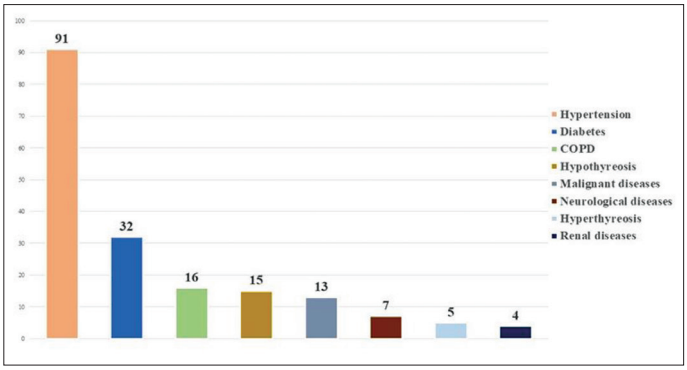

Figure 3. Comorbid diseases present in hospitalized patients with COVID-19 pneumonia

risk for transmission of the infection to health-care providers. Obtaining otorhinolaryngology symptoms data in hospitalized patients with COVID-19 disease can be useful for follow up of the patients with otorhinolaryngology dysfunction during the post-COVID period.

The aim of this descriptive clinical study was to analyse the occurrence of otorhinolaryngology symptoms in hospitalized patients with moderate to severe COVID-19 disease. The patients were hospitalized at Zvezdara Clinical Hospital Center, Belgrade, Serbia.

METHODS

This clinical observational study analyzed medical data in 230 hospitalized patients with previously confirmed SARS-CoV-2 virus infection. This study was approved by institutional ethics committee (6206/1/2022). The demographic data (sex, age), as well as the frequency of general and otorhinolaryngological symptoms were analyzed. Patients were hospitalized at Zvezdara Clinical Hospital Center, Belgrade, Serbia during the year 2021. All of them had positive polymerase chain reaction test and/or rapid antigen test for COVID-19 and had moderate to severe pneumonia which was diagnosed according to the COVID-19 clinical protocol [10]. Otorhinolaryngology symptoms as well as generalized COVID-19 related symptoms were analyzed from medical records.

Descriptive statistics were calculated for demographic characteristics and other followed parameters and presented as frequencies and percentages. Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The analyzed medical data of 230 hospitalized patients showed that 102 (44%) were males and 128 (56%) females. The mean age of the patients was 64 years.

The most common general symptoms were cough (72%), fever (52%), dyspnea (46%), and malaise (46%). Myalgia (19%), vomitus (3%), and diarrhea (3%) were observed to a lesser extent (Figure 1).

The distribution of the otorhinolaryngology symptoms showed that throat pain or pharyngodynia was present in 20% of patients, anosmia in 22%, ageusia in 19 %, headache in 16%, tinnitus in 6%, vertigo in 5%, and hearing loss in 3% of patients (Figure 2). All patients with hearing loss had hypertension, two of them had diabetes and hypertension and all patients with hearing loss had more than a three-fold increase in the value of C-reactive protein and ferritin. The similar results of biochemical analyses were present in patients with anosmia, ageusia, and vertigo.

Comorbidities were present frequently in patients older than 50 years. The hypertension was leading chronic disease in 60%. In 23% of patients with diabetes, hypertension was present at the same time. In 7% of patients was reported chronic obstructive pulmonary disease, and asthma. Hypothyroidism was present in 6%, malignant disease in 7%, and renal disease in 4% of hospitalized patients (Figure 3).

DISSCUSION

Pharyngodynia, rhinorrhea, dysfunctions of smell and taste can be the symptoms of COVID-19 in the patients with moderate to severe acute respiratory inflammation. In this study percent of anosmia and ageusia was present in 22% and 19% of patients. Özçelik Korkmaz et al. [7] reported higher incidence of otorhinolaryngological symptoms in hospitalized patients than our study: the rate of taste dysfunction was 41.3%, smell dysfunction was

37.9%, and the rate of sore throat was 32.7%, for tinnitus 11.2%, hearing loss 5.2%, and vertigo 6.1%. Johnson et al. [11] recently published results of one of the largest single institution study conducted in Mayo Clinic. The authors reported that rate of subjective altered smell and taste in 2250 COVID-19 patients was 29.6%. The rates of most common otorhinolaryngological symptoms were reported in other study as 34.5%, for taste loss, 31.8% for smell loss and sore throat as 26% [12]. Results of a meta-analysis on otorhinolaryngological symptoms pointed out that the prevalence of olfactory dysfunction in COVID-19 patients was 52.73% after having analyzed ten studies [13]. Nine studies were analyzed for gustatory dysfunction demonstrating prevalence of 43.93%. Less frequent were rates for dizziness 2.2% and hearing loss 0.9% [13]. In this study hearing loss was present in 3% of patients. The patients pointed out that they had normal hearing function before they were infected with SARS-CoV-2 virus. Objective measurements of hearing function were not performed in this study. All patients with hearing loss had hypertension, two of them had diabetes and hypertension. KIlic et al. [14] reported that sudden hearing loss could be the only sign of a COVID-19 infection in patients with no other symptoms of disease. Recently published results of meta-analysis on hearing loss, tinnitus and vertigo in patients with COVID-19 showed that hearing loss rate was 3.1% in four analyzed studies, while in analysis of six studies on tinnitus the occurrence rate was 4.5% and analysis of nine papers on vertigo demonstrates the rate was 12.2% [15]. In this study tinnitus was present in 6%of patients and vertigo in 5%. The main remarks of the authors of meta-analytical studies were the weakness of study data collection like self-reports and medical records without the objective evaluation and control groups. According to that opinion the results of our study can be observed as results of descriptive clinical study without objective measurements for otorhinolaryngological symptoms. Milisavljevic et al. [16] published one of the latest objective study on sudden hearing loss in COVID-19 disease. The results of that study showed the rate of 40.5% for sensorineural type of hearing loss. It was confirmed by audiological assessment in 74 patients with moderate form of COVID-19 disease. All patients were treated in tertiary hospital center [16].

It is not yet clarified weather SARS-CoV-2 virus affect peripheral neural structures and central nervous system by neural invasion or predominantly by affection of neural glial cells or neurotropism. One of proposed explanations for neural dysfunction was autoimmune neuronal damage, but this subject need further experimental investigation [17]. The genetic polymorphisms in ACE2 and TMPRSS2 could be the explanation for different values in prevalence of chemosensory defects. These variations in the binding affinity between the virus and the ACE2 receptor could cause oscillation in intensity and duration of anosmia, hyposmia, ageusia, hypogeusia or vertigo and hearing disorders [9, 18]. As observed by recent studies the rate of chemosensory dysfunction were significantly higher in Western countries than in countries in East Asia. Genetic polymorphism of ACE2, as well as mutation and variation of viral spike protein could be the cause of increased chemosensory disfunction rate [9, 18]. From otorhinolaryngology point of view, long duration of chemosensory dysfunction as well as hearing loss and vertigo are important for post-COVID follow-up of patients [18]. The dysfunction of the smell and taste resolve within weeks while in some patients last as persistent deficits. The therapies for COVID-19 associated olfactory loss are currently an object of intensive investigation [19]. Clinical protocols for accurate diagnosis and treatment of post COVID otorhinolaryngological conditions will be very important for otorhinolaryngological practice. Recent studies described that quality of life was significantly decreased in patients who suffered from post COVID-19 consequences [20].

Patients with prolonged anosmia and ageusia reported depressive behavior and deterioration in life quality. Clinical studies on life quality in post COVID hearing and balance disorders will be equally important for better analysis of otorhinolaryngological conditions in COVID-19.

CONCLUSION

Otorhinolaryngology conditions that should be the subject of further survey in patients who were treated for COVID-19 infection are prolonged anosmia, ageusia or hypogeusia, auditory dysfunction and vertiginous complaints.

Conflict of interest: None declared.

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Оториноларинголошки симптоми код хоспитализованих болесника са ковидом 19 – студија једног болничког центра у Србији

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САЖЕТАК

Увод/Циљ Инфективно обољење коронавирус 2019 (ковид 19) изазвано је коронавирусом 2 (вирус *SARS-CoV*-2). Болесници са ковидом 19 могу имати клиничку слику која варира од лаке до тешке.

Циљ овог истраживања је био да се анализира присуство оториноларинголошких симптома код хоспитализованих болесника са средње тешким и тешким обликом ковида 19.

Методе У дескриптивној клиничкој студији анализирани су подаци из медицинске документације 230 болесника са средње тешким и тешким обликом инфекције ковид 19 који су хоспитално лечени у Клиничко-болничком центру „Звездара" у Београду, у Србији. Оториноларинголошки симптоми, као и општи симптоми везани за обољење ковид 19 анализирани су из медицинске документације за 2021. годину. Инфекција вирусом *SARS-CoV*-2 је претходно потврђена код свих болесника позитивним тестом ланчане реакције и/или брзим антигенским тестом.

Резултати Просечна старост 230 болесника који су били укључени у ову студију била је 64 године. Најчешћи општи симптоми су били кашаљ (72%), грозница (52%), диспнеја (46%), малаксалост (46%), док су у мањој мери примећени мијалгија (19%), повраћање (3%) и дијареја (3%). Дистрибуција оториноларинголошких симптома показала је да је најчешћи симптом аносмија (22%), док је бол у грлу присутан код 20%, а агеузија код 19% болесника. Оториноларинголошки симптоми који су били присутни у нижој фреквенцији били су главобоља код 16% болесника, тинитус код 6%, вртоглавица код 5% и губитак слуха код 3% болесника. Коморбидитети су били чешћи код болесника старијих од 50 година. Хипертензија је била најчешћа коморбидна болест код 60% болесника, дијабетес код 23%, хронична опструктивна болест плућа код 7%, малигнитети код 7%, хипотиреоза код 6% и бубрежна инсуфицијенција код 4% болесника.

Закључак Оториноларинголошки симптоми који треба да буду даље праћени у периоду после ковида су пролонгирана аносмија, агеузија, поремећаји слуха и равнотеже.

Кључне речи: ковид 19; оториноларинголошки симптоми; вирус *SARS-CoV*-2

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Retroperitoneal hematoma – an unexpected complication of anticoagulant therapy in COVID-19 patients

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SUMMARY

Introduction Coronavirus disease 2019 (COVID-19) is associated with high inflammatory response, hemostatic disturbances, and high thrombotic risk. Despite thromboprophylaxis, a high incidence of thromboembolic events has been reported with a consequent increase in anticoagulant therapy from standard to intermediate or even therapeutic doses. However, published evidence on the incidence and outcome of the hemorrhagic complications of applied therapy is still limited.

Outlines of cases We present two female COVID-19 patients, treated with anticoagulant therapy who suffered from major spontaneous bleeding and retroperitoneal hematoma. The first, a 64-year-old patient, treated with non-invasive ventilation protocol in the Intensive Care Unit due to respiratory failure received a therapeutic dose of anticoagulant therapy adjusted to the anti-Xa assay. The cumulative dose of nadroparin was 150 IU/kg body weight/day. The second, a 60-year-old patient with the moderate clinical presentation on low flow oxygen support was treated with therapeutic doses of anticoagulant therapy calculated according to the body weight. Emergency open surgery was performed due to massive bleeding. No active surgical bleeding was detected, and retroperitoneal hematomas were assumed to be complications of the applied anticoagulant therapy. Both patients were discharged and fully recovered.

Conclusion Although rare, severe hemorrhage requires attention when considering anticoagulant therapy in COVID-19. Uncommon sites of spontaneous bleeding suggest additional evaluation on a case-by-case basis, given that a diagnosis is often delayed due to a lack of specific presenting symptoms. Further studies are needed to verify the risk-benefit ratio of different regiments of anticoagulant therapy in patients with COVID-19.

Keywords: COVID-19; anticoagulants; hemorrhage; retroperitoneal space

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a systemic disease characterized by immune system hyperactivity, endothelial dysfunction, and hemostasis disorders. Hemostasis disorders are one of the critical aspects of the pathophysiology of this disease, and various mechanisms such as cytokine storm, antiphospholipid syndrome, activation of macrophages and complement cascades are related to them [1]. All these derangements significantly increase the risk of thrombosis, and 20–30% of critically ill COVID-19 patients develop pulmonary thromboembolism and deep vein thrombosis [2]. On the other hand, studies published before the pandemic showed that 8–10% of patients in the Intensive Care Unit (ICU) develop thromboembolic complications regardless of prophylactic doses of anticoagulant therapy [3].

The high incidence of thrombosis in patients with COVID-19 made some clinicians increase the dose of anticoagulant therapy from prophylactic to intermediate or therapeutic doses. However, the efficacy and safety of various anticoagulant therapy protocols are still lacking [4]. Most of the published clinical trials have focused on thromboembolic complications, while the risk factors and frequency of bleeding, and its impact on patient morbidity and mortality, remain unknown.

Here we present two female COVID-19 patients, treated with anticoagulant therapy and suffering from major spontaneous bleeding and retroperitoneal hematoma. Our research database covered the period from April 2020 to December 2021 in Karaburma COVID Hospital.

REPORTS OF CASES

Case 1

A 64-year-old woman, a long-term hypertensive patient on regular therapy, obese (body weight 90 kg, body height 175 cm), and unvaccinated, was transferred from the ward of our hospital to the ICU due to respiratory insufficiency. At the time of her deterioration, she had oxygen support with a non-rebreather mask (NRM) with a flow rate of 15 l/min. She was dyspneic, with paroxysmal coughing fits, tachypneic with a respiratory rate up to 35/min, with oxygen saturation (SpO_2) of 89–92%. Immediately after admission, non-invasive ventilation was started, with the following

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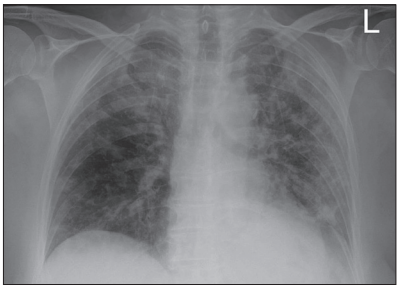

Figure 1. Case 1 – chest radiograph shows bilateral patchy pulmonary consolidations

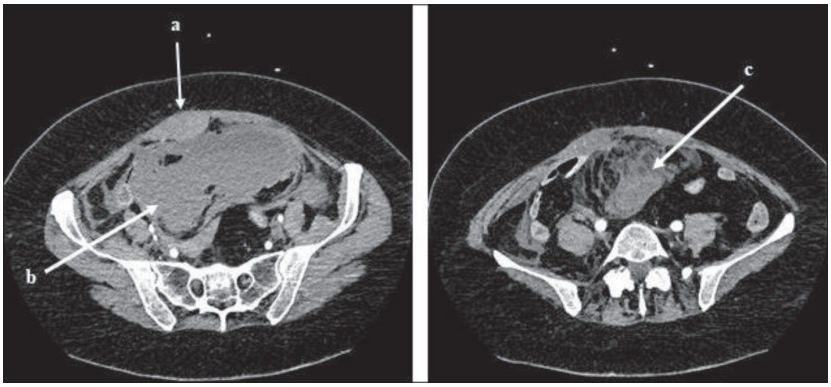

Figure 2. Case 1 – (a) axial computed tomography scans of the abdomen and pelvis show right rectus abdominis muscle hematoma (b) extending into the extraperitoneal pelvis; (c) hemorrhagic collection posterior to the anterior abdominal wall

Table 1. Case 1 – blood tests during the intensive care unit course

Data	Hgb g/l	Plt 10^9/l	Urea mmol/l	Cre mmol/l	GFR ml/min/ 1.73 m^2	CRP mg/l	IL6 pg/ ml	INR	Fib g/l	Dd mg/l	AT III U/ml	Axa U/ml
Normal range	115–165	140–450	2.5–7.5	44–88	≥ 90	0–5		0.7–1.2	2–4	0–0.5	0.8–1.2	
Day 1	137	246	9.1	56	101	18.1	19.6	0.92		2.13		
Day 3	125	291	9.0	44	107	169.3	576	1.04	6.2	3.02	0.94	0.50
Day 5	129	252	7.1	47	106	61.4			4.9	3.80		
Day 7	143	394	6.3	50	104	8.7				6.38		
Day 8								1.01	2.5	3.71	0.85	1.07
Day11	134	342	6.1	45	107	2.1				1.69		
Day 14	135	251	6.2	49	105	0.7				0.91		
Day 15	108	259	8.5	44	107	0.5		1.07		0.64		

Hgb – hemoglobin; Plt – platelets; Cre – creatinine; GFR – glomerular filtration rate; CRP – C-reactive protein; IL6 – interleukin 6; INR – international normalized ratio; Fib – fibrinogen; Dd – D-dimer; AT III – antithrombin III; AXa – anti Xa assay (therapeutic range 0.5–1 U/ml, prophylaxis range 0.1–0.4 U/ml)

parameters: FiO_2 80%, positive end-expiratory pressure (PEEP) 8 cmH_2O, Pasb 0, whereby the respiratory frequency decreased to 25/min with SpO_2 of 96–97%. Her initial X-rays showed bilateral patchy pulmonary infiltrates (Figure 1). Twelve hours after admission, and after measurement of arterial blood gas test (pH 7.46, $PaCO_2$ 33 mmHg, PaO_2 170 mmHg, HCO_3 23.5 mmol/l, BE 0.2 mmol/l, lactate 1 mmol/l), respiratory parameters were corrected to FiO_2 60%, PEEP 6 cmH_2O, Pasb 0.

Low molecular weight heparin was dosed according to the local algorithm of the hospital: Nadroparin 0.6 ml subcutaneously, once a day for patients up to 100 kg or 0.9 ml subcutaneously, once a day for patients over 100 kg, if the D-dimer values were < 2 mg/L fibrinogen equivalent units; while for patients with D-dimer > 2 mg/L fibrinogen equivalent units, an adequate dose (relative to body weight) of low molecular weight heparin was given twice a day. Thus, an initial intermediate dose of anticoagulant therapy was started with Nadroparin 0.6 ml, subcutaneously, twice daily. After four doses of nadroparin, on the third day and four hours after the morning dose, an anti-Xa test was performed together with other hemostasis parameters (Table 1). After obtaining the anti-Xa test (0.5 U/ml), anticoagulant therapy was corrected (nadroparin 0.6 ml + 0.9 ml) so that the cumulative dose of 150 U/kg body weight/day was reached. After dose adjustment, according to the same regimen, the patient's hemostatic profile was repeated on the eighth day when the anti-Xa test value was assumed satisfactory (1.07 U/ml) (Table 1).

On the third day, after checking the blood investigation, Tocilizumab was prescribed according to the drug administration protocol due to further deterioration (Table 1).

In the next few days, the patient improved, and the values of the inflammatory parameters decreased (Table 1). On day 10, her oxygen support switched from non-invasive ventilation to a NRM, with a gradual reduction in oxygen flow over the next few days.

On day 15, the patient complained of lower abdominal pain in the morning. In the afternoon, the pain became more intense with abdominal tenderness and minimal distention. She became hypotensive and tachycardic. The laboratory tests revealed a decrease in hemoglobin level to 108 mg/l (Table 1). She had oxygen support with NRM 15 l/min, and arterial blood gas test showed PaO_2 192 mmHg, $PaCO_2$ 31 mmHg, HCO_3 23.1, BE 0.2, lactates 3.1.

Due to the hospital's limited resources, the patient was transferred to another hospital for further diagnosis and treatment under suspicion of severe bleeding. The patient underwent an urgent medial laparotomy with the dominant finding of the right rectus abdominis muscle's hematoma and bilateral retroperitoneal bleeding. Approximately 1300 ml of blood with coagula were evacuated (Figure 2). The postoperative course was uneventful, and the patient was discharged from the hospital in a good general condition.

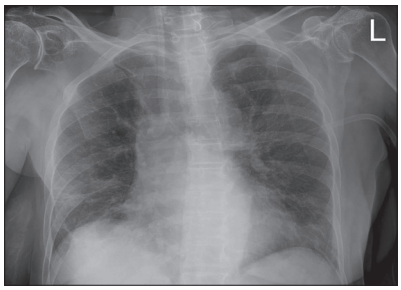

Figure 3. Case 2 – chest X-ray scan shows extensive bilateral pulmonary consolidations involving both lower lobes with a zone of reduced pericardial transparency of the left lung

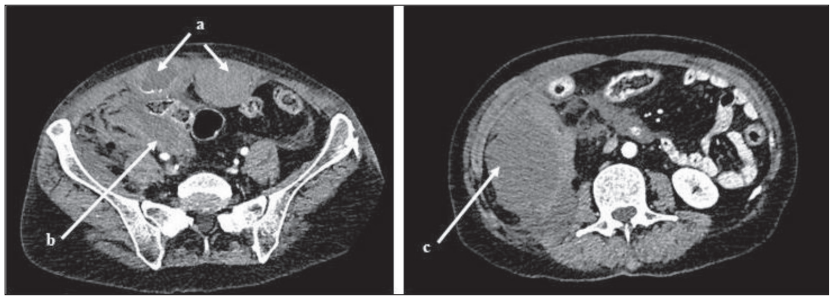

Figure 4. Case 2 – (a) axial computed tomography scans of the abdomen and pelvis show bilateral rectus abdominis muscles hematomas (b) extending into the extraperitoneal pelvis; another hemorrhagic collection in the right retroperitoneum with displaced adjacent structures (c)

Table 2. Case 2 – blood tests during the hospital course

Data	Hgb (g/l)	Plt 10^9/l	Urea (mmol/l)	Cre (mmol/l)	GFR ml/min/1.73 m^2	CRP (mg/l)	IL6 (pg/ml)	INR	Dd (mg/l)
Normal range	115–165	140–450	2.5–7.5	44–88	≥ 90	0–5			0–0.5
Day 1	144	162	5.0	66	90	18.1			0.41
Day 2	133	293	7.5	61	97	74.3	75.4		0.52
Day 6	134	337	6.6	56	99	73.0			0.73
Day 8	145	493	8.9	63	95	18.8			1.86
Day 13	136	362	8.5	53	101	1.2			0.83
Day 16	130	304	7.1	54	100	0.4		0.97	0.65

Hgb – hemoglobin; Plt – platelets; Cre – creatinine; GFR – glomerular filtration rate; CRP – C-reactive protein; IL6 – interleukin 6; INR – international normalized ratio; Dd – D-dimer

Case 2

A 60-year-old obese woman (body weight 70 kg, body height 157 cm), vaccinated, with rheumatoid arthritis, after the triage in the COVID Center in Belgrade, she was admitted to the ward of our hospital for further treatment of proven SARS-CoV-2 infection and consequential bilateral pneumonia. The disease began 10 days before admission with the appearance of cough, malaise, shortness of breath, and fever. Immediately after admission, supportive oxygen therapy was initiated using a nasal catheter with a flow rate of 2 l/min, achieving SpO_2 of 96–97%. The initial chest X-ray showed extensive bilateral pulmonary infiltrates involving both lower lobes with a zone of reduced paracardial transparency of the left lung (Figure 3).

Prophylactic thromboprophylaxis was started with nadroparin 0.6 ml, subcutaneously, once daily according to the local algorithm. In the next few days, the patient's condition worsened with a progressive increase in oxygen support. After checking laboratory results on the fifth hospital day, tocilizumab was prescribed according to the drug dosage information (Table 2). On the eighth day, due to further progression of the disease, oxygen support was increased to NRM with a flow rate of 15 l/min. The therapeutic dose of anticoagulant therapy was started according to the patient's body weight, with nadroparin 0.6 ml twice a day.

In the next few days, the patient improved with a decrease in inflammatory parameters (Table 2) and a gradual decrease of oxygen support to the nasal catheter at a flow rate of 2 l/min.

On day 16 after admission, the patient complained of abdominal pain. The abdomen was painfully sensitive to light and deep palpation during the physical examination, particularly in the ileocecal and suprapubic regions. Urine retention was assumed, but 100 ml of clear urine was obtained after the urinary catheter placement. The laboratory tests revealed a slight decrease in hemoglobin level compared to the previous result, but still within the normal range (Table 2). The patient became hypotensive and tachycardic, and because of suspicion of acute abdomen and bleeding as a complication of anticoagulant therapy, she was urgently transported to the surgical facility of another COVID hospital.

Abdominal and pelvic computed tomography scans showed hematomas of rectus abdominis muscles, 42 × 56 × 110 mm on the left and 40 × 55 × 120 mm on the right side. There were also two hemorrhagic collections: in the right pelvis with a diameter of 60 × 90 mm, which pushes the central pelvic organs contralaterally, and in the right retroperitoneum with a size of 80 × 110 mm, which luxates the ascending colon and pushes the right kidney to the anterior abdominal wall (Figure 4). The patient underwent emergency surgery when around 3000 ml of blood with coagula was evacuated. The postoperative course went well, and the patient was discharged from the hospital in a good general condition.

Data from the database of the doctoral dissertation "Hemostatic profile and effectiveness of anticoagulant therapy in patients with acute respiratory failure in COVID-19" was used, which was approved by the Ethics Committee of the Military Medical Academy on May 25, 2022.

DISCUSSION

All anticoagulation guidelines in COVID-19 suggest thromboprophylaxis for hospitalized patients [5]. Three large international clinical trials published last year, collectively called multiplatform randomized controlled trials, described the effects of different dose regimens of heparin in both non-critically and critically ill patients [6, 7]. The primary outcome was a combination of hospital mortality and organ support-free days at 21 days in non-critically ill patients or patients in the ICU (critically ill). The results showed that therapeutic anticoagulation did not improve outcomes or mortality in the critically ill (including patients receiving high-flow oxygen). Opposite to this, in patients with moderate COVID-19 and low flow oxygen support, therapeutic anticoagulation reduced the need for organ support. Although low, the incidence of bleeding was higher with therapeutic anticoagulation than with usual thromboprophylaxis in both groups of patients [6, 7]. In ICU patients, major bleeding occurred in 3.8% of the patients assigned to receive therapeutic-dose anticoagulation and 2.3% of those assigned to receive usual-care thromboprophylaxis [6]. In non-critically ill patients, major bleeding occurred in 22 of 1180 patients (1.9%) in the therapeutic-dose anticoagulation group and nine of 1047 (0.9%) in the usual-care thromboprophylaxis group. Fatal bleeding occurred in three patients in the anticoagulation group and one in the thromboprophylaxis group [7]. Our first patient was critically ill with high-flow oxygen support and a therapeutic dose of anticoagulant therapy adjusted to anti-Xa assay; the second was moderately ill on low-flow oxygen and therapeutic doses of anticoagulation calculated according to the body weight. Although current guidelines recommend a prophylactic anticoagulation for adults who require ICU-level care, including those receiving high-flow oxygen, and a therapeutic dose of anticoagulation for patients who require low-flow oxygen, both of our patients had significant bleeding as a complication of therapeutic anticoagulation therapy [8]. Moreover, they had a spontaneous retroperitoneal hematoma (SRH), an unusual and uncommon complication of anticoagulants [9].

SRH is challenging to diagnose because of the vague signs and symptoms. Patients with retroperitoneal bleeding have very subtle clinical signs of hemorrhage. Very discreet hemodynamic instability, mild hypotension and tachycardia that improve with intravenous fluids for a short period should raise the clinician's suspicion about possible retroperitoneal hematoma and further investigation [10]. It is believed that the term spontaneous means the absence of specific underlying pathology or trauma; many data implied that unrecognized, minor injuries such as vomiting or coughing can cause minor bleeding that can be promoted and augmented with anticoagulation therapy. In a small study with 12 patients, anticoagulation therapy was the reason for large hematoma of the rectus abdominis muscle; six of them had a history of coughing attacks [11]. This may be a plausible explanation of our patients' rectus abdominis muscle hematomas and retroperitoneal bleeding mechanism, considering the low bleeding risk of our patients in view of the lack of other comorbidities such as renal disease or any bleeding disorders.

SRH is usually associated with anticoagulant therapy, bleeding disorders, and hemodialysis patients [12]. Recently, spontaneous retroperitoneal bleeding with massive deep vein thrombosis has been reported in a patient with COVID-19 who was not even on anticoagulant therapy, without any history of bleeding diathesis or trauma prior to admission to the hospital [13]. This case emphasizes that the COVID-19 induced procoagulant state can cause massive thrombosis and the need for therapeutic doses of anticoagulation. However, the risk of hemorrhagic complications should always be considered, with caution regarding dose regimens of anticoagulant therapy in specific patients.

It is very delicate to keep the equilibrium between anticoagulant therapy, and thrombotic and hemorrhagic complications in patients with COVID-19. Hence, the optimal anticoagulation protocol is still debatable. Retroperitoneal hematoma, an uncommon site of spontaneous bleeding, is a rare complication of anticoagulants. Additional evaluation on a case-by-case basis is needed in light of the absence of specific presenting symptoms and delayed diagnosis. Further studies are needed to verify the risk-benefit ratio of different regiments of anticoagulant therapy in patients with COVID-19.

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Conflict of interest: None declared.

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Ретроперитонеални хематом – неуобичајена компликација антикоагулантне терапије код болесника са ковидом 19

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САЖЕТАК

Увод Болест изазвана вирусом корона (ковид 19) карактерише се хиперинфламаторним одговором, хемостатским поремећајима и високим ризиком од тромбозе. Упркос тромбопрофилакси, бројне студије су показале високу инциденцију тромбоемболијских догађаја са последичним повећањем дозе антикоагулантне терапије од стандардних, до интермедијарних или чак терапијских. Међутим, објављени подаци о учесталости и исходу хеморагијских компликација примењених протокола лечења су и даље ограничени.

Приказ болесника У тексту се приказују две болеснице са ковидом 19 и појавом масивног крварења (спонтани ретроперитонеални хематом) као последицом примењене антикоагулантне терапије. Прва, 64-годишња, болесница примљена је у Јединицу интензивног лечења због тешке респираторне инсуфицијенције. Започета је неинвазивна механичка вентилација и терапијска доза антикоагулантне терапије одређена вредностима анти-*Xa* теста. Кумулативна доза надропарина је била 150 *IU/kg* телесне масе по дану. Код друге, 60-годишње, болеснице са билатералном пнеумонијом и умерено тешком клиничком сликом примењене су терапијске дозе антикоагулантне терапије израчунате према телесној тежини. Обе болеснице су пребачене у другу установу и подвргнуте хитној хируршкој интервенцији због значајног крварења. Активно хируршко крварење није откривено, а ретроперитонеални хематоми се сматрају компликацијом примењене терапије. Обе болеснице су отпуштене са лечења у добром општем стању.

Закључак Масивно крварење представља ретку али могућу компликацију антикоагулантне терапије код болесника са ковидом 19. Неуобичајена места спонтаног крварења захтевају индивидуални терапијски приступ болеснику, с обзиром на то да се дијагноза често одлаже због недостатка специфичних симптома. Потребне су даље студије да би се испитале ефикасност и безбедност примене различитих протокола антикоагулантне терапије, посебно виших терапијских доза, код болесника са ковидом 19.

Кључне речи: ковид 19; антикоагулантна терапија; крварење; ретроперитонеум

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Histological analysis of bone three months after the treatment of oroantral communication with autologous platelet-rich fibrin – a case series

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SUMMARY

Introduction Oroantral communication (OAC) closure may be accompanied by hard and soft tissue defects. Platelet-rich fibrin (PRF) is the second-generation platelet concentrate that can be an effective therapeutic option for the closure of defects up to 5 mm in diameter. The aim of this investigation was to evaluate whether PRF could be a viable therapeutic option for OAC closure and provide sufficient bone quality/quantity for the forthcoming implant placement.

Outlines of cases The case series included eight patients treated with PRF due to the presence of OAC less than 3 mm in diameter. Three months after the surgery, at the time of implant placement, bone samples were harvested and taken for histological analysis. The results demonstrated success in all eight cases, obtaining both hard and soft tissue healing. Histological analysis showed that newly formed bone was present on all histological samples, without visible signs of inflammation and necrosis.

Conclusion PRF could be a viable therapeutic option for OAC closure in specific clinical cases, but future randomized, controlled, clinical studies are required for more conclusive results.

Keywords: bone healing; autologous platelet-rich fibrin; oroantral communication

INTRODUCTION

Surgical closure of the oroantral communication (OAC) may be accompanied by hard and soft tissue defects [1]. Although application of local soft-tissue flaps is still the most utilized technique for OAC closure, recent studies suggest that platelet-rich fibrin (PRF) can be an effective therapeutic option for the closure of defects up to 5 mm in diameter. PRF is associated with minimal postoperative morbidity and allows preservation of adjacent teeth soft tissue structures [2–5]. Additionally, the combination of PRF and bone grafting materials promotes hard tissue healing, obtaining better conditions for future implant placement [3, 4, 5].

PRF is the second-generation platelet concentrate consisting of a three-dimensional polymerized fibrin matrix in a molecular structure. It incorporates blood contents such as leukocytes, erythrocytes, platelets, growth factors, and circulating stem cells [6]. PRF membrane induces tissue regeneration due to the stimulating effects on osteoblast cells, gingival fibroblasts, pulp cells, and periodontal ligament cells [1].

This case series aimed to evaluate whether PRF could be a viable therapeutic option for the OAC closure and provide sufficient bone quality/quantity for the forthcoming implant placement.

REPORT OF CASES

This case series included eight patients treated at the Clinic for Oral Surgery, School of Dental Medicine in Belgrade (six males and two females; aged 21–43 years, mean age 34.6 ± 11.3 years). They were referred to the Clinic due to the presence of OAC and enrolled in the study according to the following inclusion criteria:

- patients in good general health without a history of systemic disease or medication that could interfere with the treatment (ASA1 and ASA2);
- fresh OAC (not more than 24 hours from the tooth extraction);
- without the clinical/radiological signs of maxillary sinusitis;
- long and narrow alveolus of the extracted tooth;
- OAC less than 3 mm in diameter;
- length from the cortical margin of the extracted tooth to the OAC being at least 6 mm;
- clinically compliant patients consent to be enrolled in the study.

The OAC was closed by autologous PRF plugs and membranes, following Choukroun's PRF centrifuge protocol (PRF DUO™, Nice, France) [7]. After the curettage and saline rinsing, wound edges were freshened, and the PRF plug was placed inside the alveolus. PRF membrane was shaped over the site in one layer, and the closure was obtained by interrupted sutures

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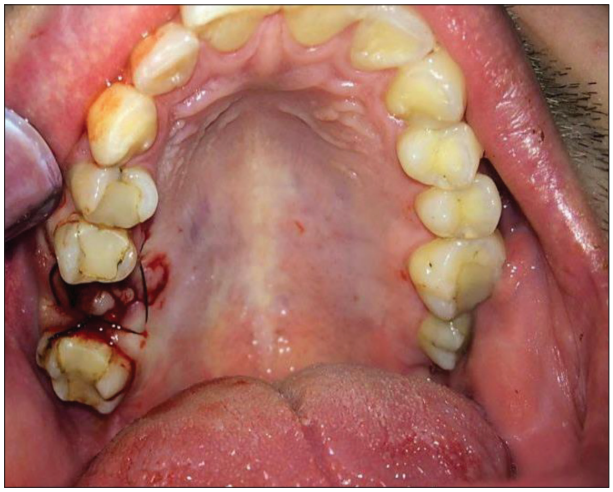

Figure 1. Platelet-rich fibrin material placed in the alveolar socket

Figure 2. Bone sample inside the trephine burr Ø 3.0 mm

– Figure 1. The follow-up was scheduled, and sutures were removed on the 10th day.

Epithelization and soft tissue healing were uneventful in all eight cases. Three months after the OAC closure, there was a sufficient amount of keratinized gingiva and the cone-beam computed tomography evaluation revealed new bone formation in the area of the previously extracted tooth. Sub-antral height of 6–9 mm (average 7.3 mm) was obtained in all eight cases. The site was reopened, bone samples for histological analysis were harvested (trephine burr; Ø 3.0 mm – Figure 2), and implants were placed. We were using bone level, tapered implants, following the maxilla protocol (avoiding the last sequence drill), and managed to obtain solid implant stability (from 20 Ncm to above).

Bone samples were stored in a 10%-formalin solution for 12–24 hours and then decalcified in a microwave oven (eight cycles of 10 seconds; at 410–430°C for 20 minutes). The material was dehydrated with 70%, 95%, and 99% ethyl alcohol, respectively, and clarified with xylene. Gathered bone fragments were embedded in paraffin blocks, cut into slices (3–4 μm), and stained with Goldner trichrome method. Analysis of samples was performed under Leica Microsystem® optical microscope (Leica Microsystems™ GmbH, Wetzlar, Germany).

The newly formed bone was present in all histological samples, without signs of inflammation and necrosis (Figure 3). Bone trabeculae were surrounded by the loose connective tissue in which no inflammatory infiltrate cells were seen, or their number was minimal. Additionally,

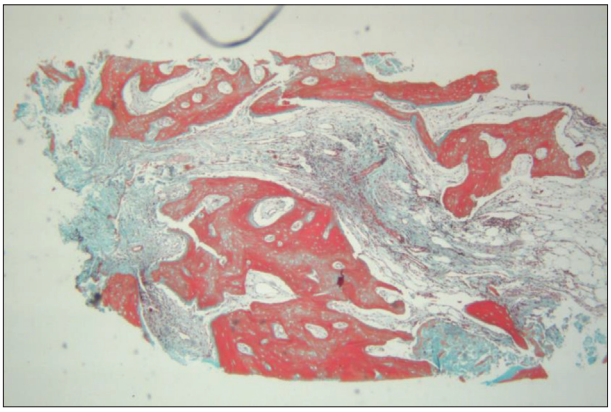

Figure 3. Newly formed bone tissue (Goldner trichrome method, 40 ×)

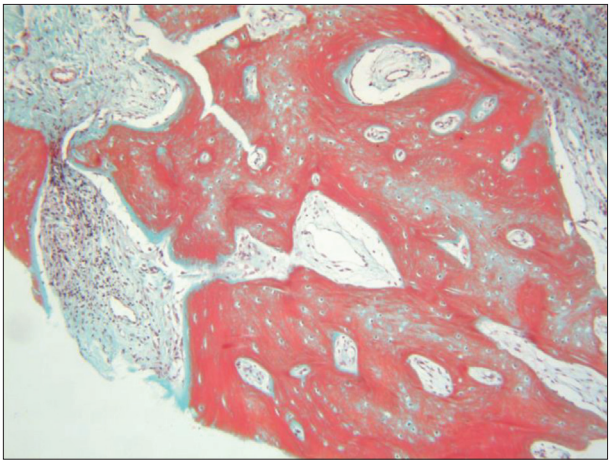

Figure 4. Newly formed bone tissue with elements of mature and immature bone (Goldner trichrome method, 100 ×)

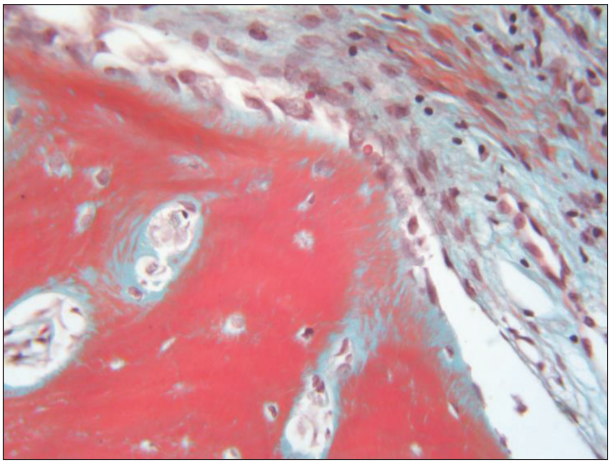

Figure 5. Osteocytes in the lacunae and osteoid and densely packed osteoblasts (Goldner trichrome method, 400 ×)

intensive bone remodeling was noticed, i.e., the presence of mature (lamellar) bone and immature (fibrous) bone (Figure 4). Haversian canals with concentrically placed bone lamellae (characteristics of osteons) were seen as a sign of mature bone, and collagen-fiber networks as a sign of immature bone. The abundant presence of osteocytes lying in lacunae confirmed bone vitality, and the presence of osteoids covered with a dense layer of osteoblasts was a sign of active osteogenesis (Figure 5).

This report was approved by the institutional ethics committee, and written consent was obtained from the patients for the publication of the report and any accompanying images.

DISCUSSION

Our findings indicate that PRF could be a viable solution for the OAC closure in specific clinical cases. It provides proper hard and soft tissue healing, obtaining sufficient bone quality/quantity. Initially, PRF acts as a boosting agent for soft tissue healing, supporting epithelization. Additionally, it promotes bone formation in the area of the extracted tooth, creating the vital bone, and shortens the healing period. The presence of mature and immature bone is a significant histological sign of intensive bone remodeling.

PRF plug acts as a core for bone healing and the PRF membrane acts as a biological membrane that promotes epithelization. Due to its properties, PRF has proven as the material of choice not only for this indication but in many other clinical studies as well. Ondur et al. [8] showed that the use of PRF for hard and soft tissue healing may have advantages due to its autogenous origin, being cheaper than the collagen membrane. The authors pointed to PRF's ability to release growth factors (TGF-β1, PDGF-β, VEGF), particularly in the first seven days, and later, up to 28 days. Similarly, Liu et al. [9] promote PRF as a bone grafting material for oral and maxillofacial bone regeneration procedures as it improves proliferation, migration, differentiation, and mineralization of the cells during bone formation. There is an indication that PRF could also diminish crestal bone resorption after tooth extraction [10], as demonstrated in periimplantitis therapy use [11]. Moreover, the application of PRF, either alone or in combination with another biomaterial, might be effective in reducing time for new bone formation and future implant placement [12, 13].

Although we were successful in all eight cases obtaining hard and soft tissue healing, it would be presumptive to state that PRF could be a universal tool for OAC closure. In this study, we had a strict case selection, requiring fresh OAC with a diameter of up to 3 mm. Post-extraction socket had to be long and narrow, and the distance between the crest and the OAC should be at least 6 mm. However, there is a question if the same healing would be obtained without the use of PRF since we did not have a control group. Additionally, the sample size was small. We did not experience any complications and are considering if the procedure could be applied to larger/shallower defects, along with the use of bone substitute materials.

This case series indicates that PRF could be a viable therapeutic option for the OAC closure providing optimal hard and soft tissue structures for the future implant placement. However, future randomized, controlled studies on larger sample sizes, with control groups, should contribute to more conclusive remarks.

Conflict of interest: None declared.

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Хистолошка анализа кости три месеца после реконструисања ороантралне комуникације аутологним фибрином богатим тромбоцитима – серија болесника

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САЖЕТАК

Увод Хируршко затварање ороантралних комуникација (ОАК) може бити праћено стварањем коштаних или меких ткивних дефеката. Аутологни фибрин богат тромбоцитима (ФБТ) јесте тромбоцитни концентрат друге генерације ефикасан у реконструкцији ОАК дијаметра до 5 *mm*.

Циљ истраживања је био да испита ефикасност ФБТ у реконструкцији ОАК и утврди да ли ће његова примена обезбедити адекватну коштану подлогу за будућу уградњу имплантата.

Приказ болесникâ Истраживање је обухватило осам пацијената код којих је ОАК била мања од 3 *mm* и реконструисана применом ФБТ. Три месеца после хируршког захвата, приликом уградње имплантата, са места ОАК узети су узорци кости ради хистолошке анализе. Мекоткивно зарастање је било успешно код свих испитаника. Резултати свих узорака показали су присуство новоформиране здраве кости, без знакова запаљења и некрозе.

Закључак ФБТ се може користити за реконструкцију ОАК у специфичним клиничким индикацијама. Ипак, неопходно је спровести рандомизоване, контролисане клиничке студије пре доношења јасних препорука.

Кључне речи: коштано зарастање; аутологни фибрин богат тромбоцитима; ороантрална комуникација

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Intraperitoneal onlay mesh laparoscopic repair of an incarcerated Spigelian hernia – case report and literature review

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SUMMARY

Introduction Spigelian hernia is a type of lateral ventral hernia, localized between the rectus abdominis muscle and the semilunar line. Current literary data indicate that the prevalence of Spigelian hernia is 1–2% of all hernias of the abdominal wall. Patients are most commonly asymptomatic.

Case outline We present a 63-year-old male patient admitted to our hospital as an emergency case due to lower abdominal pain. Upon hospital admission, radiological diagnostics, and a physical examination, the presence of a Spigelian hernia was verified, which, at the moment of the examination, was incarcerated. It was established that surgical treatment was indicated. We performed laparoscopic intraperitoneal onlay mesh plastic in the standard way. The patient was discharged from hospital on the following day with normal values of vital and laboratory parameters.

Conclusion The Spigelian hernia, although first described many years ago, remains a diagnostic challenge, which is why its occurrence requires a multidisciplinary approach for the purpose of establishing a timely and accurate diagnosis. Within the surgical treatment of this state, there are several surgical techniques, and special focus is placed on the minimally invasive surgical approach. Also, within the minimally invasive surgical approach, there are several operating techniques.

Keywords: Spigelian hernia; laparoscopy; surgery

INTRODUCTION

Spigelian hernia (SH) is a type of lateral ventral hernia, which presents as a tumefaction passing through the aponeurosis of the Spigelian fascia, localized between the rectus abdominis muscle and the semilunar line.

In literature, SH was first documented by Klinkosch in 1746. However, regardless of this first description, this hernia was named after the Flemish anatomist Adriaan van den Spiegel, who was the first to describe the semilunar line [1].

Current literary data indicate that the prevalence of SH is 1–2% of all hernias of the abdominal wall, with a higher prevalence in females. Age is a significant risk factor, which is why incidence is higher in the elderly [2, 3].

Patients with SH are most commonly asymptomatic. Rarely, they present with discomfort, abdominal pain, intestinal obstruction, etc. [4]. It is because of the abovementioned symptomatology that diagnostics regarding SH represents a challenge. In addition to a physical examination, appropriate anamnesis, abdominal ultrasound examination, especially of the anterior abdominal wall, as well as computed tomography (CT) imaging, represent an important step in establishing a timely and appropriate diagnosis.

Surgical treatment is the only curative treatment modality. Traditionally, open hernia repair surgery is applied, and the defect is closed with or without a mesh. However, after the introduction of the minimally invasive surgical approach, views regarding the best approach have been changing over time, especially when the benefits of laparoscopic surgery are taken into account. Amongst the numerous techniques, the intraperitoneal onlay mesh (IPOM) repair laparoscopic technique has a particular place [1, 5].

The aim of our study is to present a rare case of an incarcerated SH, which was safely and efficiently resolved with a minimally invasive surgical approach, as well as to present the surgical technique applied to treat the said condition.

CASE REPORT

We present a 63-year-old male patient admitted to our hospital as an emergency case due to lower abdominal pain. The patient was in good general health without comorbidities, such as hypertension, diabetes, kidney disease, etc. He did not smoke or drink alcohol. The anamnesis showed that the patient had previously experienced similar symptoms which resolved on their own. However, this time the symptoms persisted, and the intensity of the pain gradually increased. After admission to the hospital, a physical examination was performed first,

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followed by an ultrasound examination of the abdomen. After the previously mentioned procedures, the presence of SH, which was incarcerated at the time of the investigation, was verified.

It was established that surgical treatment was indicated. Therefore, firstly, artificial pneumoperitoneum was created with the use of a Veress needle, in general endotracheal anesthesia. After this, a ten-millimeter-wide port was placed directly above the umbilicus, through which a camera was introduced, which was followed by the placement of a paraumbilical five-millimeter-wide working port, positioned on the left, as well as another working port, also five millimeters in diameter, positioned two centimeters above the anterior iliac spine, diagonally, in the direction of the umbilicus. After the optic instruments were introduced, a red, discolored segment of the small intestine, intensely hyperemic, as compared to the remaining part of the small intestine, was verified (Figure 1), which was the result of pervious incarceration and spontaneous desincarceration that occurred at the moment when pneumoperitoneum was created.

Exploration of the abdomen was performed first, and a normal finding was noted. The vascularization of the observed red segment was not compromised, which is why, after a few minutes, it regained the same coloring and texture as the rest of the intestine. After the aforementioned steps were undertaken, the defect on the abdominal wall was first verified, after which the hernia sac was first prepared and then resected, with the use of the LigaSure dissector (Medtronic, Minneapolis, MN, USA) (Figure 2). The diameter of the defect on the abdominal wall was about 7 × 5 cm. The next step was introducing a composite polytetrafluoroethylene (PTFE) mesh size 14 × 11 cm into the abdomen via the widest port and positioning it in such a way as to cover the defect on the abdominal wall, after which it was fixed to the abdominal wall, from the inside, with the use of a tacker (Figure 3). Finally, the gas from the abdomen was released, and the surgical incisions were closed in anatomical layers.

The patient was discharged from hospital on the following day with normal values of vital and laboratory parameters. After regular follow-up visits, within the first month after surgery, the patient returned to normal everyday activities, without any limitations.

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments and comparable ethical standards.

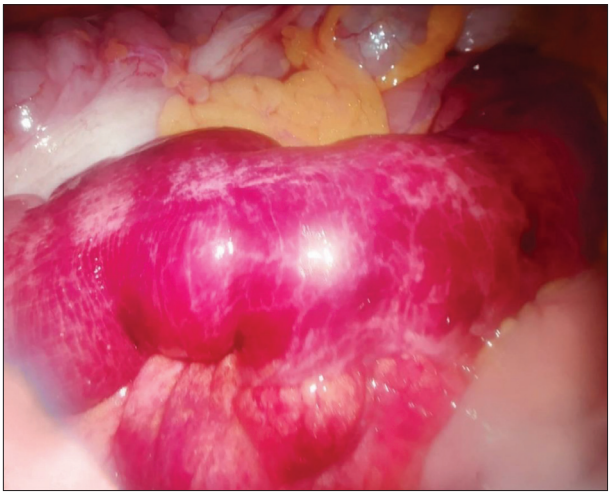

Figure 1. Intraoperative view of the segment of the small intestine that was in the hernial sac

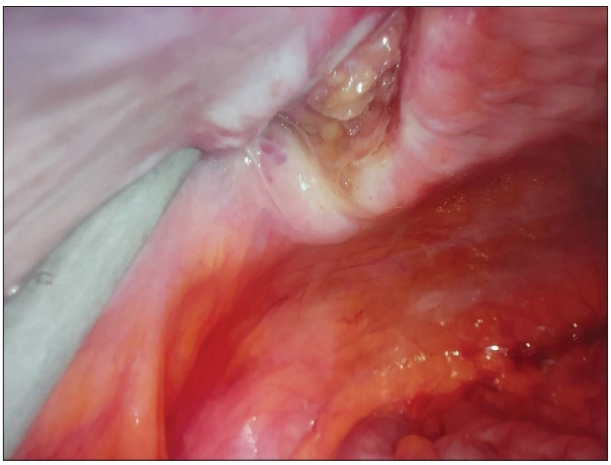

Figure 2. Intraoperative view of the hernial defect after resection of the hernial sac

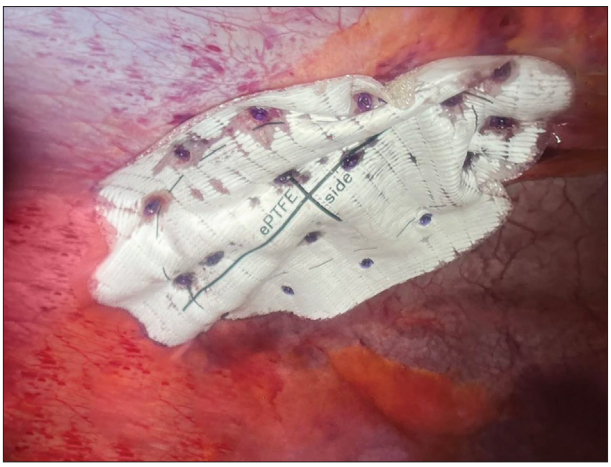

Figure 3. Intraoperative view of the placed and fixed composite mesh

DISCUSSION

SH itself is an uncommon occurrence, while it is safe to say that an incarcerated SH is a true rarity. The hernia sac usually encompasses the omentum, a segment of the small intestine, or the appendix [6, 7, 8].

In the case of our patient, a segment of the small intestine was incarcerated, which was found within the hernia sac.

The diagnosis of SH is a challenge, both surgically and radiologically. In our patient's case, we established a diagnosis based on a physical examination, which revealed a tumefaction in the region of the semilunar line. After this, an abdominal ultrasound examination was performed, which confirmed a defect of the anterior abdominal wall located in that particular site.

In patients with pronounced symptoms and in whom SH is suspected, some authors propose performing an abdominal CT scan as a diagnostic method very useful in establishing the definitive diagnosis [9, 10].

Most authors propose surgical treatment of SH, since, according to data from current literature, there is the possibility of the occurrence of incarceration and strangulation of the hernia. Specifically – incarceration occurs in 24–27% of the cases, while strangulation occurs in 2–14% of the cases [5, 9].

The first laparoscopic hernia reparation was performed and documented in literature by Carter and Mizes, in 1992. There are several laparoscopic techniques applied in the treatment of SH, with different benefits. Namely, the IPOM is considered to be the most popular approach (39.2%), followed by transabdominal preperitoneal patch plasty (TAPP) (26.1%), total extraperitoneal patch plasty (TEP) (19%), and the laparoscopic suturing technique (8.3%) [11].

In our case report, we present the application of the laparoscopic IPOM technique in the treatment of SH. We chose the mentioned technique primarily because of its safety, efficiency, and ease of application. Considering the previously mentioned size of the abdominal wall defect, we opted not to suture the SH defect before mesh placement. There was no need for additional fixation of the mesh to the abdominal wall.

In the current literature, there are opinions that the defect of the abdominal wall in SH should not be closed with sutures, before placing the mesh, especially when it comes to PTFE mesh. In cases where the defect of the abdominal wall is up to 3 cm, a suture defect can be applied before placing the mesh, i.e. the IPOM-plus technique. According to the results of Moreno et al. [12], in emergency cases like the one we presented in our work, priority should be given to the IPOM and TAPP approach, because an examination of the abdominal cavity can be performed, and therefore an adequate decision on further surgical steps can be made [13].

Also, a review of current literature, in both English and Serbian, did not reveal a report on any cases or series of cases, in Serbia, documenting the treatment of an incarcerated SH with the minimally invasive surgical approach.

SH, although first described many years ago, remains a diagnostic challenge, which is why its occurrence requires a multidisciplinary approach for the purpose of establishing a timely and accurate diagnosis. Within the surgical treatment of this state, there are several surgical techniques, and special focus is placed on the minimally invasive surgical approach. Also, within the minimally invasive surgical approach, there are several operating techniques, amongst which the IPOM approach, due to its simplicity, safety, and efficiency, represents one of the most commonly applied procedures, with all its benefits.

Conflict of interest: None declared.

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Лапароскопска техника интраперитонеално положене мрежице у лечењу уклештене Спигелове киле – приказ болесника и преглед литературе

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САЖЕТАК

Увод Спигелова кила је врста латералне вентралне киле, која је локализована између мишића *rectus abdominis* и семилунарне линије. Актуелни литерарни подаци указују да је инциденца Спигелове киле између 1% и 2% свих кила трбушног зида. Болесници најчешће немају симптоме.

Приказ болесника Представљамо болесника старог 63 године, који је хитно примљен у нашу болницу због болова у доњем делу трбуха. Приликом пријема у болницу, радиолошке дијагностике и физикалног прегледа, констатовано је присуство Спигелове киле, која је у тренутку прегледа била уклештена. Постављена је индикација за хируршко лечење. Урадили смо лапароскопску пластику интраперитонеално положене мрежице на стандардни начин. Болесник је наредног дана отпуштен из болнице са уредним виталним и лабораторијским параметрима.

Закључак Спигелова кила, иако је први пут описана пре много година, остаје дијагностички изазов, због чега њена појава захтева мултидисциплинарни приступ у циљу постављања правовремене и тачне дијагнозе. У оквиру хируршког лечења овог стања постоји неколико хируршких техника, а посебан фокус је на минимално инвазивном хируршком приступу. Такође, у оквиру минимално инвазивног хируршког приступа постоји неколико оперативних техника.

Клучне речи: Спигелова кила; лапароскопија; хирургија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Ileal perforation by accidentally ingested animal bone – rare cause of acute abdomen

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SUMMARY
Introduction In healthy adults, accidental ingestion of foreign bodies is uncommon. Intestinal perforation by ingested bone fragments is rare, but can be presented as a life-threatening condition, especially when the diagnosis is delayed.
Case outline We present an uncommon case of a 73-year-old female with acute abdominal symptoms due to ileal perforation caused by accidentally ingested animal bone. Pneumoperitoneum revealed by abdominal X-ray and abdominal free fluid revealed by abdominal ultrasound as well as the general condition of the patient required urgent laparotomy, when the diagnosis of ileal perforation was made. A foreign body was removed from the intestine, along with partial resection of the intestine and end-to-end anastomosis.
Conclusion Surgical treatment of life-threatening complications arising after ingestion of foreign bodies is the only method of choice in the treatment of such patients.
Keywords: ingested foreign bodies; intestinal perforation; surgery

INTRODUCTION

Ingested foreign bodies (IFB) are not uncommon, can be found at any age in both adults and children and are usually asymptomatic and excreted without disturbance. The majority of patients, about 80%, are children, who accidentally swallow foreign bodies [1]. In adults, it occurs more often among the elderly, in psychiatric patients, alcoholics and drug addicts, and in some specific professions like tailors, carpenters, etc. [2]. Most IFB, > 90%, pass through the intestine uneventfully in a week [1, 2], and among them food particles, such as bones, are the most common [3].

Uncomplicated cases are usually managed conservatively, but some cases can develop complications such as abscess, diverticulitis, perforation, obstruction. Perforation of the gastrointestinal tract by IFB is rare. Less than 1% of IFB will cause bowel perforation requiring surgical treatment [2, 4].

We present a case of small bowel perforation caused by an ingested animal bone in a patient with no intestinal disease and previous abdominal surgery.

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CASE REPORT

A 73-year-old female patient was admitted to the Department of General Surgery due to abdominal pain, malaise, fever, flatulence, nausea and vomiting. The complaints started two days before the admission, with the appearance of severe pain in the epigastrium followed by vomiting. Despite the signs of diffuse peritonism and abdominal sensibility revealed by the abdominal examination, the patient was in good general condition. Signs of pneumoperitoneum were observed on the X-ray of the abdomen and lungs (Figure 1). Ultrasound of the abdomen revealed free fluid after which the decision to proceed with an emergency laparotomy was taken. Exploratory laparotomy was performed with a medial laparotomy under general anesthesia. A large amount of free fluid in the abdominal cavity was identified – a sample was taken for microbiological analysis. Subphrenic bilateral, as well as interintestinal and small pelvis abscess collections, with fibrin deposits on all organs of the abdominal cavity were found. Perforation of the ileum was identified (Figure 2). A foreign body, an animal bone, was identified in the intestine, which caused necrosis of the wall and perforation of the intestine (Figure 3). A 10-cm-long bowel resection was performed, with an end-to-end anastomosis. Abundant lavage of the abdominal cavity with a larger amount of physiological solution was performed. Postoperatively, the patient was treated empirically with antibiotics (ceftriaxone, metronidazole, amikacin) and other supportive therapy. On the third postoperative day, a microbiological analysis of the contents of the abdomen (*Klebsiella* sp.) was obtained and treatment continued according to the antibiogram (ciprofloxacin, metronidazole, piperacillin/tazobactam). There was an improvement in the general condition and a decrease in inflammatory parameters. From the eighth day of hospitalization, the patient was subfebrile with an increase of biochemical inflammatory markers. Computed tomography (CT) of the abdomen found subcapsular liver abscesses

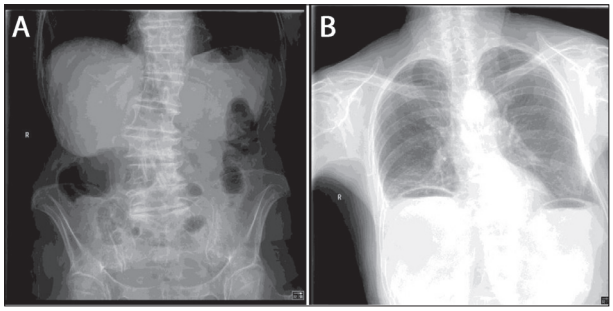

Figure 1. Abdominal (A) and chest (B) X-ray

and right pleural effusion. Continued treatment with vancomycin 1 g every 12 hours and meropenem 1 g every six hours for another 10 days and other supportive therapy. The prescribed therapy leads to a complete stabilization of the general condition. Abdominal control CT showed no signs of liver abscess, and the patient was discharged from the ward on the 23rd day of hospitalization. Postoperative ultrasound follow-up was carried out for another three months, without postoperative complications.

We obtained verbal and signed consent of the patients to publish the case report. This article was planned in compliance with the Patient Rights Directive and ethical rules by considering the principles of the Declaration of Helsinki.

DISCUSSION

IFB are a common cause of presentation in the emergency room and mostly occurs in children and in the elderly with an incidence of 4% [5]. Eighty to ninety percent of patients with IFB do not require any intervention, 10–20% of patients who ingest foreign bodies require an endoscopy intervention, and up to 1% of patients require surgery [6].

In adults, IFB are most often found in patients with psychiatric and addictive diseases as well as and in the elderly with dental prostheses. Accidental ingestion of various foreign bodies, such as toothpicks, teeth, fish and chicken bones, screws, coins, dentures, and spoon handles, has been reported [7, 8]. Foreign body sticking can be seen in any part of the digestive tube. IFB sticking in the esophagus depends on the anatomical characteristic of the esophagus, associated pathology, and the nature of the foreign body (sharp, spherical, etc.) [5]. There are three physiological narrowings in the gastrointestinal tract that can represent the site of foreign body entrapment: pylorus, duodenal C-loop, and the ileocecal junction. The most common locations for objects to get stuck in the large intestine are appendiceal lumen, cecal-ascending colon junction, colonic flexures, and haustra [9]. Obstruction, hemorrhage, necrosis and abscess, peritonitis, and perforation are the main complications of IFB and may occur in all segments of the gastrointestinal tract. Although perforations have been recorded in the duodenum, ileum, and the right colon, the ileum is considered the most common perforation site, followed by the rectosigmoid junction [6]. According to literature data, fish bones are the most common cause of gastrointestinal perforation.

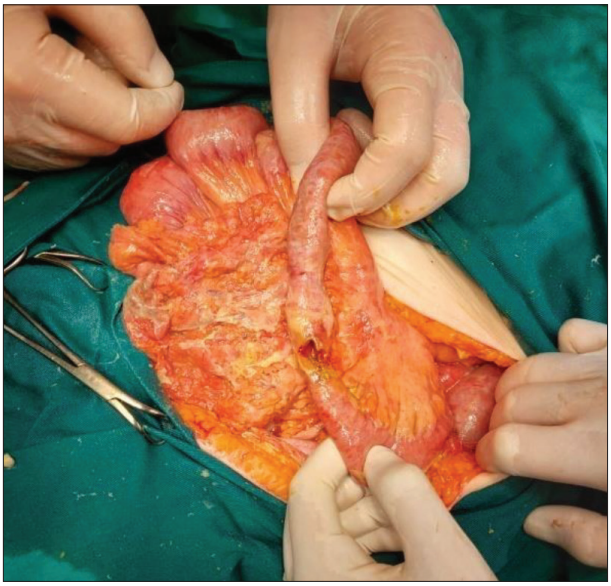

Figure 2. Intraoperative finding: bowel perforation

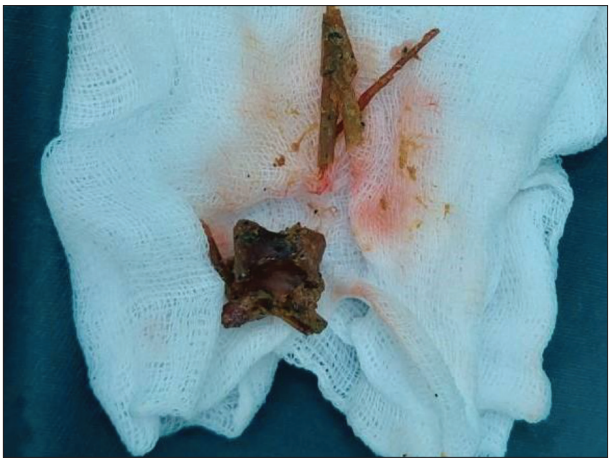

Figure 3. Extracted foreign body – animal bone

Most gastrointestinal foreign bodies can be removed by gastroscopy or enteroscopy. According to recommendations of the European Society for Gastrointestinal Endoscopy, an emergency endoscopy for IFB causing complete esophageal obstruction, and for sharp-pointed objects or batteries must be performed within six hours and in incomplete obstruction within 24 hours. Urgent endoscopy for IFB in the stomach, such as sharp objects, magnets, batteries, etc is recommend to be performed within 24 hours and for medium-sized blunt foreign bodies in the stomach within 72 hours [10].

Our patient was without significant comorbidities and previous abdominal surgery procedures, who requested medical help two days after the onset of the symptoms with signs of acute abdomen.

Preoperative diagnosis of IFB bowel perforation can be difficult because the patients are often unaware that they have swallowed a foreign body. The clinical presentation can vary and depends of the site of perforation and the amount of spilled intestinal contents and can include abdominal pain, fever, nausea, vomiting, peritonitis, sepsis, inflammatory mass, fistulas, bowel obstruction, and gastrointestinal hemorrhage [6, 11].

In addition to the clinical picture, imaging methods for preoperative diagnosis include plain radiograph (with low sensitivity for radiographically insensitive material), ultrasonography, and CT scan with high sensitivity and specificity. The presence of pneumoperitoneum is not reliable as it is not found in many cases. Nevertheless, definitive diagnosis has been reached during laparotomy in more than 90% of the cases [2]. Our patient was unaware that she had swallowed a foreign body, which initially made the preoperative diagnosis difficult. The final diagnosis was made during the surgery.

The management of an IFB depends on the patient symptoms, the type and the location of the ingested object. Management of bowel perforation is mostly surgical for cases with peritonitis, abscess, inflammation, bleeding, fistula, and ileus and implies surgical repair – suture of the defect, or segmental bowel resection with primary anastomosis or ileostomy/colostomy [2]. Surgical intervention includes laparoscopic or open methods. Some authors recommend Non-surgical management for limited cases. This treatment consists of intravenous fluid, nutrition support, antibiotics, and other supportive therapy and depends on the size and the location of perforation, time of diagnosis, patient condition, and contamination degree [6, 12].

According to literature the morbidity attributable to bowel perforation by IFB is around 24% and the mortality is up to 6.5%. Reported complications include intra-abdominal abscess, intestinal fistula, perianal abscess, respiratory distress, endocarditis, Fournier's gangrene, ileus, wound infection, inflammatory mass, intestinal occlusion, and diffuse peritonitis. The cause of death is usually multiple organ failure due to severe sepsis [2].

In conclusion, even though accidental or intentional foreign body ingestion are rare causes of intestinal perforation, they cannot be ignored as causes of acute surgical abdomen. Endoscopy for sharp and large IFB must be performed whenever is possible to avoid intestinal perforation. When complications occur, surgical solution of the problem is the only way to save the patient.

Conflict of interest: None declared.

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Перфорација илеума узрокована случајно прогутаном животињском кости – редак узрок акутног абдомена

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Општа болница Нови Пазар, Нови Пазар, Србија

САЖЕТАК

Увод Код здравих одраслих особа случајно гутање страних тела није уобичајено. Перфорација црева прогутаним коштаним фрагментима је ретка, али може бити стање опасно по живот, посебно када се дијагноза одложи.

Приказ болесника Представљамо неуобичајен случај 73-годишње жене са акутним абдоминалним симптомима услед перфорације илеума изазване случајно прогутаном животињском кости. Пнеумоперитонеум потврђен рендгенским снимком абдомена и присуством слободне течности верификоване ултразвуком абдомена, као и опште стање болеснице захтевали су хитну лапаротомију, када је постављена дијагноза перфорације илеума. Страно тело је уклоњено из црева, уз делимичну ресекцију црева и термино-терминалну анастомозу.

Закључак Хируршко лечење животно опасних компликација које настају после ингестије страног тела једини је метод избора у лечењу оваквих болесника.

Кључне речи: прогутано страно тело; перфорација црева; операција

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Mini/one anastomosis gastric bypass in an obese depressive patient

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SUMMARY

Introduction There is a high prevalence of psychiatric disorders, especially depression, in patients who are preparing for metabolic operations. Mini/one anastomosis gastric bypass (MGB/OAGB) is a bariatric operation with the possibility of complete restoration of the digestive tract or "tailoring" of a biliopancreatic limb if the patient regains weight.

We present an obese patient with depression who underwent the first MGB/OAGB in Serbia with a follow-up period of one year.

Case outline An obese patient with a body weight of 144 kilograms and a body mass index (BMI) of 46.8 kg/m^2 and depression as an accompanying comorbidity underwent MGB/OAGB with a follow-up period of one year. The operation was performed using the inventor's technique in his presence and the recovery was uneventful. The patient completely stopped taking psychiatric or any other therapy, with no difficulties, and full occupational and social recovery. After the follow-up period, he has lost 49 kg, BMI = 30. 9 kg/m^2, and the percentage of excess weight loss (%EWL) has been 73.1%.

Conclusion In psychiatric obese patients, a metabolic procedure should be carefully selected. MGB/OAGB proved to be a successful bariatric procedure in our patient, leading to remission of depression and discontinuation of psychiatric therapy, as well as to a significant reduction in body weight in the period of one year after surgery.

Keywords: mini gastric bypass; one anastomosis; depression; metabolic procedure

INTRODUCTION

There is a high prevalence of psychiatric disorders in obese patients who are preparing for a metabolic operation [1]. Depression before and after bariatric surgery can affect not only the health-related quality of life but also can endanger surgical procedures and lead to late surgical and nutritional complications [2]. Changes in lifestyle and eating habits may influence different postoperative conditions. It is important to choose an appropriate surgical bariatric/metabolic procedure after the expertise of a multidisciplinary team, especially psychological examination [3, 4].

Mini gastric bypass (MGB), also known as one anastomosis gastric bypass (OAGB), is a metabolic procedure invented by an American surgeon Dr. Robert Rutledge. First published results on 1274 cases operated on between 1997 and 2001 were promising regarding weight loss and metabolic control on co-morbidities [5]. Later on, other surgeons also published good results [6, 7, 8]. The procedure is completely reversible and could easily be transformed into a stronger malabsorptive operation, with minimal morbidity and mortality [9, 10]. There were concerns about bile reflux, but recently published papers on this subject did not show a significant influence of bile reflux on long-term results [11, 12]. Today, MGB/OAGB is worldwide recognized as a good operation, with comparable results in treating obesity, as well as type 2 diabetes mellitus, even better than Roux-en-Y gastric bypass (RYGB) [13, 14]. Bile reflux, as a more prominent problem of the operation, rarely needs to be solved by Braun anastomosis or a conversion into RYGB [15, 16].

We present a first MGB/OAGB obese patient with depression operated on in Serbia with a follow-up period of one year.

CASE REPORT

The patient was male, Caucasian, 26 years old, with a BMI of 46.8 kg/m^2 and with a five-year clinical history of depression. We performed the MGB/OAGB on May 28, 2016 under the guidance of Dr. Robert Rutledge, who was a visiting physician at the clinic using his original laparoscopic technique. Five ports were placed in the upper abdomen and after the first stapling at the gastric incisura, a bougie was properly placed against the small curvature and staple line. The stomach was transected along bougie to the gastro-esophageal junction but several centimeters away from the fat pad. The antecolic biliopancreatic limb was lifted up and 180–200 cm from Treitz ligament anastomosis between stomach and jejunum was created, with 4.5 cm blue cartridge and V-Loc™ device (Medtronic,

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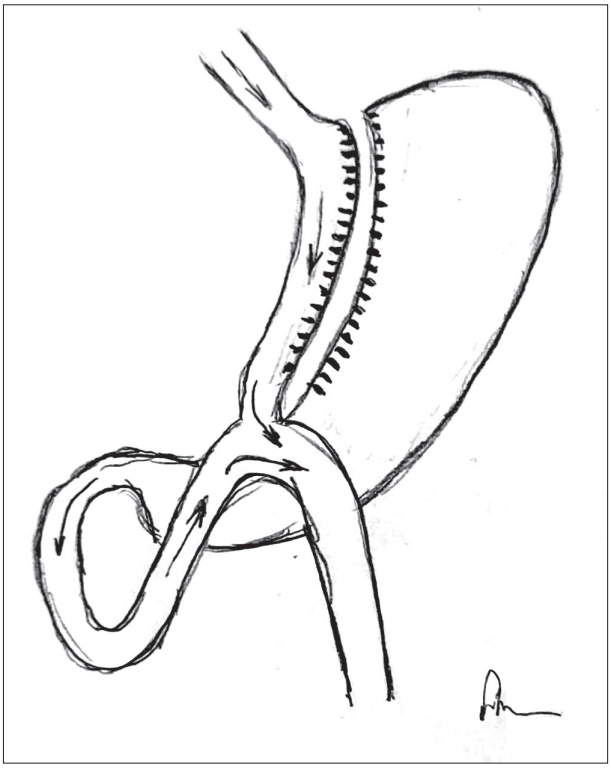

Figure 1. Mini/one anastomosis gastric bypass

Minneapolis, MN, USA) (Figure 1). The patient was discharged from the hospital on the fourth postoperative day with one-month prophylactic anticoagulative therapy (low-molecular-weight heparin). Regular controls were on the first, the second month after the operation, and later on every six months. The result of BMI and percentage of excess weight loss (%EWL) are shown in Table 1.

Table 1. Results one year after procedure

Months	0	1	6	12
Weight (kg)	144	126	114	95
BMI (kg/m^2)	46.8	41	37	30.9
%EWL	/	26.9	44.7	73.1

Percent excess weight loss (%EWL) = (initial weight) – (postoperative weight) / (initial weight) – (ideal weight) × 100

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

DISCUSSION

MGB/OAGB is currently the third most frequently performed bariatric procedure in the world with a share of 7.6% [17]. According to the latest consensus conference, MGB/OAGB is an appropriate option for a single-stage procedure in elderly patients, patients with low BMI (30–35 kg/m^2) and associated metabolic problems, and patients with a BMI greater than 50 kg/m^2 [18].

It is a powerful combination of restrictive and malabsorptive metabolic operation, with only one anastomosis [11]. This feature of the gastric tube (15–20 cm long) and one anastomosis gives "non-obstructive" passage of food, without increasing pressure in the stomach [7]. MGB/OAGB is a completely reversible procedure [9]. Restoration of the digestive tract could be done with a combination of laparoscopic two steps: "mini gastro-gastroplasty", in which surgeon creates lateral–lateral "tube-remnant stomach" anastomosis and a simple transect previous stapling line on gastro-jejunostomy with one stapler and leaves the bowel non-obstructive. If the obese patient changes his habits and starts to regain weight, then a surgical option in MGB/OAGB could be the addition of an extension on a biliopancreatic limb of up to 2.5 meters, or even more. In the laparoscopic procedure, a surgeon does a transection of the previous gastro/jejunostomy and creates a new anastomosis 50 cm away from the previous anastomosis between the gastric tube and the jejunum [16].

In individuals with a history of depression, bariatric surgery is associated with an improvement in mental health. For those with five years of pre-existing depression, just over 20% of post-surgical patients had no further depression episodes [19]. According to some recent studies, in terms of weight loss, MGB/OAGB is superior to laparoscopic gastric sleeve resection, but it also gives very good results in the treatment of type 2 diabetes [20, 21].

In our case, there was a satisfactory response regarding %EWL, as well as the cessation of psychiatric therapy and remission of depression. But in patients with severe depression, there is doubt whether any surgery is sufficient and successful enough for treating obesity combined with the eating disorder. Some authors do not recommend any metabolic procedure [22]. That's why in this group of patients metabolic operation should be taken very carefully, regarding the complex postoperative period. Needs for maintaining psychiatric therapy and lifestyle (sweets- or binge-eaters), especially regarding alcohol taking and smoking, must be observed [23]. In our patient, we chose MGB/OAGB as an operation with the possibility of complete restoration of the digestive tract, and with preoperative anamnestic data of cessation of alcohol consumption.

In psychiatric obese patients, the metabolic procedure should be carefully selected. MGB/OAGB is the ideal bariatric/metabolic procedure in this group of patients: completely reversible and can be easily reverted or "tailored" to the profound malabsorptive component, depending on the patient's habits after the operation. MGB/OAGB is a powerful operation with low mortality and low morbidity and is especially indicated in the psychiatric group of obese patients.

In conclusion, MGB/OAGB proved to be a successful bariatric procedure in our patient, leading to remission of depression and discontinuation of psychiatric therapy, as well as to a significant reduction in body weight, with a %EWL of 73.1% one year after surgery.

Conflict of interest: None declared.

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Мини/једноанастомозно желудачно премошћавање код гојазног болесника са депресијом

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САЖЕТАК

Увод Код гојазних болесника који се припремају за метаболичку операцију постоји релативно висока учесталост психијатријских поремећаја, нарочито депресије. Мини/једноанастомозно желудачно премошћавање баријатријска је процедура код које постоји могућност потпуног враћања односа у дигестивном тракту или продужења жучно-панкреасне вијуге уколико болесник почне да добија на телесној тежини.

Представљамо гојазног болесника са депресијом код кога је урађено прво мини желудачно премошћавање у Србији, са периодом праћења од једне године.

Приказ болесника Гојазном болеснику са телесном тежином од 144 килограма и индексом телесне масе 46,8 *kg/*m^2, као и депресијом као пратећим коморбидитетом, урађено је мини желудачно премошћавање са периодом праћења од једне године. Операција је урађена оригиналном техником уз присуство изумитеља процедуре и са некомпликованим постоперативним током. Болесник је престао да узима психијатријску или било коју другу терапију, потпуно је без тегоба и са радним и социјалним опоравком. После периода праћења од једне године изгубио је 49 *kg*, актуелни индекс телесне масе био је 30,9 *kg/m*^{2}, а проценат вишка губитка телесне масе 73,1%.

Закључак Код гојазних болесника са психијатријским обољењима метаболичка процедура се треба пажљиво одабрати. Мини желудачно премошћавање се показало као успешна баријатријска процедура код нашег болесника, што је довело до ремисије депресије и прекида психијатријске терапије, али и до значајног смањења телесне тежине у периоду од годину дана после операције.

Кључне речи: мини желудачно премошчавање; једна анастомоза; депресија; метаболичка процедура

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Monitoring of pregnancies with successful deliveries in a Niemann–Pick disease type B patient – case report and literature review

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SUMMARY

Introduction Niemann–Pick disease type B is an autosomal recessive disease caused by sphingomyelinase deficiency resulting in sphingomyelin accumulation in macrophages of various organs. Visceral involvement includes spleen enlargement, thrombocytopenia, dyslipidemia, sphingomyelin deposition in lung and liver, and bleeding risk. This is a rare disease and literature data about pregnancy in this setting are scarce. We present two favorable pregnancy outcomes in a patient with Niemann–Pick disease type B along with the review of the literature.

Case outline At the time of the first intended pregnancy, the patient was 34 years old. She had an extremely enlarged spleen, mild restrictive pulmonary disorder, hyperlipoproteinemia type IIb, thrombocytopenia with impaired aggregation tests. Cesarean section was indicated. She was prepared for delivery with platelet concentrates and prophylactic use of antibiotics. In the 36th week of gestation, a Cesarean section without complications was performed. The newborn's anthropometric parameters were BW 2490, BL 47 cm, HC 32 cm, and Apgar score was 7/8. The infant's development was normal. Three years later, in the second wanted pregnancy, the same examinations were done. The planned Cesarean section was done without complication after the same procedures, including prophylactic use of antibiotics and platelet concentrates, and a healthy female child was born.

Conclusion A multidisciplinary approach in female patients who suffer from lysosomal storage disease such as Niemann–Pick disease type B is essential and a favorable course is possible despite all risks.

Keywords: lysosomal storage diseases; platelet aggregation; splenomegaly; histiocytes

INTRODUCTION

Niemann–Pick disease type A and B are rare autosomal recessive diseases with an incidence of 0.4–0.6 per 100,000 newborns [1]. It is caused by sphingomyelinase deficiency resulting in sphingomyelin accumulation in macrophages of various organs. Niemann–Pick disease type C is a distinct disorder. Usually, in type B there are no neurological findings and patients survive in adulthood. Visceral involvement includes spleen enlargement, thrombocytopenia, dyslipidemia, sphingomyelin deposition in the lungs and the liver causing functional impairment and bleeding risk [1–5]. Pregnancy in this condition is always risky and a multidisciplinary approach is needed. Medline search revealed only three case reports of childbirth by women with this condition [6–8], and one with fatal postpartum hemorrhage [9].

CASE REPORT

We present two consecutive pregnancies in a 34-year-old woman with Niemann–Pick disease type B. Disease was suspected when she was 15 months old and splenectomy was suggested to her parents, but they refused it. A hematologist was consulted during the second hospitalization when the patient was 13 years old. She had abdominal pain after a minor trauma and an ultrasound examination revealed an enlarged spleen, which reached the pelvis and left lobe of the liver, without signs of injury. Bone marrow aspiration was performed and foam histiocytes and sea-blue histiocytes were seen. She started to visit a hematologist occasionally when she was a 23-year-old woman. A bone marrow biopsy was done and histology revealed hypocellularity, mild fibrosis, and groups of large cells with more stained cytoplasm, but there were no clear criteria for Niemann–Pick disease. Enzyme activities in cultured skin fibroblasts

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were determined at Universitätsklinik für Kinder und Jugendheilkunde in Graz, Austria. Clear deficiency of acid sphingomyelinase was detected and Niemann–Pick disease has thus been proven at the age of 23 years.

Before the intended pregnancy at the age of 34, marked splenomegaly, mild thrombocytopenia, and partial respiratory insufficiency were documented. According to her medical history, she had had two artificial abortions without recorded complication. She underwent inguinal hernioplasty at the age of 32, with postoperative bleeding that required platelet transfusion. Risk factors for pregnancy were presented to her: uterus pressure on the spleen and vice versa – spleen pressure on the uterus, potential for the worsening of respiratory symptoms, pressure on blood vessels, infection and hemorrhage, lower possibility that a child could carry the same disease according to recessive pattern of inheritance, and a realistic possibility for the fetus to have growth restrictions due to reduced space in the uterus. Hence, the patient decided to continue the pregnancy. Physical and laboratory findings were monitored monthly, and ultrasound examinations of the abdomen and portal vein system, lung capacity and echocardiography were done every three months. Results of complete blood count were stable, with mild anemia and platelet count 80–90 × 10^9/l. Repeated tests of hemostasis (fibrinogen, thrombin time, prothrombin time, activated partial thromboplastin time, fibrinolysis, D-dimer) were normal, while bleeding time was eight minutes (Ivy reference range being 2–7 minutes). Hyperlipoproteinemia type IIb with hypo-HDL cholesterolemia was present: cholesterol 5.8 mmol/l (2.6–5.2), triglyceride 2.38 mmol/l (0.1–1.7), HDL cholesterol 0.72 mmol/l, (1.6–3.88), Fried; LDL 4 mmol/l (2.07–3.4), non-HDL 5.08 mmol/l (0–3.86), LDL/HDL 5.55 (0–3), non-HDL/HDL 7.06 (0–3.25), cholesterol/HDL 8.06 (0–4.5). Platelet function test was performed prior to planned amniocentesis, revealing pathological findings, platelet aggregation was below lower limit: adenosine diphosphate 43 U (55–117), thrombin receptor-activating peptide 71 U (92–151), col. 30 U (61–108). Also, ultrasound examination of the abdomen and portal vein system was done: anteroposterior diameter of the liver was 17 cm, craniocaudal diameter of the spleen 22 cm, portal vein was not noticed. There were no signs of thrombosis in portal branches, flow speed was around 0.2 m/s. Platelet concentrates were reserved during the amniocentesis, but intervention was done without complication and there was no need for substitution. Normal male karyotype was found, but we had no possibility of genetic analyses for Niemann–Pick disease or enzyme activity measurement and the patient was given information that this result does not exclude the possibility that the child carries the same disease. We decided to prepare the patient for the planned Cesarean section with platelet concentrates. She was given corticosteroids for maturation of the fetal lungs. In the 35th + 5d gestational week Cesarean section was performed, with seven concentrates of platelets (1 per 10 kg of body weight) given before and seven during the procedure. She also received antibiotic prophylaxis. Newborn's anthropometric parameters were as follows: body mass 2490 g, body length 47 cm, head circumference 32 cm, and Apgar score was 7/8. There was no major blood loss and no need for red blood cell transfusion or transfusion of platelets in our patient's follow-up period. Three years later, she came to a hematologist in the sixth month of the second wanted pregnancy and the same examinations were performed. There was no sign of health deterioration in comparison with the previous pregnancy. A planned Cesarean section was done without complication after the same procedures, previously described, including prophylactic use of antibiotics and platelet concentrates before surgery, and a healthy female child was born. Infant development was normal in both cases.

The report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of the case report.

DISCUSSION

As aforementioned, Niemann–Pick disease is a rare disease and in clinical settings every health issue in these patients is challenging and searching for published data and learning from other's experience is mandatory. We decided not to do a splenectomy or partial resection of the spleen as spleen measurements did not differ significantly before and during the pregnancy, and there was no sign of spleen trauma. Also, we found the data about worsening of the lung function after this procedure in literature, caused by increased sphingomyelin accumulation in the pulmonary tissue [1–3, 10, 11]. We decided not to treat her for hyperlipoproteinemia because there is no proof about efficiency of that treatment in Niemann–Pick, and we tried to avoid potential elevation of liver enzymes [12]. Improvement in Niemann–Pick disease after injections of amniotic pooled placentas was described in literature and Porter et al. [6] mentioned improvement in liver function tests in their patient during pregnancy but without influence on hepatomegaly.

Searching on Medline we found only three reports of childbirth in women with Niemann–Pick disease type B. In the first one, published by Porter et al. [6], puerperal fever of unknown origin was observed, and according to the second one, Fried and Langer [7] used antibiotic prophylaxis. We decided to do the same due to our patient's splenomegaly and interstitial lung disease. In a case report published in 1997, the authors reported abnormal bleeding despite prophylactic treatment with vasopressin and need for blood and platelet substitutions [6, 7]. That data and findings of abnormal platelet function in our patient and experience with previous abdominal surgery led to our decision to give her platelet concentrates before the Cesarean section and according to the obstetrician's estimation during the operation. During the drafting of this work, we found a report of a fatal postpartum hemorrhage in a 23-year-old nulliparous woman with Niemann–Pick disease type B who concealed her disease from the obstetrician and her family [9]. In a study about cause of death in patients with Niemann–Pick disease type B, Cassiman et al. [13] reported that the main causes of deaths were respiratory and liver diseases, but hemorrhage was among the

leading causes and every patient who died of hemorrhage had splenomegaly and thrombocytopenia and half of them had liver disease or cirrhosis. Deaths associated with hemorrhage were reported after trauma, surgery, splenic vein tear, and gastrointestinal bleeding, and incidence was the same in patients who develop symptoms before and after the age of 18 years [13]. Due to a better diagnostic and supportive treatment and enzyme replacement therapy with olipudase alfa expected in the near future, other important issues come to horizon [14, 15, 16]. Prolonged survival and a better life quality are expected. Birth control in patients of reproductive age is another important issue and decisions about the type of contraceptives must be guided with their efficacy, metabolic effects and patient's adherence [17].

This case report emphasizes the importance of a multidisciplinary approach in female patients who suffer from lysosomal storage diseases such as Niemann–Pick type B and a favorable course is possible despite all risks [8]. Bleeding risk is not linked only to platelet count, but also to their function and the degree of splenomegaly. Liver impairment could exist and can influence hemostasis. Experience with previous pregnancies and invasive procedures in our patient along with the literature data influenced our treatment decisions. Pregnancies did not cause notable health deterioration in our patient and there are no clinical findings of Niemann–Pick disease or other significant health issue in children according to the pattern of inheritance of autosomal recessive diseases.

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NOTE

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Праћење трудноћа са успешним порођајима болеснице са Ниман–Пиковом болешћу тип Б – приказ болесника и преглед литературе

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САЖЕТАК

Увод Ниман–Пикова болест тип Б је проузрокована дефицитом сфингомијелиназе, што доводи до накупљања сфингомијелина у макрофагима различитих органа. Висцерални облик обично укључује присуство спленомегалије, тромбоцитопеније, поремећаја метаболизма липида, таложење сфингомијелина у јетри и плућима и повећан ризик од крварења.

Мултидисциплинаран приступ трудноћи код ових болесница је кључан. Ради се о реткој болести и подаци о трудноћи у овој ситуацији су изразито оскудни. Представљамо случај мултидисциплинарног праћења две трудноће са успешним порођајима болеснице са Ниман–Пиковом болешћу типа Б уз преглед литературе.

Приказ случаја У време прве жељене трудноће болесница је имала 34 године. Слезина је била изразито увећана, постојао је благ рестриктивни поремећај вентилације, хипер-липопротеинемија тип IIб, тромбоцитопенија с патолошким тестовима агрегабилности тромбоцита. Индикован је царски рез и болесница је припремљена концентратима тромбоцита уз профилактичку примену антибиотика. Оперисана је, без компликација, у 36. гестацијској недељи. Антропометријске мере новорођенчета су биле: ТМ 2490 *g* ТД 47 *cm*, ОГ 32 *cm*, Апгар скор је био 7/8. Три године касније у другој жељеној трудноћи урађени су исти прегледи и планирана секција без компликација, уз исте процедуре и припрему антибиотском профилаксом и концентратима тромбоцита.

Закључак Мултидисциплинаран приступ вођењу трудноће је неопходан код болесница са лизозомним болестима накупљања као што је Ниман–Пикова болест тип Б, а повољан исход је могућ упркос свим ризицима.

Кључне речи: лизозомне болести накупљања; агрегабилност тромбоцита; спленомегалија; хистиоцити

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Cesarean delivery under neuraxial anesthesia in a patient with a liver transplant

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SUMMARY

Introduction Improved outcomes after liver transplantation contribute to a successful pregnancy and delivery in transplant recipients. Anesthesiology teams face challenges when providing perioperative care to patients who have a liver transplant and undergo cesarean delivery, which include: an increased rate of cesarean delivery, a high risk of infection, and a high risk of interaction between immunosuppressant and anesthetic drugs.

Case outline We report the case of a 28-year-old patient with a liver transplant (from a live donor) who underwent elective cesarean delivery under neuraxial anesthesia. Appropriate anesthetic management is critical to ensure optimal perioperative maternal and fetal outcomes. Cardiovascular stability after neuraxial anesthesia was maintained with adequate perioperative intravenous fluid management and early vasopressor(s) administration to preserve hepatic perfusion. Multimodal postoperative analgesia was administered; however, caution is required when prescribing drugs that have the potential for hepatic and renal side effects.

Conclusion Multidisciplinary team evaluation, planning, and preparation are vital for optimizing safe care and delivery of pregnant patients with transplanted organs.

Keywords: anesthesia; cesarean delivery; liver transplant

INTRODUCTION

In 1967, the first successful liver transplant was performed at the University of Colorado in the United States, and the first successful pregnancy in a patient with a liver transplant was reported in 1978 [1]. The inaugural liver transplant in Serbia was performed in 1995 [2]. The liver is the second most commonly transplanted organ, with a one-year survival rate greater than 90% and a three-year graft survival rate of 80% [1]. Out of all liver transplant recipients, female patients of reproductive age represent 8%, and female children represent 5%, the majority of whom will reach reproductive age [3]. There are a few publications that describe the anesthetic management of cesarean delivery (CD) and labor analgesia management in patients who have undergone a liver transplant. This case report describes the first successful pregnancy and CD performed in a patient with a liver transplant in Serbia.

CASE REPORT

In 2015, a multidisciplinary team that included an anesthesiologist, obstetrician, hepatologist, and cardiologist provided care to a 28-year-old patient (G1P0) at 38 weeks gestation who underwent an elective CD under neuraxial anesthesia at Narodni Front Clinic for Gynecology and Obstetrics, Belgrade. The patient's past medical history included a living-donor liver transplant (donated by the patient's father) due to fulminant hepatic failure secondary to Wilson's disease nine years earlier. Nine months post-transplant, hepatitis B infection was diagnosed, and the patient received treatment with lamivudine (antiviral drug) which was replaced with tenofovir after several years due to seroconversion. The patient also received immunosuppressive therapy with tacrolimus and had stable serum levels and liver function tests (within normal limits) prior to and during pregnancy. The patient was American Society of Anesthesiologists classification 3 and had a body mass index of 22.1 (height 1.78 m, weight 70 kg).

Preoperative liver and kidney function tests were within normal limits, and the platelet count was 127 × 10^9/L (reference range 140–450 × 10^9/L). Two large-bore peripheral intravenous (IV) cannulas (16 G) were placed, and preoperative prophylactic drugs were administered, including ranitidine 50 mg IV, metoclopramide 10 mg IV, dexamethasone 4 mg IV and ceftriaxone 2 g IV. Preoperative vital signs were stable (blood pressure 149/89 mm Hg; heart rate 104 beats per min; oxygen saturation 98% (room air)), and a combined spinal-epidural anesthetic technique using the

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loss of resistance to saline was performed in the sitting position at the L3/4 interspace (Perican® 18G Tuohy needle, Pencan® 27G spinal needle, Perifix® 20G nylon epidural catheter, Espocan® docking system; B. Braun Medical Inc., Melsungen, Germany). Isobaric bupivacaine 12 mg, morphine hydrochloride trihydrate 200 mcg, and fentanyl 15 mcg were administered intrathecally using a needle-through-needle technique to produce a bilateral T4 dermatome sensory block to cold and sharp sensation. Vital signs remained stable post-neuraxial anesthesia, requiring only four doses of phenylephrine 50 mcg IV throughout the 22-minute surgery. A healthy male infant was delivered weighing 3150 g, with Apgar scores of 8 and 9 (at minutes one and five, respectively). Post-delivery, an oxytocin IV infusion was administered at 5 IU/h. The total fluid volume was 1500 mL of Ringer's lactate solution with an estimated blood loss of 500 mL.

Postoperative multimodal analgesia included acetaminophen 1 g IV (eight-hourly) and two 5 mL boluses of 0.25% bupivacaine with fentanyl 5 mcg/mL via the epidural catheter in the first 24 hours, which produced a visual analog scale score < 4/10.

Breastfeeding did not occur since there were no definitive recommendations regarding immunosuppressive therapy. Liver, renal, and platelet count results remained stable with no postoperative complications. The patient met discharge criteria on the second postoperative day (the minimum standard at Narodni Front Clinic), but discharge was delayed until the fifth postoperative day due to neonatal hyperbilirubinemia.

DISCUSSION

Liver transplantation can be a lifesaving treatment for patients with acute and chronic hepatic disorders, including end-stage liver disease, decompensated cirrhosis, acute liver failure due to Wilson's disease, or benign or malignant liver tumors [4, 5, 6].

Metabolic, endocrine, nutritional disorders, and sexual dysfunction associated with some hepatic disorders can contribute to infertility [7]. Increased estradiol and testosterone levels suppress the hypothalamic-pituitary axis, which leads to anovulation and amenorrhea [7]. In 90% of premenopausal patients, libido, menstruation, and fertility return by 6–10 months following successful liver transplantation [8, 9, 10]. However, persistent sexual dysfunction and *de novo* sexual dysfunction after transplantation are reported in men and women [8]. The American Association for the Study of Liver Diseases and the American Society of Transplantation recommend that pregnancy be delayed for at least one year following liver transplantation to ensure graft stability and function and to achieve immunosuppression at low maintenance levels [8, 11]. Therefore, liver transplant recipients should receive appropriate counseling for contraception and pregnancy planning [8, 11, 12].

Commonly administered immunosuppressive drugs include tacrolimus and cyclosporine (calcineurin inhibitors) with or without steroids [9]. While fetal/infant risk cannot be ruled out, the reported incidence of fetal malformations in liver transplant recipients is the same as in the general population, so these calcineurin inhibitors can be administered during pregnancy [9]. Due to the increased volume of distribution during pregnancy, an increased dose of immunosuppressant drug(s) is required (with regular monitoring) to avoid acute graft rejection [8, 13]. If the transplanted liver function is stable prior to conception, pregnancy itself should not cause graft dysfunction [7, 12, 14]. Graft loss within two years after delivery occurred among 1.4–1.9% of patients. There was no difference in short-term graft loss based on the mode of delivery [15].

Immunosuppression makes patients prone to infection, so close surveillance during pregnancy and the perioperative/peripartum period is prudent [8, 13, 16]. There are no recommendations regarding specific antibiotic prophylaxis [16]. It is unclear if antibiotics in the immunosuppressed transplant population would decrease the risk of infection [15]. In the case of hemorrhage requiring blood transfusion, leukocyte-reduced, and irradiated blood products are necessary to avoid leukocyte-related reactions, such as graft-versus-host disease [12, 16]. Blood product transfusion and sepsis were the most common factors associated with severe maternal morbidity in liver transplant parturients [15].

Published data suggest pregnancy is well tolerated, and favorable neonatal outcomes can be expected if graft function is stable prior to conception [7, 12]. However, pregnancy post-liver transplant is considered a high-risk pregnancy with increased maternal and fetal complications, including gestational hypertension, preeclampsia, premature labor, low birth weight, and fetal mortality [8, 9, 13, 17–21].

The rate of successful delivery among liver transplant women who attempted vaginal delivery was approximately 70%. There was no difference in maternal morbidity by mode of delivery, and of importance, the risk of graft loss within two years after childbirth was not associated with mode of delivery [15, 20]. In liver transplant recipients, successful vaginal delivery was associated with a lower composite neonatal morbidity rate [15, 20]. These findings are consistent with data from general population-based studies demonstrating an association of CD with increased rates of neonatal morbidity, primarily respiratory morbidity [20]. However, there is an increased incidence of CD in patients with a liver transplant versus non-transplant patients (45–68% *vs.* 24–32%, respectively, due to temporal changes in illness severity and/or patient and physician attitudes towards the mode of delivery [9, 15, 18, 22, 23]. Anesthesiologists must optimize labor analgesia and surgical anesthesia techniques when managing a patient with a liver transplant to preserve function [16].

Renal dysfunction after liver transplantation (prevalence 30–50%) is multifactorial and includes chronic exposure to calcineurin inhibitors, hypertension, diabetes mellitus, obesity, atherosclerosis, hyperlipidemia, chronic hepatitis C infection, pre-transplant renal dysfunction, and perioperative acute kidney injury [8].

Some liver dysfunction may remain post-transplant, so renal and hepatic drug metabolism and excretion should be considered [16]. Liver dysfunction may cause hepatopulmonary syndrome, characterized by portal hypertension, hypoxemia, and intrapulmonary shunting, so anesthesia could be life-threatening due to cardiovascular and/or respiratory instability [24].

Thrombocytopenia can persist in many patients for several years post-liver transplant due to the late resolution of splenomegaly despite improvement in portal blood flow [12]. With a normal coagulation profile, there are no contraindications to neuraxial labor analgesia or neuraxial anesthesia for CD, and epidural catheter removal should follow standard practice [13].

Standard prophylactic procedures to avoid post-neuraxial anesthesia hypotension, such as IV fluid pre- or co-loading and early administration of vasopressor(s), should be instituted, particularly due to the potential of an atypical response of the denervated liver allograft to stress [25]. The vasopressor of choice in patients with liver dysfunction is norepinephrine because it affects circulation through the splanchnic organs the least compared to vasopressin and epinephrine [26]. The normal compensatory mechanism of splanchnic blood volume being redistributed to the central circulation as a response to hypovolemia or blood loss is lost in liver transplant recipients. Furthermore, the hepatic blood flow autoregulation is also decreased, making the liver allograft more susceptible to hypoperfusion and hypovolemia [12, 27]. Transthoracic echocardiography is a good modality to monitor cardiac function and volume status (or transesophageal echocardiography during general anesthesia) [16].

With normal hepatic and renal function, there are no contraindications to standard anesthetic and analgesic drugs (including acetaminophen and nonsteroidal anti-inflammatory drugs); however, titration is advised because drug effects can be unpredictable [26]. Anesthetic and analgesic drugs with non-organ-dependent elimination (e.g., remifentanil, atracurium, or cisatracurium) are advised, and caution is recommended with depolarizing muscle relaxants (e.g., succinylcholine) in patients receiving calcineurin inhibitors or with renal dysfunction due to risk of hyperkalemia [12].

There are no published recommendations regarding breastfeeding in patients with liver transplants [8, 12, 10].

Multidisciplinary team management is recommended to optimize safe delivery planning for pregnant patients with transplanted organs. Neuraxial and general anesthesia techniques are safe in this patient population and should be individualized based on co-existing comorbidities, immunosuppression, and liver and renal function tests.

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Царски рез у неураксијалној анестезији код трудница са трансплантираном јетром

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САЖЕТАК

Увод Напредак у лечењу трансплантираних болесника омогућио је да све већи број болесница са трансплантираним органом успешно изнесе трудноћу. Анестезиолошки тимови се сусрећу са многим изазовима у збрињавању породиља које имају трансплантирану јетру, као што су: повишена стопа царског реза, висок ризик за развој инфекције и развој интеракција између имуносупресива и анестезиолошких лекова.

Приказ болесника Приказујемо извођење неураксијалне анестезије за елективни царски рез код 28-годишње труднице са трансплантираном јетром (од живог донора). Адекватан анестезиолошки приступ је пресудан како би се обезбедио оптимални периоперативни матернални и фетални исход. Одржавање кардиоваскуларне стабилности благовременом надокнадом течности и раном применом вазопресора је важно за очување адекватне перфузије јетре. Препоручује се мултимодални приступ у терапији постоперативног бола уз опрез приликом примене лекова са могућом хепатореналном токсичношћу.

Закључак Мултидисциплинарна евалуација, планирање и припрема су кључни за безбедни ток порођаја код трудница са трансплантираним органима.

Кључне речи: анестезија; царски рез; трансплантација јетре

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Basal cell carcinoma presented and mistreated as chronic venous ulcers – report of five cases

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SUMMARY

Introduction Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer in Caucasians and one of the most frequent malignancies in general, especially in older adults. Squamous cell carcinoma is the most frequent tumor developing on chronic leg ulceration, while BCC rarely occurs and is often misdiagnosed. In addition, since older adults commonly have coexisting chronic vein insufficiency, the ulcerated BCC is frequently mistaken as being of venous origin.

Outlines of cases We present five cases of BCC presenting as chronic venous ulcers.

Conclusion Long-lasting ulcers with no healing tendency must be considered malignant until proven otherwise. Knowing the characteristics of malignant ulceration may help in early detection and treatment.

Keywords: malignancy; skin cancer; ulcers; chronic vein insufficiency

INTRODUCTION

Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer in humans and one of the most frequent malignancies in general [1]. Although BCC is a slow-growing cutaneous cancer with a low rate of metastasis (0.0028% to 0.5%), if left untreated, it can cause extensive and deep tissue destruction [2]. It may be an ulcer or malignant transformation of existing chronic leg ulceration (CLU). Since the most common cause of CLU is chronic vein insufficiency (CVI), malignant CLUs are frequently misdiagnosed [3]. Early diagnosis prevents the development of giant forms of skin cancers and improves prognosis. Therefore, it is crucial to differentiate between malignant (either primary malignant or CLU that underwent malignant transformation) CLU and venous leg ulcers (VLU). In this article, we will describe five cases of BCC that were misdiagnosed as VLU and mistreated for years until finally diagnosed as skin cancers.

CASE REPORTS

We present five patients aged 75–82 years with non-healing ulcers of the lower legs, which were present 1–21 years. All the patients had coexisting CVI. The characteristics of patients are summarized in Table 1.

The first patient had a history of long-lasting CVI and excessive sun exposure without sun protection creams; he denied exposure to chemicals and any trauma of this region. Physical examination revealed an irregular bleeding ulcer on the anterior part of the left lower leg, with a granulated base filled with fibrin and raised edges (Figure 1A). Histopathology showed micronodular BCC (Figure 1B).

The second patient had no history of sun exposure and denied any trauma to the area. However, clinical examination revealed an ulcer on the anterior part of the right lower leg with a base filled with granulation tissue that formed elevated, translucent structures (Figure 2A). Biopsy showed nodulo-infiltrative BCC. The lesion was excised, and split-thickness skin graft placement was performed. In the follow-up period of 10 months, no recurrence was observed (Figure 2B).

The third patient had a history of type 2 diabetes mellitus and congestive heart failure. No record of sun exposure or previous trauma was reported. Physical examination showed an ulcer with flat edges and a transparent, granulated base (Figure 3A). The histopathological finding revealed nodular BCC. The lesion was excised, and split-thickness skin graft placement was performed. In the follow-up period of 10 months, no recurrence was observed (Figure 3B).

The fourth patient denied exposure to the sun or any trauma. Physical examination revealed an oval ulcer with raised edges on the left lower leg, above the lateral malleolus, filled with granulation tissue. No signs of inflammation were observed. Later, after one month on check-up, the ulcer became hyper granulated, and a biopsy was indicated (Figure 4A). Histopathological findings of edges and base showed infiltrative BCC (Figure 4B).

The fifth patient had a long history of CVI and a history of breast cancer. Physical examination revealed an oval ulcer with a clear, granulated base on the distal anterior part of

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Table 1. Summarized characteristics of the patients

Case	Age (years)	Sex	Duration of ulcers (years)	Diameter (cm)	Localization	Histopathology	Therapy
1	79	M	21	7 × 4	anterior part	Micronodular BCC	Excision
2	75	M	4	4.5 × 3.5	anterior part	Noduloinfiltrative BCC	Excision
3	82	F	5	2 × 2.5	anterior part	Nodular BCC	Excision
4	75	F	1	1 × 1.5	above the lateral malleolus	Infiltrative BCC	Excision
5	79	F	2	2 × 2	anterior part	Carcinoma basosquamosus	Radiotherapy + Excision

BCC – basal cell carcinoma; M – male; F – female; + – positive; - – negative

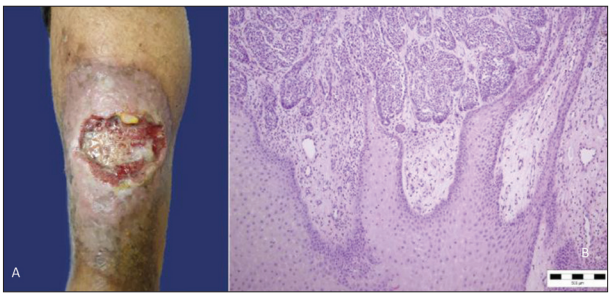

Figure 1. A: An irregular, bleeding ulcer located on the anterior part of the left lower leg; B: histopathology of the ulcer; H&E, 100 ×

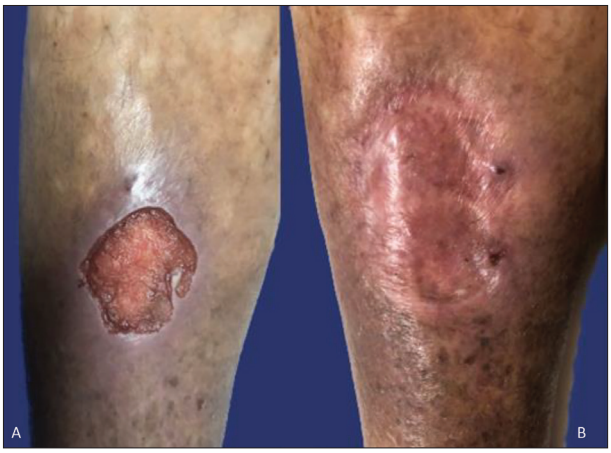

Figure 2. A: An ulcer with the base filled with granulation tissue that formed elevated, translucent structures; B: the ulcer eight months after reconstruction

Table 2. Differences between malignant and venous ulcer

Characteristics	Malignant ulcer	Venous ulcer
localization	atypical	medial malleolus
size	small (< 3 cm^2)	varying size
margins	elevated	sharp, irregular
depth	deep	shallow
base	soft pink granular tissue	fibrinous material

the right lower leg. The histopathological finding showed basosquamous carcinoma (Figure 5A). The patient was referred to the Oncology department and treated with radiotherapy. The ulcer showed central epithelization during radiotherapy, but small shallow ulcers covered with crusts on elevated livid edges have occurred (Figure 5B). This was highly suspected to be a cancer recurrence, so the patient was referred to the Department of Oncology for total excision of the lesion.

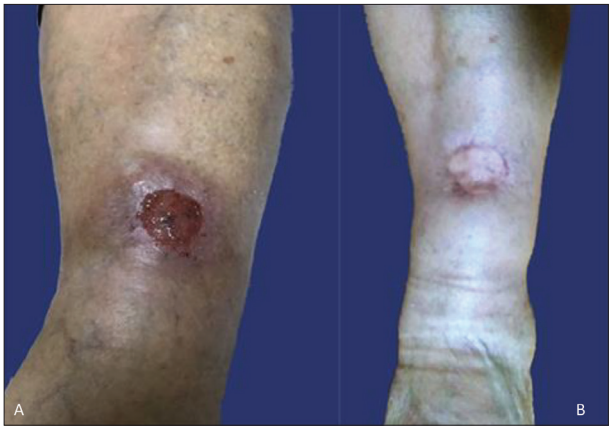

Figure 3. A: An ulcer with flat edges and a clear, granulated base; B: the ulcer eight months after reconstruction

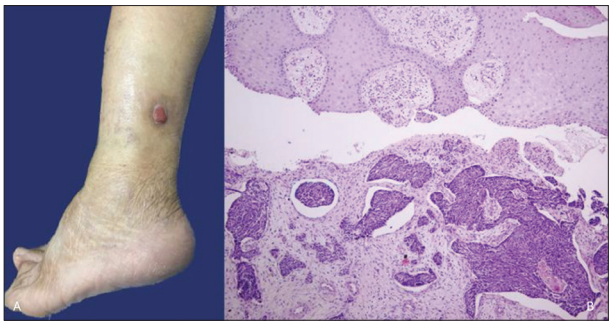

Figure 4. A: An oval ulcer on the left lower leg above the lateral malleolus filled with granulation tissue and with elevated livid edges; B: histopathological finding; H&E, 100 ×

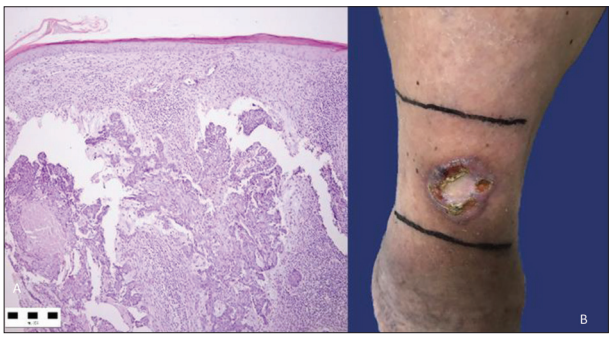

Figure 5. A: Histopathological finding before treatment; H&E, 100 ×; B: ulcer with central epithelization and small shallow ulcers covered with crusts on elevated livid edges

The patients have given written consent for the publication of this article. This study was done in accordance with the institutional committee on ethics.

DISCUSSION

Although BCC most commonly occurs on the head and neck, BCC occurs on limbs in approximately 3.3% of cases [4]. On extremities, BCC may present as a chronic leg ulcer [3]. Since older adults commonly have coexisting CVI, the ulcerated BCC may be mistaken for the venous origin. Besides cases of primary BCC of lower extremities, some articles also show the malignant transformation of existing VLUs [5–10]. The most common malignancy arising from non-healing chronic ulcers is squamous cell carcinoma (SCC), but a few cases of BCC are also described. In a retrospective study of 85 malignantly transformed ulcers, 98% were SCC, whereas just 2% represented BCC [5].

On the other hand, Yang et al. [9] recorded that 2.2% of reported leg ulcers were skin cancers – 75% BCC and 25% SCC. Their results also indicated that 2.4% of venous ulcers would undergo malignant transformation. Factors that promote this transformation are chronic inflammation and tissue proliferation due to long-lasting nature of the ulcer. Kirsner et al. [6] estimated that 1–7% of all chronic wounds would develop malignant properties; this number may be lower than real, primarily due to frequent misdiagnosis. Gil et al. [7] described some of the clinical features when CLU should be investigated in the direction of malignancy. Tchanque-Fossuo et al. [8] recommended taking biopsy samples of the edges and the base to rule out malignancy. Serial biopsies every 3–6 months of ulcers that do not tend to heal have been proposed by various authors [11, 12].

We have to point out that typical characteristics of chronic venous ulcers were absent in our patients. On the contrary, all patients had a history of long-lasting CVI. Furthermore, the study, which included 125 cases of BCC, found that 25% of patients had concomitant chronic venous stasis, suggesting a relationship between venous disease and BCC [13]. Since patients were initially treated in other institutions and no biopsies were performed in the early stages of lesions, we can only speculate if BCC in our patients resulted from malignant transformation of pre-existing ulcers or *de novo* lesions. However, a biopsy was performed at our institution, and histopathological findings were similar in all the patients, showing histopathological features of BCC.

Mohs micrographic surgery is the best management option for these cancers since it provides maximal margin control and minimal defect in the already compromised areas of stasis dermatitis and poor wound healing on the shins. Also, the procedure is performed under local anesthesia, with minimal impact on general health in older individuals, and is well tolerated in ambulatory settings. On the other hand, radiation therapy should be avoided in treating ulcerated BCCs, not just to avoid further compromise of already damaged vascularization in the area but also due to the risk of future cancerization and the appearance of new tumors in the treated skin, years post radiation therapy.

Long-lasting ulcers with no healing tendency must be considered malignant until proven otherwise. This article aims to point out the possible malignancy in chronic venous insufficiency. Carcinomas may mimic granulation tissue which can mislead the correct diagnosis. Atypical wound morphology, localization, and refractoriness to conventional treatments may suggest malignant transformation. Most of these ulcers are managed in primary care clinics, and only a minimal number of such ulcers are referred to the specialized tertiary clinic. The education of practitioners about the possibility of malignant transformation of chronic venous ulcers is essential. Further investigations are necessary to clarify the exact algorithm for diagnosing malignant ulceration.

Conflict of interest: None declared.

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Базоцелуларни карцином погрешно дијагностикован и лечен као хронична венска улцерација – приказ пет болесника

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САЖЕТАК

Увод Базоцелуларни карцином најчешћи је немеланомски кацином код припадника беле расе и један од најчешћих малигнитета генерално, нарочито код старије популације. Сквамоцелуларни карцином је тумор који се најчешће развија на терену хроничних улцерација, док се базоцелуларни карцином ретко јавља и често се погрешно дијагностикује. С обзиром на то да се код старије популације на доњим екстремитетима често јавља и хронична венска инсуфицијенција, егзулцерисани базоцелуларни карцином се често погрешно дијагностикује и третира као венска улцерација.

Приказ болесника Приказујемо пет болесника са базоцелуларним карциномом доњих екстремитета, са клиничком презентацијом хроничних венских улцерација.

Закључак Улцерације које дуго трају без тенденције зарастања морају се схватити као малигнитет, док се не докаже супротно. Познавање карактеристика малигне улцерације може помоћи у раној детекцији и лечењу.

Кључне речи: малигнитет; карцином коже; улцерације; хронична венска инсуфицијенција

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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Challenges and suggestions for healthcare insurance of internal migrants in China

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SUMMARY

With its rapid social and economic development, China's medical and healthcare services are also continually evolving. At present, China's medical and healthcare field mainly comprises two aspects: service institutions and insurance systems. Healthcare insurance refers to the basic security system that provides medical services to the population and pays part of their remedial expenses by rationally organizing financial resources. It is not only a safety net but also a social stabilizer for the population. It is also an important part of China's medical and healthcare reform. Internal migrants are those who do not belong to the household registration system within a city's jurisdiction and constantly move between districts. They primarily include temporary residents, people in transit and registered tourists. The main purpose of healthcare insurance is to meet the needs for medical funds in line with the current level of economic development. In short, it is a basic security system that grants people access to a doctor, regardless of their income. However, since internal migrants move between districts, it can be difficult to guarantee their healthcare insurance. Healthcare service needs of the internal floating population are constantly growing, but the coverage of remedial services provided by medical insurance is still not comprehensive, and the guarantee is not sufficient. We should solve the medical security problem of the internal floating population by improving the measures of transferring medical insurance, implementing a more reasonable medical insurance system for employees, lowering the threshold for participation and expanding the scope of assistance.

Keywords: healthcare insurance; internal migrants; research progress

INTRODUCTION

China has built a relatively complete healthcare insurance network covering urban and rural areas per its economic and social development needs [1]. Its security expenditure and level have been continuously improving, meeting the country's current economic and social development needs. At the same time, however, the development of China's healthcare insurance is facing many problems, especially with internal migrants [2]. Internal migrants are individuals who move within the borders of a country, usually measured across regional, district, or municipal boundaries, resulting in a constant change of residential places [3]. Most of China's internal migrants are rural, and the level of healthcare insurance for countryside migrants is usually relatively low. Some scholars have suggested that, since the mid-1990s, the health problems of the domestic rural internal migrants have been the main focus and challenge for medical and health work. Domestic immigrants are usually difficult to manage. Some areas still encounter difficulties and unfairness in that the new rural cooperative medical system cannot work, the management of premium payment is not perfect, and the health status of low-income individuals is even worse [4]. Because of this, the rights of internal migrants in the labor market and social security have increasingly attracted the attention of scholars [5].

This article will analyze the current status of internal migrants' healthcare insurance in China and propose specific measures to deal with the present challenges for the medical coverage of this population.

ANALYSIS OF THE CURRENT MEDICAL SITUATION OF THE INTERNAL MIGRANTS IN CHINA

The demand for delivering healthcare services to internal migrants in China has increased

Leng and Zhu [6] stated that basic public health services are a major institutional way for China to deepen medical and health system reform and promote the Healthy China 2030 strategy. Population mobility is the most critical, yet the weakest, link in the current public health service system. According to data from the Seventh National Population Census, the internal migrants in 2020 were nearly 380 million, 150 million more than that in 2010 (data source: National Bureau of Statistics of China, 2020) [7]. With the rapid progress of China's urbanization process, this population is increasing substantially.

Domestic immigrants face many uncertainties and risks in spatial mobility, among which health risks are the most prominent. Domestic

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migrants are usually healthier than their urban counterparts in the initial stage of their stay. However, due to the generally low education level and lack of professional and technical skills, most of them are engaged in occupations with long working hours and poor work environments, alongside poor living standards. Their health is threatened by infectious, occupational, and psychological diseases, and their health advantages change into disadvantages [8].

Insufficient utilization of healthcare services for internal migrants in China

Although China's current healthcare insurance system is relatively complete, the number of people participating in medical insurance exceeds 95% of the total population and a basic low-level, wide-coverage medical system has been implemented, there are still significant variations in the healthcare insurance of internal migrants in different regions [9, 10]. Most of the internal migrants are young or middle-aged and have strong adaptability. Their physical condition is generally better than that of the urban resident population from both subjective and objective perspectives. Their main health problems are the common cold, infection, and other general illnesses. However, the proportion of elderly internal migrants is still around 7.2% [11], and chronic ailments that are common in the elderly, such as hypertension, diabetes, and coronary heart disease, cannot be ignored. In addition, extensive research shows that internal migrants, which are mainly a rural population, have a higher risk of developing infectious diseases [12]. Due to the limited economic and health conditions of this population, some serious infectious diseases may be latent before an infected person moves into a city or town. Furthermore, when an internal migrant sees a doctor, his/her illnesses are usually treated uniformly, and the treatment is less targeted. A majority of this population do not take corresponding treatment measures until they get sick, causing their health problems to become more serious. Therefore, internal migrants usually have a high demand for remedial services, but their medical needs are often not met [13].

Current problems in the healthcare insurance of the internal migrants

According to relevant reports, 60.9% of the internal floating population have long-term residence intentions [14], and medical insurance will play an important role in safeguarding their multi-stage healthcare rights and interests. Therefore, we should not only pay attention to the participation rate of medical insurance for the internal floating population but also fully consider the diversity and convenience of healthcare service needs of special groups, such as pregnant women and seriously ill patients.

The participation rate of internal migrants is relatively low

China is still a developing country and has a large informal sector [15]. In addition to the employees of private and public industrial and commercial businesses, the informal sector is mostly composed of unregistered employees, such as stall vendors and hourly workers [16]. Their employment scale is often small, and their income is unstable. Even though most migrant workers are employed, companies do not sign formal labor contracts with them, and their salaries and basic security differ from those of regular employees. Because the insurance relationship is not portable, the payment period is long and the burden on enterprises is heavy, there is no effective supervision, and, at the same time, it is difficult for employers to provide them with basic medical insurance on their initiative, which is one of the main problems of medical insurance for internal migrants in China [17].

Except for private and self-employed employees, the informal sector is mostly composed of unregistered employees, such as stall vendors, babysitters and part-time workers. They are unorganized and have an unstable income, making it difficult to get them to participate in insurance. The income of China's internal migrants is also generally low, and most of them are poor. The inequality between migrant workers and urban citizens is particularly significant, and the high threshold of urban medical insurance hinders insurance access for low-income internal migrants [10].

Qin Xuezheng and Chen et al. [18] used the employment and healthcare survey data of migrant workers in Beijing in 2011 to study the pull-back and absorption effects of migrant workers' employment. The results showed that the internal migrants were more inclined to participate in the new rural cooperative medical system, which only costs tens of yuans a year, than in the basic remedial insurance for urban employees, which charges thousands of yuans annually. In addition, Tang [19] stated that the insurance participation rate of migrant workers in China is relatively minimal due to contradictions between the high mobility of migrant workers and long payment years of medical insurance, low disposable income and elevated cost of medical insurance and little expected income from medical insurance benefits and high actual payment.

Internal immigrants have some difficulties in using medical insurance

Furthermore, even the insured internal migrants still encounter problems, such as cross-provincial and remote medical treatment [20]. Previously, the medical insurance reimbursement in China was that, if the insured sought remedial treatment in a medical institution outside the overall planning area, the medical insurance fund could not be settled in real time, and the individual could only pay in advance and then return to the insured place for repayment [21]. With China promoting the direct settlement of non-local remedial treatment and hospitalization costs, it has achieved real-time payment of hospital expenses for non-local medical treatment personnel – in July 2020, the payment proportion of inter-provincial direct settlement funds for hospital expenses was 58.6% – but the charges for ordinary outpatients and outpatient serious diseases still cannot be reimbursed by the medical insurance fund

[22]. Notably, migrants of childbearing age were five times less likely than residents to attend antenatal check-ups and three times less often to see a doctor after delivery or receive health education during pregnancy [23].

Previously, internal migrants mainly sought migration from rural areas to cities to pursue economic improvement. However, in recent years, the rural internal migrants have tended to be based on urban development, and the mobility of this population has changed from temporary stay to permanent residence. Therefore, to ensure that their medical needs are met, it is necessary to improve the healthcare insurance system for internal migrants [24].

Countermeasures and suggestions for improving healthcare insurance of internal migrants

To effectively solve the issues of healthcare insurance for China's internal migrants, the current problems need to be addressed at their roots. This paper puts forward suggestions, based on previous research and China's development and needs, to address these problems on three levels: national (state), corporate, and institutional.

Relevant systems for delivering the basic healthcare insurance of internal migrants need improvements at the national level. Since internal migrants usually seek jobs across urban and rural areas, in different regions and across various systems, the connection of their medical insurance has always been a serious problem. Xiao [25] stated that the operation of China's basic insurance system is constrained by its inability to coordinate urban and rural areas and by the fragmented management of medical cover funds; furthermore, the incapability to smoothly connect basic remedial coverage in various regions has become an important factor hindering labor mobility. As internal migrants are eager to receive medical protection from governments in their inflow and outflow areas, the efficient connection of basic remedial insurance in different regions is particularly critical. In addition, China's medical insurance system has different standards, diverse management methods and uneven remedial coverage levels, which is not helpful to the mutual transfer of health protection between regions. To ensure that internal migrants can be continuously enrolled in basic medical insurance during their employment, relevant national departments should consider local conditions and issue specific implementation measures and operating rules for efficient medical insurance relationships; this will avoid repeated enrolment or failure to participate in insurance in time.

The protection level of the new rural cooperative medical insurance also needs improvement. The current level of security for this system is still of a low standard [26]. Due to significant differences in economic development between urban and rural areas, the security for the new rural cooperative medical system is relatively limited. Considering that internal migrants are more inclined to participate in the new rural cooperative medical insurance, it is necessary to improve its level of protection. Small medical subsidies and healthcare insurance must be considered when solving the most basic healthcare coverage problems for insured personnel, and serious illness medical insurance should be given attention to overcome the issue of people returning to poverty due to sickness [27].

Another solution on a national level is to implement an incentive mechanism for medical treatment among internal migrants. Establishing a division of labor and a cooperation mechanism among different levels and categories of healthcare institutions is one way to deepen medical reform to carry out graded diagnosis and treatment [28]. Therefore, incentive mechanisms, such as initial consultation with internal migrants at a grassroots level and the priority settlement of chronic disease treatment costs in community clinics, can be used to create order for medical therapy in different places among internal migrants.

Finally, proficiently integrating the medical insurance system is realized through efficient national medical insurance.

Businesses should implement the internal healthcare insurance system for every employee at a company level. Corporates should treat residents and members of the internal migrants fairly, sign formal labor contracts uniformly, and purchase the same medical insurance for all employees, thereby ensuring the basic healthcare protection rights of all members of the workforce, including the internal migrants.

The basic responsibility of medical and health service organizations is to provide treatment and rescue services for patients. At present, the proportion of the floating population without medical insurance in China is relatively high. If an internal migrant suffers from a serious disease, he/she may not be able to afford the medical expenses; furthermore, the basic healthcare insurance services given to some migrant workers may not be enough to meet their current remedial needs. Medical and healthcare service institutions should coordinate and cooperate with financial, health and relevant administrative departments to provide medical assistance for uninsured or poorly insured internal migrants, formulate relevant assistance policies and systems and establish more perfect and inclusive medical assistance funds. At the same time, to create a safety net for the basic medical protection of internal migrants, the threshold for implementing assistance should be appropriately lowered, and the scope and standard of assistance should be increased.

CONCLUSION

The new generation of internal migrants in China aims to not only survive but also develop in urban areas, which will call for special medical services – such as childbirth and old-age care – that are no longer satisfied with basic remedial and healthcare services. However, at present, there are still difficulties in medical insurance, such as imperfect payment systems for some occupations, unsmooth settlements in various places, and heavy burdens on low-income people, which lead to internal migrants not being able to enjoy medical care in the inflow areas and their health level being reduced. It is expected that internal migrants' medical security problem can be solved by improving the

transfer and connection measures of remedial coverage, enhancing the payment system of employee medical insurance, lowering the threshold of participation, and expanding the scope of assistance.

New knowledge added by the study

- The current status of the floating population's medical security in China was analyzed.
- Because internal migrants constantly move between districts, it can be difficult to ensure their medical security.
- Specific measures to deal with the current challenges for the medical security of this population were proposed.

Implications for clinical practice or policy

- To better adapt to the current development trend of the domestic migrant population, the establishment of a healthcare insurance system for this group should be fully integrated with related disciplines, and, at the same time, the exploration of system-related theories should be encouraged.

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Изазови и сугестије за здравствено осигурање унутрашњих миграната у Кини

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САЖЕТАК

Са брзим развојем социјалне економије, кинеске здравствене услуге се стално развијају. Здравствени сектор у Кини тренутно углавном укључује два аспекта: институције и осигурање. Медицинско осигурање се односи на основни гаранцијски систем који пружа медицинске услуге људима и плаћа делимичне медицинске трошкове кроз рационалну организацију финансијских ресурса. То није само сигурносна мрежа већ и социјални стабилизатор за популацију. Такође је важна компонента реформе здравствене заштите Кине. Унутрашња миграција се односи на људе који не спадају у систем здравствене заштите домаћинстава на нивоу града и често се крећу између региона. То су углавном привремени становници, људи у транзиту и регистровани туристи. Главна сврха медицинског осигурања је испуњавање захтева за медицинске трошкове на тренутном нивоу економског развоја. Укратко, ово је основни сигурносни систем који омогућава људима приступ услугама доктора без обзира на њихов приход. Међутим, због мобилности домаћих миграната између различитих регија, тешко је осигурати њихово медицинско осигурање. Захтев за здравствене услуге за домаћу мигрирајућу популацију стално расте. Постојеће медицинско осигурање пружа ограничене услуге и недовољну заштиту за ову групу људи. Морамо побољшати мере медицинског осигурања, спровести разумнији систем медицинског осигурања, смањити праг за учествовање, проширити област помоћи и решити проблем медицинске сигурности за унутрашње мигранте.

Кључне речи: здравствено осигурање; унутрашњи мигранти; напредак истраживања

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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Endodontic glide path – importance and performance techniques

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SUMMARY
Glide path is a procedure that precedes mechanical instrumentation of the root canals. It is defined as a procedure used to expand or create a smooth tunnel from the coronal part of the root canal to its physiological terminus. It is performed using small-size hand files or specially designed mechanical NiTi instruments. An adequately created glide path extends the life of rotary NiTi instruments, enables better mechanical and chemical debridement and easier preservation of original morphology of endodontic space during further mechanical instrumentation.
Frequent use of mechanical instrumentation in daily practice requires better understanding of the glide path, its significance, and instruments and techniques used for its creation.
Keywords: glide path; hand K-files; rotary NiTi instruments

INTRODUCTION

Modern endodontic therapy involves mechanical instrumentation of root canals with instruments made of nickel-titanium (NiTi) alloy, in accordance with modernized and adapted procedures based on Schilder's principles [1]. Due to superelasticity and unique design, NiTi rotary files enable more efficient and predictable cleaning and shaping of the root canals with less possibility of procedural errors when compared to manual instruments [2, 3, 4].

Nevertheless, flexural, and torsional stresses, especially in curved canals, may result in unexpected fractures of NiTi instruments during clinical use [1, 2, 3]. New techniques and instruments have been introduced to overcome this problem [5]. Special attention has been paid to the creation of the glide path, a procedure that precedes mechanical instrumentation, with the aim of reducing cyclic fatigue or torsional stress and safer use of NiTi rotary files during further shaping and cleaning of the canals [6, 7, 8].

However, the concept of glide path preparation in many endodontic schools is not clearly defined. Most world schools of dentistry do not include glide path preparation training in its courses.

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GLIDE PATH – DEFINITION

The first definition of the term 'glide path' was given by West [9] in 2010, explaining that "the glide path is a smooth radicular tunnel from the coronal orifice of a root canal to the physiologic terminus (apical constriction)." Ruddle et al. [10] redefined this term as "clinical procedures to expand or create a smooth tunnel from the coronal part of the root canal to its physiological terminus before its final enlargement, aiming to control torsional stress and reduce the odds of NiTi instruments fracture." Berutti et al. [11] and Patiño et al. [12] used the term 'micro glide path' for initial scouting/exploring and apical patency of the canal with small precurved stainless steel files using gentle watch-winding movements. In case of curved and obliterated canals, further enlarging is necessary, with manual or specially designed NiTi instruments, in order to create a 'macro glide path' [11, 12].

SIGNIFICANCE OF THE GLIDE PATH

With the introduction of mechanical NiTi instruments into endodontic practice, the glide path gains special importance. Blum et al. [13] first proposed the formation of a smooth glide path using small flexible stainless steel hand files to facilitate the application of rotary NiTi endodontic instruments.

Berutti et al. [11] and Patiño et al. [12] observed that creating the glide path with hand files leads to a reduction in torsional stress and cyclic fatigue of rotary instruments. The formation of the glide path contributed to an increase in the average life of mechanical files almost six times and a drastic reduction in the risk of file breakage [11–14].

The glide path improves mechanical and chemical debridement, creating space for instruments and irrigants to process and disinfect endodontic space more easily and efficiently [7]. Glide path enables conical instrumentation

Table 1. Manual glide path instruments

Name (company)	Alloy	Design (cross section)	Sizes (ISO)	Motion (movement)
K-file (Kerr)	Stainless steel	Square	6, 8, 10, 15, 20	0.6–15 clockwise 20 combined clockwise and balanced force
C file (Dentsply/Tulsa)	Special thermal hardening steel	Twisted file	6, 8, 10	Clockwise
C+ file (Dentsply/Maillefer)	Special thermal hardening steel	Square	6, 8, 10, 15	Clockwise
D finder (Mani)	Stainless steel	D-shaped	8, 10, 12, 15	Clockwise
Hi-5 file (Miltex)	Stainless steel	Pentagon	6, 8, 10, 15	Clockwise
Pathfinder CS (SybronEndo)	Stainless steel	Square	7 (K1) 9 (K2)	Clockwise
S finder (JS Dental)	Stainless steel	Incomplete circle with two parallel straight edges	8	Clockwise
C-Pilot files (VDW)	Special thermal hardening steel	Square; inactive Pilot tip	6, 8, 10, 12.5, 15	Clockwise
FlexoFiles (Dentsply/Maillefer)	Stainless steel	06–10 square; 15–20 triangular	6, 8, 10, 12, 15, 17, 20	Clockwise
Senseus FlexoFiles (Dentsply/Maillefer)	Stainless steel	06–10 square; 15–20 triangular	6, 8, 10, 15, 20	Clockwise

ISO – International Organization for Standardization

while preserving the original position of apical foramen, so 3D obturation is more certain [8, 15, 16].

Numerous studies have indicated reduced extrusion of apical debris if glide path creation preceded mechanical instrumentation [16, 17, 18]. Detritus extrusion into periapical tissue negatively affects the success of endodontic therapy, consequently leading to postoperative pain and persistent inflammation [19].

Glide path significantly contributes to easier preservation of original morphology of the endodontic space in all aspects (curvature, volume dimension, and centering) during mechanical instrumentation [15–19].

Thus, the importance of the glide path is primarily in increasing the safety and efficiency during the use of rotary NiTi instruments in the following stages of endodontic therapy [6, 7, 8, 12, 20].

THE SIZE AND SHAPE OF THE GLIDE PATH

Properly created glide path faithfully reflects the appearance of original morphology of the root canal, and can be short or long, narrow, or wide, straight, or curved [10].

For efficient and safe preparation of root canals, it is very important to establish adequate glide path dimensions. The minimum size of glide path according to West [9] is ISO 0.10. More precisely, after the formation of the glide path, the dimensions of the canal should correspond or be one size larger than the size of the tip of the first NiTi rotary instrument used for canal instrumentation [11]. This facilitates application and activation of rotary, extremely flexible NiTi instruments that usually have a non-cutting tip [21].

GLIDE PATH PREPARATION TECHNIQUES

The creation of a glide path can be realized with manual or mechanical instruments.

The use of hand files with smaller diameter is a standard, long-standing procedure that maintains better tactile sensation, less possibility of instrument fracture and easier overcoming of canal obstructions. Due to the retention of shape after removal from the canal, the hand files provide information to the operator about the curvature and complexity of the canal [22].

Apart from K-files, which are the instruments most commonly used for initial patency and creation of the micro glide path, other hand instruments can also be used (Table 1).

Disadvantages of manual techniques are hand fatigue, fatigue of the operator, longer duration of procedure, risk of procedural errors, greater chances for changing original canal anatomy and increased apical extrusion [14].

In order to avoid errors of a manually created glide path, special and innovative mechanical NiTi instruments are being introduced. Those instruments were launched for the macro glide path and the first system appeared in 2009 (PathFiles, Dentsply Sirona, Charlotte, NC, USA) [7].

Mechanical glide path instruments with their basic characteristics and methods of application are presented in Table 2 [8].

The first mechanical glide path systems were made from a conventional, austenitic, superelastic alloy with full rotation activation, and were suitable for preparation of straight or slightly curved canals. Instruments with different dimensions and conicity were also launched [14].

Glide path systems were further developed with the aim of reducing the number of instruments, which decreases the possibility of errors and significantly speeds up the procedure [7, 8]. Also, the emergence of new technological solutions, design modifications and transformation of conventional NiTi alloy and different thermal treatments led to the optimization of microstructure and resistance to cyclic fatigue of glide path instruments [20, 21]. The improvement of cutting efficiency, passability and flexibility of glide path systems (especially in curved canals)

Table 2. Mechanical glide path instruments*

Name (company)	Alloy	Sizes (ISO) Taper	Speed and torque	Method of use
PathFiles (Dentsply Sirona)	NiTi	1–13, 2% 2–16, 2% 3–19, 2%	CR 300 rpm 5 N/cm	Used in sequence after hand file ISO 10
RaCe ISO 10 (FKG Dentaire)	NiTi Electrochemical polishing	1–10, 2% 2–16, 4% 3–10, 6%	CR 600–800 rpm 1.5 N/cm	Used in sequence after hand ISO 06 and 08
ScoutRaCe (FKG Dentaire)	NiTi Electrochemical polishing	1–10, 2% 2–15, 2% 3–20, 2%	CR 600–800 rpm 1.5 N/cm	Used after estimated working length with hand ISO 06 - 08
G-Files (Micro-Mega, Besançon, France)	NiTi	G1–12, 3% G2–17, 3%	CR 250–400 rpm 1.2 N/cm	Used in sequence after hand file ISO 10
ProGlider (Dentsply Sirona)	NiTi M-Wire	1–16, progressive tapers 2–8%	CR 300 rpm 2–5 N/cm	Used after estimated working length with hand file ISO 10
Instrument One G (Micro-Mega)	NiTi	1–14, 3%	CR 250–400 rpm 1.2 N/cm	Used after estimated working length with hand file ISO 10
X-Plorer Canal Navigation NiTi Files (Clinician's Choice Dental Products Inc.)	NiTi	1–15, 1% 2–20, 1% 3–20, 2% 4–25, 2%	CR 400 rpm 2 N/cm	Used after estimated working length with hand file ISO 8 or 10
Hyflex Glide Path File Sequence (Coltene)	1-NITi 2&3 NiTi CM-Wire	1–15, 1% 2–15, 2% 3–20, 2%	CR 300 rpm 1.8 N/cm	Used after estimated working length with hand file ISO 10
Hyflex EDM Glide Path (Coltene)	NiTi CM-Wire EDM process	10, 5%	CR 300 rpm 1.8 N/cm	Used after estimated working length with hand file ISO 10
PathGlider AK03 (Komet, GmbH)	NiTi	15, 3% 20, 3%	CR 300 rpm 0.5 N/cm	Used after estimated working length with hand file ISO 10
R-Pilot (VDW)	NiTi M-Wire	12.5, 4%	Reciprocating motions at Reciprocating settings	Used after estimated working length with hand ISO 06 and 08
WaveOne Gold Glider (Dentspli Sirona)	NiTi Gold heat treated	15, variable tapers from 2%	Reciprocating motions at WaveOne settings	Used after estimated working length with hand file ISO 10

*Modified table of Ajina et al. [8];
ISO – International Organization for Standardization; NiTi – nickel titanium conventional alloy; M – memory NiTi alloy; CM – controlled memory NiTi alloy; EDM – electrical discharge machining NiTi alloy; CR – continuous rotation

was achieved by manufacturing instruments from a martensitic alloy [23, 24].

Different activation techniques of glide path instruments (full rotation or reciprocating motion) were introduced with the aim of improving blade efficiency and resistance to cyclic fatigue. Studies have shown that an increase in resistance to cyclic fatigue is influenced by advanced metallurgical solutions as well as the kinematics of movement [17–20, 23, 24, 25]. The researchers point out that instruments activated by reciprocating motion have a higher resistance to cyclic fatigue since they are exposed to lower stress compared to instruments with full rotation. De-Deus et al. [20] noticed a small percentage of fractures and deformation rates of glide path instrument with reciprocating motion (R-Pilot) after a previously established micro glide path with the size 08 hand file.

Instruments activated by reciprocating motion show higher cutting efficiency, reduced extrusion of dentin filings, and better centricity compared to instruments with full rotation [20]. According to Keskin et al. [17], WaveOne Gold (Dentsply Sirona) showed greater resistance to cyclic fatigue than R-Pilot, although both are reciprocating instruments, but made of different type of alloy. WaveOne is made of Gold NiTi alloy while R-Pilot is made of M-Wire. In the same study, R-Pilot showed greater resistance to cyclic fatigue than Pro Glider (both from M-Wire), demonstrating less exposure to instrument stress in reciprocating motion.

Generally, the advantages of glide path NiTi files are shorter preparation time, reduced possibility of procedural errors, better maintenance of the original anatomy, less operator and hand fatigue, reduced apical extrusion, and postoperative pain [26, 27]. The possibility of instrument fracture, reduced tactile sensation, and instruments' cost are disadvantages of using mechanical glide path systems [22].

CONCLUSION

Although glide path preparation requires time and adherence to technical protocols, it is one of the crucial stages during the processing of complex endodontic systems. Proper creation of a glide path can extend the life of mechanical NiTi instruments and impact the necessary quality control of mechanical and chemical debridement and predictable, hermetic obturation. Although the development of new methods and mechanical glide path systems is intensive, the role of manual instruments should not be neglected, and it is up to the therapist to decide on a specific method and system, depending on the diagnosis, canal morphology, and primarily on knowledge, experience, and technical capabilities.

Ethics: This article was written in accordance with the ethical standards of the institutions and the journal.
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Ендодонтски инструментациони пут – значај и технике извођења

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САЖЕТАК

Формирање инструментационе путање је процедура која претходи машинској препарацији канала корена. Подразумева успостављање/проширење јасног и глатког каналског тунела од његовог коронарног дела до апексне констрикције. Може се формирати ручним турпијама малог промера од нерђајућег челика, као и специјално дизајнираним машинским никл-титанијумским инструментима. Инструментациона путања продужава трајање машинских инструмената, омогућава ефикасније чишћење и дезинфекцију канала, као и очување оригиналне морфологије ендодонтског простора током даље машинске инструментације. Све чешћа примена машинске инструментације у свакодневној пракси намеће потребу за бољим разумевањем ове процедуре, њеног значаја и начина формирања.

Кључне речи: инструментациона путања; ручни инструменти; машински *NiTi* инструменти

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови**,** наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh)*.

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°*C*), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

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