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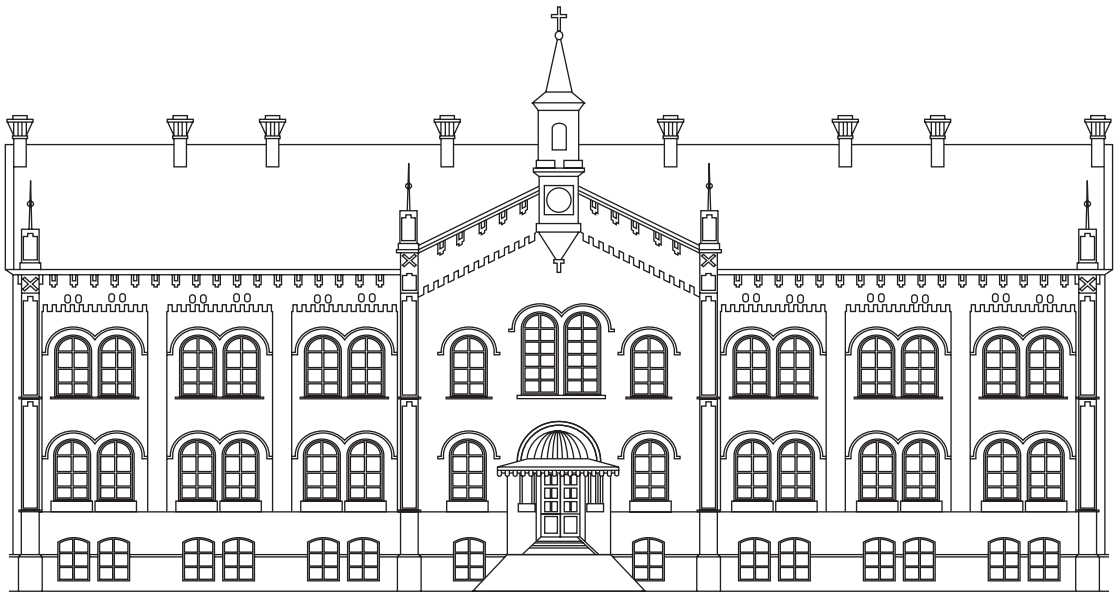

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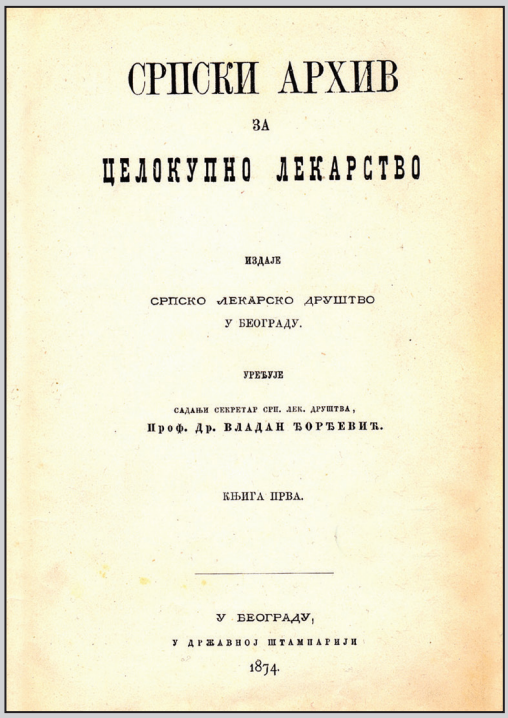


СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

ИЗДАЈЕ

СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

УРЕЂУЈЕ

САДАШЊИ СЕКРЕТАР СРП. ЛЕК. ДРУШТВА,

Проф. Др. ВЛАДАН ЂОРЂЕВИЋ.

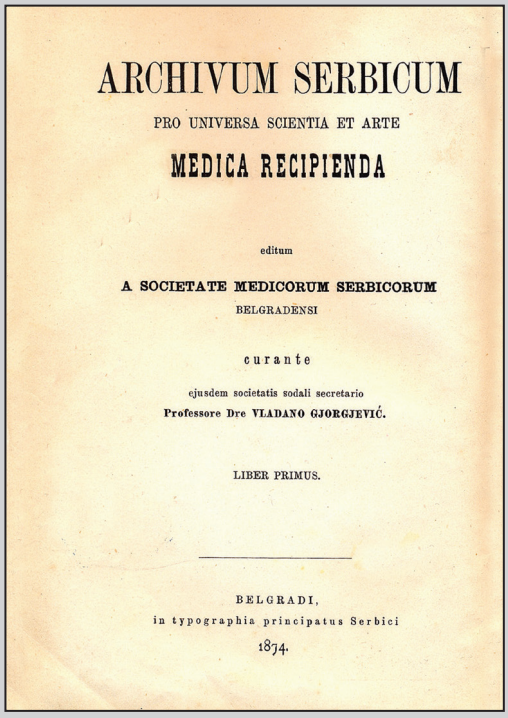
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



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in typographia principatus Serbici

1874.

The title page of the first journal volume in Latin

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Concept of green dentistry in Serbia

Dejan Zdravković, Milica Jovanović, Anđela Milojević-Šamanović, Mirjana Papić, Miloš Papić, Marko Milosavljević, Kosovka Obradović-Đuričić

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SUMMARY

Introduction/Objective Green dentistry as a term has been introduced into dental practice in Serbia in recent years. Minimal amount of research on the topic of medical waste disposal in health care institutions is available at the moment.

The aim of this research is to determine how familiar the professional public as well as dental students are with this term and whether they apply the recommended environmental protection measures in their daily clinical work.

Methods The study was conducted in the form of a survey that referred to the attitude of the professional public regarding environmentally friendly dental practice, in the period from June 1, 2022 until November 1, 2022. The survey includes demographic information, as well as 21 questions related to awareness and application of green dentistry in daily clinical practice.

Results Results indicate a very low level of information among the professional public regarding the mentioned concept, where as much as 36% of the total number of respondents do not have any information about green dentistry (n = 45) and only 6% (n = 8) are fully informed about the given concept.

Conclusion On the basis of the obtained results, it can be concluded that the professional public's attitude towards green dentistry is such that its application is expected to reduce the consumption of available resources, as well as to improve the environment.

Keywords: green dentistry; sustainability in dentistry, ecological dentistry; medical waste

INTRODUCTION

Reflections on a healthy environment, cost-effective long-term life resources, and ecological aspects of human progress are the topics to which today's population pays significant attention, most often with the idea of reducing general pollution and the present global warming [1]. The greatest influence on the occurrence of global warming is human activity. In recent years, in Serbia, we have witnessed substantial air pollution in both urban and rural areas [2]. In addition to air pollution, other environmental factors, such as water and soil pollution, are significant concerns [3].

Environmental pollution on a global level has far-reaching consequences that pose a threat to the survival of the entire living population. Therefore, it is important to emphasize that professional dental practice, when using different materials without proper application and training, represents a significant potential risk to the survival of a healthy ecosystem [4, 5, 6]. The term "green dentistry" (GD) or "eco dentistry" has been introduced into dental practice in recent years [7]. The goal of incorporating "green" programs into dental reality is to inform and train dentists to use conventional energy (electricity, water) rationally, minimize the amount of waste and properly dispose of that waste, and make their practices more economical and less risky [8]. This concept has been present for some time in dental practice in environmentally conscious countries, where the GD principle is systematically applied through laws issued by competent institutions or the state and is aimed at health institutions that implement health protection measures [9, 10, 11]. In Serbia, there is a lack of extensive research on the topic of medical waste disposal in both public and private clinics [12].

The strategic postulates promoted by GD are represented by the four R letters (English transcription) which illustrate the initial letters of nouns that support the concept of environmentally friendly and sustainable dentistry (eco-friendly dentistry): "R – rethink, reduce, reuse, recycle" [13].

Rethink

Environmental awareness and healthy sustainability of civilizational laws are considered a state of mind. Changing the way we think about the way dental offices are operated is the first step in trying to significantly modernize the practice. Thus, by implementing simple changes, it is possible to reduce energy and water consumption in the daily work of dental services.

Reduce

To decrease the consumption of natural resources, it is necessary to modify established habits and reduce the consumption of available resources to a reasonable extent. For instance, reducing paper consumption and properly managing paper waste can help prevent deforestation and mitigate global warming.

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Reuse

This strategy encourages the prolonged use of various items. Certain objects can be repurposed after their primary use, thereby extending their use value. Reusing products also reduces the amount of energy required for producing new products.

Recycle

A significant amount of waste found in landfills can be reprocessed and recycled into new products. Intentional, purposeful use of products would reduce the waste of raw materials and energy required for the production of new materials [13, 14].

In addition to the mentioned 4R principles, for the purpose of easier application and modernization of GD, it is proposed to use protocols represented by four letters 'A' [15] In practice, the issue of dental waste disposal would be addressed through the following four suggested settings:

1. Ask – (questionnaires): collecting basic data about the habits of a dental clinic;
2. Assess – (estimation, assessment): evaluating possible modifications and improvements of daily dental practice towards ecologically sustainable dentistry;
3. Advice – (recommendation): clear guidelines and instructions for implementing the principles of GD;
4. Assist – (help, aid): assistance in implementing all environmental procedures and their specific application.

The introduction of the 4A principle requires forming teams that would be ready to carry out training through continuous medical education, as well as ensure its implementation in daily practice.

Considering the topicality of the stated views, the objective of this research is to determine how familiar Serbian dentists, dental nurses, dental technicians, and dental students are with the term GD, whether they apply it, and which recommended environmental protection measures they utilize in their daily clinical work.

METHODS

This study was designed as a cross-sectional study and included all employees in the dental profession (public and private sector) who perform part of their specialist training or internship at the Department of Dentistry, Faculty of Medical Sciences, University of Kragujevac.

The study was conducted in the form of a survey to assess the attitude of the professional public towards environmentally friendly dental practices from June 1, 2022, until November 1, 2022. Prior to filling out the survey, respondents were informed that all obtained data would be used exclusively for research purposes, personal data would not be used, and complete anonymity would be guaranteed. After completing the survey by circling one of the offered answers for each question, they return the survey to the researcher, and the researcher in charge of conducting the survey (M.J.) must pack it in an envelope, seal it, and forward it to the main researcher (D.Z.) for data processing. The survey includes demographic information about survey participants, but in addition to this data, it also contains 21 questions related to the awareness and application of GD in daily clinical practice (Figure 1).

The inclusion criteria for the study involved respondents from the dental profession with varying years of service

Survey (survey is voluntary and anonymous)					
Demographic information of survey participants					
Gender	M	W			
Age	20–29	30–39	40–49	50–59	60–69
Education	Dentist	Dental assistant	Dental technician		Student
Work experience	0–5 years	5–10 years	10–15 years	15–20 years	Over 20 years
If you answered "Student" to the question about education, complete the year of study.	1. Third year of study 2. Fourth year of study 3. Fifth year of study				
1. I am familiar with the term "green dentistry" or "ecological dentistry"					
1) I totally disagree					
2) I partially disagree					
3) Thread I agree nor disagree					
4) I partially agree					
5) I totally agree					
2. Do you agree that dental practice improves the overall "healthy environment"					
1) I totally disagree					
2) I partially disagree					
3) Thread I agree nor disagree					
4) I partially agree					
5) I totally agree					
3. Do you agree that eco-dentistry protocols can contribute to energy savings and reduced water consumption					
1) I totally disagree					
2) I partially disagree					

3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
4. Do you agree that changing the existing dental practice to “green” is feasible in the near future
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
5. Do you agree that changing the existing dental practice to “green” will be an additional financial burden
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
6. Do you agree that dental products that are the result of environmental practice are readily available on the market
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
7. Do you agree that waste recycling is an additional financial burden for conducting dental practices
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
8. Do you agree that a recycled instrument or accessories for work is not as “clean” as conventional instruments or accessories that are sterilized by standard procedures?
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
9. Do you agree that energy consumption is increased by using recycled materials
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
10. Do you agree that water consumption increases using recycled materials
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
11. Do you agree that the application of digitized radiography is environmentally friendly
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
12. Do you agree that the radiography material should be disposed of as municipal waste
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree

13. Do you agree that the application of composite materials is more environmentally friendly than the application of amalgam for fillings
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
14. Do you agree that amalgam for fillings should be disposed of as medical waste according to the set protocols
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
15. Do you agree that the separation of medical from municipal waste in everyday practice contributes to environmental protection
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
16. Do you agree that the separation of medical waste into infectious and non-infectious in everyday practice contributes to the protection of the environment
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
17. Do you agree that mercury has a detrimental effect on the patient, therapist and the environment
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
18. Do you agree that your current knowledge of the concept of green dentistry is satisfactory
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
19. Do you agree that green dentistry should be introduced into the study program of integrated academic studies of dentistry
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
20. Do you agree that your colleagues from other universities are more familiar with this term
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree
21. Do you agree that the current handling of medical and non-medical waste while conducting practical classes is environmentally friendly
1) I totally disagree
2) I partially disagree
3) Thread I agree nor disagree
4) I partially agree
5) I totally agree

Figure 1. Survey parameters implemented in the study

Table 1. Overview of questions that showed great significance compared to gender, age, education, and work experience

Question number	Gender Mann–Whitney	Age Kruskal–Wallis	Education Kruskal–Wallis	Work experience Kruskal–Wallis
1	0.434	0.018*	0.000*	0.004*
2	0.901	0.026*	0.000*	0.012*
3	0.216	0.794	0.393	0.049*
4	0.056	0.062	0.555	0.017*
5	0.612	0.358	0.388	0.086
6	0.979	0.051	0.417	0.006*
7	0.932	0.012	0.171	0.118
8	0.012*	0.068	0.001*	0.421
9	0.743	0.807	0.558	0.455
10	0.622	0.479	0.106	0.104
11	0.348	0.523	0.436	0.689
12	0.344	0.076	0.173	0.015*
13	0.958	0.095	0.015	0.050*
14	0.155	0.047*	0.092	0.173
15	0.582	0.054*	0.019*	0.006*
16	0.152	0.443	0.365	0.307
17	0.375	0.000*	0.004*	0.000*
18	0.664	0.683	0.014*	0.044*
19	0.016*	0.099	0.090	0.144
20	0.349	0.279	0.423	0.161
21	0.466	0.154	0.128	0.163

*p < 0.05 – Mann–Whitney test;
*p < 0.05 – Kruskal–Wallis test

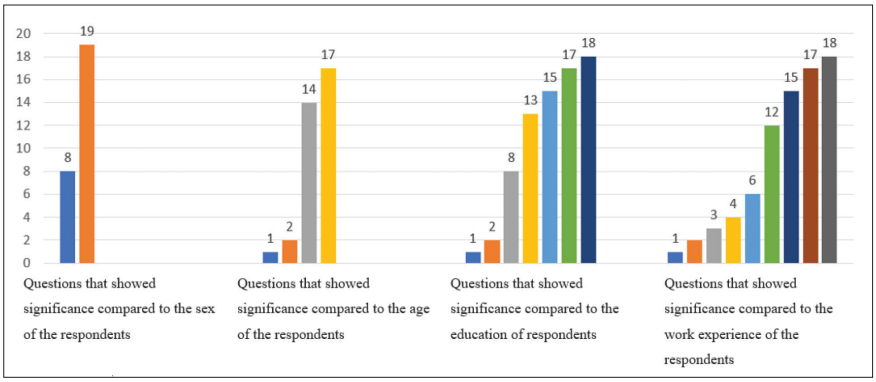

Figure 2. Questions that showed great significance compared to the demographic characteristics of the survey respondents

who agreed to participate, while the exclusion criteria encompassed individuals who were not interested in participating in the study as well as those who incorrectly or inadequately filled out surveys.

After data collection, further processing was carried out by the main researcher using the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

The sample size was determined based on studies of similar designs [16]. The study sample was determined taking into account the following initial parameters: a study power of 80%, as well as a type 1 error probability (α) of 0.05. The sample size was calculated using the G Power v. 3.1 program for the t-test. The minimum required sample (number of respondents) in the research is 120 respondents.

The research was approved by the Ethics Committee of the Faculty of Medical Sciences of the University of Kragujevac (number 01-6013 on May 20, 2022).

RESULTS

The results of the research are presented in table and graph form (Table 1, Figure 2). The research included a total of 124 respondents (n = 124), with the majority being students enrolled in integrated academic studies in dentistry (n = 68). The next largest group of respondents in terms of sample size were dentists (n = 42) who were either employed at the Faculty of Medical Sciences of the University of Kragujevac or were completing part of their specialist internship in various fields of dentistry at this institution. Considering the size of the clinic and the staffing needs of the Faculty of Medical Sciences for dental nurses and dental technicians, a reasonably smaller number of respondents included these two groups (dental nurses: n = 6; dental technicians: n = 8). Regarding the two largest groups of respondents (students: n = 68; dentists: n = 42), among students, the gender distribution was in favor of the female gender with 78% (n = 53), while among dentists, the percentage of females was slightly higher at 83% (n = 35). Overall, this indicated, that, of the total number of respondents, a significant majority of respondents were female, with 81% (n = 100). The age of respondents was categorized into five age groups, with the largest number of respondents falling into the 20–29 years age group (71%), which was directly influenced by the numerically largest group of respondents – students. The work experience of the respondents was divided into five groups, excluding the group of students. Among dentists, the years of work experience were almost equally distributed in the first two groups, with a total percentage of 38% for the group with 0–5 years of work experience, while the group with 6–10 years of work experience accounted for a total percentage of 36%.

The research findings related to the concept of GD indicate a very low level of awareness among dental professionals; in fact, 36% of the total number of respondents had no information about GD (n = 45) and only 6% (n = 8) had a comprehensive understanding of the concept. Despite the low level of knowledge, it can be inferred that the professional public holds a positive attitude towards GD,

expecting its application to reduce resource consumption and improve the overall "healthy environment."

However, it is noteworthy that respondents also anticipate an increase in the overall costs of daily work associated with the implementation of GD principles. It is also important to note that respondents have a positive opinion about material recycling, while also demonstrating a high level of awareness regarding the harmful effects of amalgam and mercury on the environment as well as on therapists and patients. The encouraging data obtained from this survey is that a significant portion of the student group supports the idea of including GD concepts in the curriculum of integrated academic studies of dentistry.

Using the Mann–Whitney test for independent samples to compare the different groups, statistically significant results were obtained, indicating a strong association between certain survey questions and the gender of the respondents (Table 1).

Furthermore, significant statistical results were also observed when analyzing the age groups and their responses to the survey questions using the Kruskal–Wallis test. The most prominent statistical result was found when comparing the survey questions related to the relationship between GD and education level, as well as years of service (Table 1).

Regarding the comparison of the years of study among students and the survey questions, two questions showed statistically significant results based on the Kruskal–Wallis test. Question 11 illustrated the application of digital radiography, and question 17 was related to the respondents' awareness of the harmful effects of mercury on patients, therapists, and the environment. These findings highlight the students' knowledge and awareness about the positive impact of digital radiography, and potential mercury side efect. These findings highlight the students' knowledge and awareness in these areas, demonstrating their understanding of the benefits of digital radiography and the potential risks associated with mercury.

DISCUSSION

The implementation of ecological principles has been receiving increasing attention in recent years [17]. While our country may not be densely populated, air pollution remains a significant issue, adversely affecting the quality of life for residents. The development of environmental awareness and the pursuit of a sustainable, healthy environment are global concerns [18, 19, 20]. Therefore, it is necessary to apply ecological principles to all aspects of life [21]. This led to the establishment of the "Eco-Dentistry Association" in 2008, based in Berkeley, USA.

Today, the scientific literature contains an increasing number of scientific papers addressing this problem.

A study conducted by Al Shatrat et al. [22] focused on the implementation of GD principles specifically related to the proper management of amalgam fillings and the associated waste. The problem of amalgam waste was also addressed by Hiltz [23], who discussed potential pollution directly stemming from the material itself. The study highlighted the evaporation of mercury from the amalgam alloy, the residual amalgam during material preparation, excess amalgam created in modeling fillings, and the presence of amalgam particles in drainage systems, filters, and dental chair components.

In this pioneering study, the first of its kind and scope within the Serbian dental community, there was a high level of awareness among respondents regarding the harmful effects of amalgam and mercury on the environment, therapists, and patients. These findings coincide with the results of the aforementioned study by Al Shatrat et al. [22], which also indicated high awareness about the harmfulness of mercury and amalgam.

Apart from these findings, the conducted study demonstrates that the dental profession supports the adoption of modern digital radiography as the preferred method in daily practice.

Richardson et al. [24] have conducted interesting research on the presence of various types of waste in dental clinical practice. Their findings reveal that paper waste constitutes the highest percentage of infectious waste at 33%, followed by gloves at 26%, and sterile packaging for instruments at 11%. When considering the types of materials used in dental practice, plastic waste was found to be the most common at 34%, while paper waste accounted for the largest mass.

Hancocks [25] explored the materials used in dental and oral hygiene products. The author emphasizes the importance of the trend toward using natural materials for toothbrushes and toothpaste. This is recommended to reduce the amount of plastic waste, which takes a long time to decompose.

Passi and Bhalla [14] provide a definition of GD as defined by the Eco Dentistry Association, which consists of 15 clear guidelines for dentists on how to apply GD principles in their daily practice and minimize the harmful impact on the environment.

While previous authors have mainly focused on the problem of waste management in dental practice, few authors have addressed the root of the problem, which is the education of dental students and dental staff. A study conducted in Brazil at two dental schools and a healthcare institution revealed that the private school had the highest amount of non-infectious waste due to incorrect sorting, while the public school had the highest percentage of infectious and potentially infectious waste [26]. The healthcare institution had the lowest amount of waste compared to school institutions.

In addition, a study conducted at Hacettepe University in Turkey by Ozbek and Sanin [27] revealed that the largest amount of waste, measured in grams, was generated by the prosthetics clinic, totaling 13,403 grams over a period of two months. The results presented in this research support the adoption of modern principles in dental practice, particularly the utilization of digital technologies in the manufacturing process of dental restorations.

During a conference in Berlin in August 2019, the topic of GD was discussed, and a short questionnaire was used to assess dentists' understanding of sustainability in dental practice. To address this, a graph was created to illustrate

the concept of GD in a more accessible manner, aiming to educate and facilitate the implementation of sustainable dentistry for all dental professionals [28, 29].

CONCLUSION

This research highlights that the protocols of ecological dentistry are largely unknown among dental professionals in Serbia and that fundamental changes are needed within the field. However, there is promising interest among young individuals, particularly dental students, regarding the concept of GD and the potential inclusion of this eco-friendly and rational approach in the curriculum of higher education institutions in Serbia. Given that this study is the first of its kind in the field of dentistry in Serbia, it is recommended that further research on this topic is supported by various entities (faculties, ministries, and medical chambers) with the aim of protecting the dental profession and the community as a whole.

Conflict of interest: None declared.

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Концепт зелене стоматологије у Србији

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САЖЕТАК

Увод/Циљ Зелена стоматологија као појам уведена је у стоматолошку праксу у Србији последњих година. У Србији постоји минималан број истраживања на тему одлагања медицинског отпада у државним и приватним клиникама. Циљ овог истраживања јесте да се утврди колико су стручна јавност и студенти стоматологије упознати са овим појмом и да ли примењују препоручене мере заштите животне средине у свакодневном клиничком раду.

Методе Студија је спроведена у виду анкете која се односила на ставове професионалне јавности у вези са еколошки прихватљивом стоматолошком праксом, у периоду од 1. 6. 2022. до 1. 11. 2022. године. Анкета је обухватала демографске информације о учесницима анкете, као и 21 питање у вези са информисаношћу и применом зелене стоматологије у свакодневној клиничкој пракси.

Резултати Резултати истраживања који се односе на концепт зелене стоматологије указују на недовољну информисаност професионалне јавности у вези са поменутим концептом, при чему чак 36% од укупног броја испитаника нема никаквих информација о зеленој стоматологији ($n = 45$), док је само 6% ($n = 8$) потпуно информисано о датом концепту.

Закључак На основу добијених резултата може се закључити да је став професионалне јавности о зеленој стоматологији такав да се њеном применом очекује смањење потрошње расположивих ресурса, као и побољшање животне средине.

Кључне речи: зелена стоматологија; одрживост у стоматологији, еколошка стоматологија; медицински отпад

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Severity of radiographic changes in patients with COVID-19 pneumonia – experience from secondary-level hospital

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SUMMARY

Introduction/Objective Chest X-ray (CXR) is a common diagnostic procedure for monitoring the course and outcome of pneumonia. The aim of the study was to examine the frequency, type and degree of CXR changes in COVID-19 pneumonia and compare it with demographic data and the presence of comorbidities.

Methods In this retrospective study, CXRs taken on the day of admission were analyzed for 620 patients with COVID-19. CXR were defined as ground-glass opacification (GGO), consolidation, reticular changes, pulmonary nodules, and pleural effusions. CXR severity score (CXR-SS) was determined based on the adjusted Radiographic Assessment of Lung Edema score. SPSS version 17.0 was used for statistical analyses.

Results The average age was 62.75 ± 14.8 years 66.5% of analyzed patients had comorbidities. CXR changes were bilateral in 53.2%, dominant in the lower lung in 68.1% and diffuse in 24.5%. GGO were present in 55%, reticular changes in 37.3%, and consolidations in 24% of patients. Based on CXR-SS, 47.2% of patients had mild pneumonia, 40.2% moderate, 7.9% severe, and 4.6% very severe. Severe/very severe pneumonia was in 71.8% of older than 65 years. Bilateral changes were found in 97.4% of people with severe/very severe pneumonia, diffuse in 56.4%, and consolidation in 66.7% of the patients. GGO were in 58.1% of subjects with mild/moderate pneumonia.

Conclusion CXR in patients with COVID-19 pneumonia are more frequently bilateral, dominantly peripheral, in the lower lung zone. The degree of diffuse changes is proportional to older age and more frequent comorbidities. In a severe form of the disease, consolidation and reticular opacification dominate.

Keywords: chest X-ray; pulmonary severity score; COVID-19 pneumonia

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has different clinical manifestations. In 80–90% of cases, the disease has no symptoms or the symptoms are mild [1]. A severe clinical course can occur in patients with comorbidities [2]. Severe courses of COVID-19 are often complicated by acute respiratory distress syndrome [3].

Chest X-ray (CXR) is an important part of non-invasive diagnostics of lung diseases. It represents an easy-to-implement and affordable method. In addition to the clinical examination, there was a common diagnostic procedure for monitoring the course and outcome of COVID-19 pneumonia. The ability of CXR to visualize changes typical of pneumonia caused by the SARS-CoV-2 virus was highlighted [4].

Ground-glass opacity (GGO) is the most common radiographic finding in COVID-19 pneumonia [5].

The aim of the research was to examine the frequency and type of radiographic changes in our patients with COVID-19 pneumonia, determine the CXR score and compare it with demographic characteristics and comorbidities.

METHODS

The study included a total of 620 patients with COVID-19 who had been treated in the Užice General Hospital, from June 1 to December 31, 2020. All collected data were analyzed retrospectively. The diagnosis of COVID-19 is established by the detection of SARS-CoV-2 virus in the nasopharyngeal swab. Testing was performed in reference laboratories in the Republic of Serbia. A rapid immunochromatographic antigen test and a polymerase chain reaction (PCR) test were used according to international guidelines [6].

Demographic data (sex and age), comorbidities and CXR were collected from the day of admission. Radiography was performed in the anteroposterior view for immobile patients and for others, also in the anteroposterior view, during full inspiration.

This version keeps the meaning but improves the flow. The recording was made with a portable device (Vision M, Visaris d.o.o., Belgrade, Serbia).

The Fleischner Society nomenclature was used to determine the CXR changes described as GGO, consolidation, reticular alteration, pulmonary nodules and pleural effusion [7]. The

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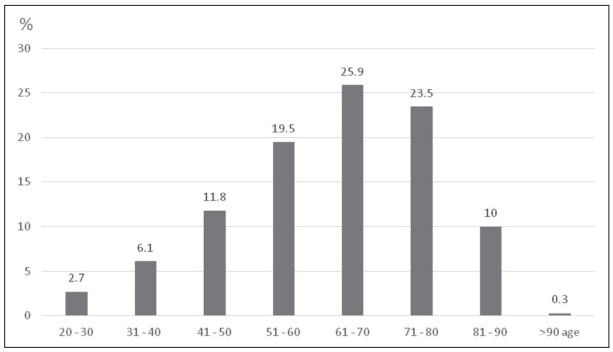

Figure 1. Age groups of the respondents

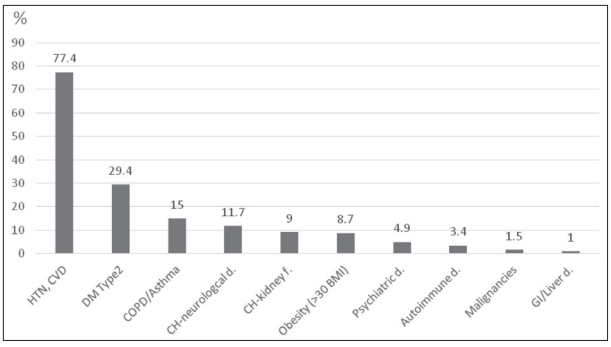

Figure 2. Comorbidities in patients with COVID-19

HTN – hypertension; CVD – cardiovascular diseases; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease; CH – chronic; BMI – body mass index; GI – gastrointestinal

Table 1. Characteristics of patients with COVID-19

Variable		N 620	% patients Total 100	p-value
Age group	≥ 65 < 65	313 307	50.5 49.5	0.920
Sex	Men Women	355 265	57.3 42.7	0.144
Comorbidity	Yes No	412 208	66.5 33.5	< 0.001

Table 2. Radiographic alterations in COVID-19

Variable		N	% patients
Positive CXR		620	100
Lung field involvement	Bilateral Left unilateral Right unilateral Lower zone Diffuse Upper zone Peripheral Perihilar	330 158 132 422 152 46 434 186	53.2 25.5 21.3 68.1 24.5 7.4 70 30
Type of alteration	GGO (alone) Reticular alteration (alone) Consolidation (alone) Pulmonary nodules Pleural effusion GGO (total) Reticular alteration (total) Consolidation (total) Pulmonary nodules (total) Pleural effusion (total)	258 152 63 10 3 341 231 149 22 17	41.6 24.5 10.2 1.6 0.5 55 37.3 24 3.5 2.7

CXR – chest X ray; GGO – ground-glass opacity

distribution of pulmonary changes was defined as perihilar or peripheral. The dominance of changes was described based on the involvement of the upper and middle lung fields, or a diffuse distribution of the changes.

CXR severity score (CXR-SS) was determined based on the Radiographic Assessment of Lung Edema score. This type of radiographic assessment was first performed by Warren et al. [8].

Each lung field is scored from 0 to 4 depending on the presence of changes. A score of 0 means no lung changes, score of 1 means that they are present in less than a quarter of the lung field. Scores 2 and 3 indicate involvement of 25–50% and 50–75%, respectively. A maximum score of 4 means that more than 75% of the lung field is affected. The maximum total score for changes in both lungs was 8 [9].

Statistical analysis

The Statistical Package for Social Sciences SPSS Statistics (SPSS Inc., Chicago, IL, USA) version 17.0 was used for statistical analyses.

The results were expressed as means ± SD and as percentages. Non-parametric variables were calculated by χ^2 test. A probability value of $p < 0.05$ was considered significant.

The manuscript was approved by the Ethics Committee of the Užice Health Center, on February 2, 2024, number 0303/850.

RESULTS

A total of 620 patients with confirmed SARS-CoV-2 infection were examined. The median age was 62.75 ± 14.8 (range 20–92 years). Age groups of the respondents is shown in Figure 1. The largest number of our patients were aged 61–70 (25.9%). Two patients were over 90 years old. Age, sex, and the presence of comorbidities are shown in Table 1.

The presence of comorbidities was significant (66.5%). The most common comorbidities found were hypertension (HTN) / cardiovascular diseases (CVD) (77.4%) and diabetes mellitus (DM) (29%), followed by chronic obstructive pulmonary disease (COPD) / asthma in 15%, chronic neurological diseases in 11.7%, kidney diseases in 9%, obesity in 8.7%. Psychiatric diseases, autoimmune diseases, malignancies, gastrointestinal, and liver diseases were the least common (4.9%, 3.4%, 1.5%, 1%, respectively) (Figure 2).

CXR alteration are shown in Table 2. In relation to the CXR, alterations were bilateral in 330/620 patients (53.2%), unilateral in the left lung in 158/220 (25.5%) and right lung in 132/220 (21.3%). Alterations were predominantly in the lower lung field in 411/620 (68.1%), diffuse in 152/620 (24.5%) and in the upper zone in 46/620 (7.4%). Changes in the peripheral lung fields were in 434/620 (70%),

Table 3. Chest X-ray severity score (CXS-SS) in patients with COVID-19

Variable		N	% patients
Positive chest radiographs		620	100
CXR-SS	1	131	21.1
	2	162	26.1
	3	140	22.6
	4	109	17.6
	5	32	5.2
	6	17	2.7
	7	17	2.7
	8	12	1.9
CXR-SS (total)	Mild (1–2)	293	47.2
	Moderate (3–4)	249	40.2
	Severe (5–6)	49	7.9
	Very severe (7–8)	29	4.6

Table 4. The relationship between patients characteristics and chest X-ray severity in COVID-19

Variable		Mild/moderate Total 542		Severe / very severe Total 78		p-value
		N	% patients	N	% patients	
Age group	≥ 65	251	46.3	56	71.8	0.019
Sex	Men	305	56.3	50	64.1	0.477
Comorbidity	Yes	339	62.5	73	93.6	0.013
	HTN, CVD	253	46.7	66	90.4	< 0.001
	DM type 2	84	15.5	22	30.1	0.031
	Obesity (> 30 BMI)	39	7.2	17	23.3	0.004
	COPD/Asthma	37	6.8	12	16.4	0.046
	CH-Neuro disorders	37	6.8	7	9.6	0.489
	CH-kidney failure	25	4.6	12	16.4	0.010
	Psychiatric disorders	16	2.9	4	5.5	0.369
	Autoimmune diseases	14	2.6	1	1.4	0.549
	Malignancies	6	1.1	2	2.7	0.412
	GI/liver disease	3	0.6	0	0	0.439

HTN – hypertension; CVD – cardiovascular diseases; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease; CH – chronic; BMI – body mass index; GI – gastrointestinal

Table 5. The relationship between radiographic alterations and chest X-ray severity in COVID-19

Variable		Mild/moderate Total 542		Severe /very severe Total 78		p-value
		N	% patients	N	% patients	
Lung field involvement	Bilateral	254	46.9	76	97.4	< 0.001
	Left unilateral	156	28.8	2	2.6	< 0.001
	Right unilateral	132	24.4	0	0	0.00
	Lower zone	390	72	32	41	0.004
	Diffuse	108	19.9	44	56.4	< 0.001
	Upper zone	44	8.1	2	2.6	0.093
	Peripheral	377	69.6	5	73.1	0.769
	Perihilar	165	30.4	2	26.9	0.644
Type of alteration	GGO (alone)	254	46.9	4	5.1	0.00
	Reticular alteration (alone)	138	25.5	14	17.9	0.249
	Consolidation (alone)	51	9.4	12	15.4	0.228
	Pulmonary nodules	10	1.8	0	0	0.179
	Pleural effusion	3	0.6	0	0	0.439
	GGO (total)	315	58.1	26	33.3	0.009
	Reticular alteration (total)	185	34.1	46	59	0.009
	Consolidation (total)	97	17.9	52	66.7	0.00
	Pulmonary nodules	19	3.5	3	3.8	0.913
	Pleural effusion	13	2.4	4	5.1	0.324

GGO – ground-glass opacity

central zones in 186/220 (30%). GGO alone was present in 258/620 (41.6%), reticular alteration alone in 152/620 (24.5%), consolidation alone in 63/620 (10.2%), pulmonary nodules in 10/620 (1.6%), pleural effusion in 3/620 (0.5%). In total (with/without other changes), GGO was present in 341/620 (55%), reticular alteration in 231/620 (37.3%), consolidation in 149/620 (24%). The total number of pleural nodules was 22/620 (3.5%), pleural effusion 17/620 (2.7%).

Bilateral alterations were significantly more frequent than unilateral left ($p = 0.002$), or right ($p < 0.001$). Lung changes were significantly more frequent in the lower fields compared to the upper zone ($p = 0.00$) or diffuse changes ($p < 0.001$).

The described changes of the peripheral zones were significantly more frequent than perihilar ($p < 0.001$). The total frequency of GGO was significantly higher than the total frequency of consolidation ($p < 0.001$). GGO alone was significantly more frequent than reticular alteration alone ($p = 0.035$).

No significant difference was observed in the total number of GGO and reticular alterations ($p = 0.065$). Pulmonary nodules and pleural effusion, alone or in combination with other findings, were significantly less frequent than other alterations ($p < 0.001$ in every relationship).

CXR-SS is shown in Table 3. Score from 1 to 8 was in 21.1%, 26.1%, 22.6%, 17.6%, 5.2%, 2.7%, 2.7%, 1.9% of patients, respectively. CXR showed mild involvement (score 1–2) in 293/620 (47.2) patients. Moderate involvement (score 3–4) was found in 249/620 (40.2%) patients, severe involvement (score 5–6) was found in 49/620 (7.9%) patients and very severe involvement (score 7–8) was found in 29/620 (4.6%) patients.

In relation to the severity of the disease according to the CXR-SS, respondents were grouped into two groups. The first group included patients with CXR-SS from 1 to 4, the second group included patients with CXR-SS from 5 to 8.

Characteristics by patient groups are shown in the Table 4.

Persons over 65 years of age had a statistically significantly more severe disease (71.8%, $p = 0.019$).

Patients with a more severe form of the disease had more frequent comorbidities (93.6%, $p = 0.013$). The most common comorbidities were HTN/CVD and DM, found in 77.4% and 29.4%, respectively. Patients with severe disease significantly more often had HTN/CVD, DM, obesity and chronic kidney failure ($p < 0.001$,

p = 0.031, p = 0.004, p = 0.010, respectively). Radiographic alterations by patient groups are shown in Table 5.

Bilateral (97.4%) and diffuse (56.4%) alterations were significantly more common in patients with severe diseases (p < 0.001 for both parameters). The zonal distribution of lung changes was not significantly different between the groups. Consolidations in combination with other findings (66.7%) were significantly more frequent in the group of severe diseases (p = 0.009). Patients with mild/moderate disease had significant unilateral frequency of alterations by type of GGO. This was in both cases, alone GGO (46.9%) and with other findings (58.1%) (p = 0.00, p = 0.009, respectively). In relation to the presence of unilateral changes, there was no difference between the left and right sides. Reticular alterations in combination with other findings were most common in severe disease (59%) (p = 0.009).

DISCUSSION

Regular CXR was the most important method of rapid diagnosis of pneumonia during the COVID-19 pandemic. The evaluation of changes was often crucial for the decision on further treatment. Baseline CXR sensitivity in literature is estimated between 69% and 90% [9]. Modified and improved radiological techniques are presented in the literature [10]. They are based on a number of characteristics of the radiological image. New methods will contribute to the precise diagnosis of lung changes by selecting the lung region of interest according to pixel intensity. The improvement of the X-ray image is achieved by the filtering process with equalization of the histogram [10]. These techniques are not yet available in other institutions.

In our study, CXR findings and CXR-SS of patients with COVID-19 upon admission in the hospital were analyzed. All our subjects had CXR changes. Some authors describe a third or a quarter of negative CXR [9, 11]. The first CXR of their subjects was done at the onset of symptoms, which does not apply to our patients. Užice General Hospital is a secondary-type medical institution, so patients were usually treated in primary care facilities beforehand.

Most of our respondents had a lower CXR-SS (1–4). Progression of the CXR-SS during the course of the disease is expected [11, 12]. The low CXR-SS of our patients indicate a shorter time from the onset of the disease.

The largest number of our patients were aged 61–70 (25.9%). We did not observe a significant difference between younger and older than 65, while patients older than 65 showed a higher CXR-SS. The result is expected and in accordance with other authors [13]. Older age is accompanied by comorbidities and a decrease in the defense functions of the immune system. Regression of defense mechanisms implies reduced function of immune cells, such as dendritic cells and macrophages. Consequently, the activation of T lymphocytes was reduced. The mentioned processes create conditions for the occurrence of pneumonia [13].

Most of our respondents were men (57.3%). A similar result is presented in the literature [14]. At the beginning of the pandemic, patients were often male. With the increase in the number of patients, there were no differences according to sex [14]. The authors agree that immunoregulatory functions of sex hormones, physiological factors, and different lifestyles play an important role in the development of infection [13].

The frequency of presence of comorbidities in our patients was significant. Our subjects most often had HTN, CVD and DM. More than half of respondents in a study by Fang, et al. [15] had associated diseases. HTN and DM were most often present, as in our subjects.

These comorbidities were significantly more common in our patients with severe CXR score. The results by Zhang et al. [2] also showed the frequent presence of associated diseases in patients with severe form of COVID-19 pneumonia. We also agree in the conclusion with other authors that COPD and asthma are not risk factors for COVID-19 infection, nor for higher CXR-SS. The explanation of this finding assumes the use of long-acting beta agonists and muscarinic antagonists in asthma and COPD therapy. These drugs reduce viral load in nasopharyngeal and tracheal tissue cultures [16].

Severe COVID-19 pneumonia was common in our patients with previously diagnosed HTN and diabetes. HTN and cardiac strain are caused by the angiotensin II. This is affected by SARS-CoV-2 binding to the enzyme converter [17]. This mechanism is also used by SARS-CoV-2 to affect lung tissue, as well as other organs such as the pancreas. An elevated level of pro-inflammatory cytokines was measured in the serum of patients with diabetes. SARS-CoV-2 also leads to an increase in the level of these cytokines. The consequence of an increased level of pro-inflammatory cytokines can be the appearance of a cytokine storm in diabetics with COVID-19 pneumonia [18]. Some authors also report DM as a predictive factor for poor prognosis of COVID-19 pneumonia [19].

Due to the diffuse alveolar damage caused by SARS-CoV-2, GGO occur, which was a common CXR finding in COVID-19 pneumonia. This finding was confirmed by computed tomography [20].

GGO, alone or with other alterations, was most often in our subjects. The GGO present on both sides was also the most frequent finding of subjects with COVID 19 pneumonia analyzed by Kuhajda et al. [5]. This finding corresponds to result of other authors and confirms the assumption that not much time has passed from the onset of symptoms to admission [11]. The conclusion of Yasin et al. is the most frequent presence of consolidations [12]. This is also the finding of Wong et al. [9].

Total described consolidations and reticular alteration were significantly more frequent in our subjects with severe pneumonia, which correlates with the findings of other authors [9]. Pleural effusion and pulmonary nodules were uncommon, both here and in literature [9, 12]. A pronounced pleural effusion was seen in a patient with COVID-19 pneumonia and associated with rheumatoid arthritis [21].

Lung field involvement on CXR in our subjects was most often bilateral with peripheral distribution and more

present in the lower lung. Our result is similar to the findings of other authors [9, 12, 22, 23]. In the mentioned studies, the relationship between the distribution of pulmonary changes and the severity of pneumonia was not analyzed. The result of our research showed that mostly bilateral, at the peripheral and dominance diffuse lung alterations corresponded to a higher CXR-SS.

Yacobi et al. [4] suggest that CXR is an easy and accessible procedure for diagnosing lung changes in COVID-19 pneumonia. According to them, SARS-CoV-2 most often causes reticular opacities and GGO. Basal positioned consolidations are typical changes in pneumonia caused by this virus. CXR changes are usually in the peripheral lung zones, as in our patients [24].

CXR changes in COVID-19 pneumonia differ according to disease stages. The first stage is characterized by rapid progression of only GGO, GGO with reticular pattern or consolidation. This stage lasts up to seven days. Advanced stage also lasts up to seven days and is characterized by GGO associated with consolidations and reticular changes. The absorption stage occurs after the 14th day of the disease. In this stage, absorption occurs. CXR absorption indicators are subpleural and fibrotic changes [25]. As in the case of other pathogens, the most severe consequence of COVID-19 pneumonia is the development of pulmonary fibrosis [25]. A significant occurrence of pulmonary fibrosis after six months from the onset of the disease in patients with COVID-19 pneumonia was described [15]. Spontaneous pneumothorax, pneumomediastinum, and subcutaneous emphysema were also complications of COVID-19 pneumonia described in the literature [5]. Thromboembolic complications were also described, and not only in the lungs [26]. The pathogenetic mechanism of SARS-CoV-2 leads to coagulopathy and consequent damage to the endothelium of blood vessels [27].

There are different phases of the body's response to inflammation caused by the SARS-CoV-2. The beginning of the infection is characterized by a high level of virus and the activation of interferon and macrophages. The second phase is characterized by a lower level of virus and less presence of defense cells. In this way, the evolution of diffuse alveolar damage and CXR alterations occurs [28].

We analyzed only the radiographic changes on the day of admission to the hospital, without further follow-up, which would certainly be interesting and important. We analyzed patient data when vaccines were still not in use in our population. Vaccination protection for COVID-19 was important factor for the occurrence and clinical course of the diseases. Vaccination had a significant effect on the reduction of CXR-SS [29]. The clinical course and prognosis of vaccinated patients was more favorable [30].

CONCLUSION

The radiographic changes in patients with COVID-19 pneumonia were often present in both lungs. Their distribution was most often peripheral. The changes were dominantly present in the lower lung zones. The most present alterations were GGO.

Pulmonary changes were more severe in elderly patients with comorbidities, the most often CVD and DM. The severity of the lung field involvement is accompanied by diffuse distribution of lung changes by type of consolidations and reticular opacification.

Conflict of interest: None declared.

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Степен радиографских промена код болесника са пнеумонијом изазваном ковидом 19 – искуство из болнице секундарног нивоа

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САЖЕТАК

Увод/Циљ Радиографија грудног коша је уобичајен дијагностички поступак за праћење клиничког тока и исхода пнеумоније изазване ковидом 19.

Циљ истраживања био је да се испитају учесталост, тип и степен радиографских плућних промена код пнеумоније изазване ковидом 19 и упореде са демографским подацима и присуством коморбидитета код лечених болесника.

Методе Подаци су прикупљени ретроградно, на дан пријема у болницу, код 620 болесника са пнеумонијом изазваном ковидом 19. Радиографске промене су дефинисане као опацификације зрнастог стакла или *ground glass* опацификације (ГГО), консолидације, ретикуларне промене, плућни нодули и плеуралне ефузије. Степен промена је одређиван према адаптираној радиографској процени едема плућа. За статистичку обраду је коришћен статистички пакет *SPSS*, верзија 17.0.

Резултати Просечна старост болесника била је 62,75 ± 14,8 година. Коморбидитете је имало 66,5% болесника. Радиографске промене су биле обостране код 53,2% болесника, доминантно у доњим плућним пољима код 68,1%, а дифузне код 24,5% испитаника. ГГО су виђене код 55%, ретикуларне промене код 37,3%, а консолидације код 24% болесника. На основу радиографског скоринг система, 47,2% болесника је имало лаку пнеумонију, 40,2% умерену, 7,9% тешку, а 4,6% врло тешку. Код 71,8% старијих од 65 година виђена је тежа упала плућа. Билатералне промене су виђене код 97,4% особа са тежом пнеумонијом, дифузне код 56,4%, а консолидације код 66,7% истих болесника. ГГО промене су виђене код 58,1% испитаника са лакшом упалом.

Закључак Радиографске промене код болесника са ковидом 19 најчешће су обостране, доминантно периферне и у доњој плућној зони. Степен дифузних промена пропорционалан је старијем узрасту и учесталијим коморбидитетима. Код тешког облика болести доминирају консолидације и ретикуларне опацификације.

Кључне речи: радиографски налаз; степен плућних промена; пнеумонија изазвана ковидом 19

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Long-term follow-up of the patients with pacemaker leads implanted through persistent left superior vena cava

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SUMMARY

Introduction/Objective Persistent left superior vena cava (PLSVC) is the most common congenital malformation of the thoracic venous system and may often complicate cardiac implantable electronic device (CIED) lead implantation. The purpose of this study was to assess feasibility and safety of CIED lead implantation through PLSVC and its long-term efficacy.

Methods This is a retrospective observational study performed in a tertiary center from July 2005 to July 2019 among patients with fully successful implantation of all intended CIED leads through PLSVC.

Results CIED implantation was successfully completed with left-side approach in 26 of 32 (81.3%) patients with PLSVC. The average implantation time was 62, 73.5, 120, 74, 103.3, and 130 minutes and the average fluoroscopy time was 13.3, 20.8, 35.7, 17.1, 45.6, and 42.6 minutes for single and dual-chamber pacemakers, ICD-VR, ICD-DR, CRT-P, and CRT-D devices, respectively. The average follow-up period was 43.5 ± 29.9 months. During the follow-up period no CIED leads-related complications were noticed.

Conclusion The results of our study showed that the presence of PLSVC is not an obstacle for CIED implantation. The long-term follow-up proved stability of CIED leads implanted through PLSVC.

Keywords: persistent left superior vena cava; cardiac implantable electronic device; lead; implantation

INTRODUCTION

Persistent left superior vena cava (PLSVC) is the most represented congenital malformation of thoracic venous system that affects less than 0.5% of the general population and up to 10% of individuals with congenital heart defects [1, 2]. It represents the residue of the left cardinal vein that predominantly regresses in the early stages of fetal life [2, 3]. Most often, PLSVC drains into the right atrium through the dilated coronary sinus, but in 8–20% it drains in the left atrium directly or via an unroofed coronary sinus causing right to left cardiac shunt with paradoxical embolism potential [4, 5]. Beside PLSVC, right superior vena cava (RSVC) is usually present and bridged with PLSVC via an innominate vein. Rarely, in less than 10% of cases, PLSVC exists without RSVC and that phenomenon is called "isolated PLSVC" or "absent RSVC" [6, 7]. PLSVC is primarily an asymptomatic anomaly that can be suspected based on the echocardiographic finding of a dilated coronary sinus in the absence of elevated right-sided pressures [8]. However, it is typically identified incidentally during anesthetic, nephrological, oncological, and cardiological procedures involving a left cephalic or subclavian venous approach, along with instances occurring during cardiac surgery. It can be confirmed by contrast venography [9, 10]. Heart rhythm disturbances related to the formation and conduction of impulses can be observed among these patients, requiring pacemaker therapy [3, 11]. The unusual venous anatomy may complicate cardiac implantable electronic device (CIED) leads implantation [8, 12].

The purpose of this study was to assess feasibility and safety of CIED lead implantation through PLSVC and its long-term efficacy.

METHODS

This retrospective, observational study was conducted at the Pacemaker Center of the University Clinical Center of Serbia. The investigation conforms to the principles outlined in the Declaration of Helsinki. The study was approved by an institutional review committee. We included patients who underwent CIED implantation for the first time, from July 2005 to July 2019, in whom PLSVC was incidentally recognized during procedure and implantation of all intended leads was completed with left-side approach through PLSVC. All patients signed informed consent before the implantation procedure. All the procedures were performed by four experienced physicians in the cardiac catheterization laboratory, under local anesthesia, commenced with left-sided approach, opposite the patients' dominant arm.

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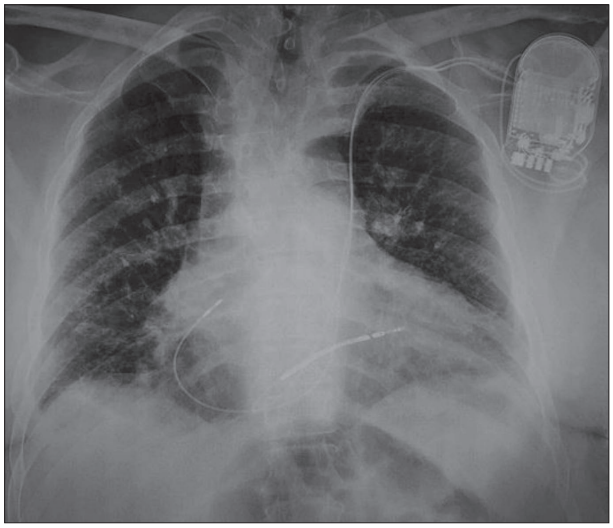

Figure 1. Chest X-ray demonstrating dual-chamber implantable cardioverter defibrillator implanted through persistent left superior vena cava

For venous access we used the cephalic vein cutdown technique (always when possible) or the subclavian/axillary vein puncture. The atypical transvenous lead tracing was suspected on PLSVC and confirmed by intraprocedural venography. Afterwards, CIED lead implantation was proceeded through PLSVC. For the right ventricle (RV) lead implantation we used the loop technique – making a loop in the right atrium (RA) before fixing the lead in the RV (as shown in the Figure). The rest of the procedure was performed in the usual manner. After implantation, follow-up, with device function assessing, was exerted after one, three, and six months, and later on six to 12 months according to the type of the implanted device. All the data were collected from the patients' medical records. The patients in whom it was not possible to implant at least one of intended CIED leads through the PLSVC were excluded from the study.

Statistical analysis

For data processing, descriptive and analytic statistic methods were used. Data are presented as mean ± standard errors, or n (%) depending on data type. Normal distribution of data was checked by the Shapiro–Wilk test. T-test and χ^2 test were used to assess differences between examined groups. All p-values less than 0.05 were considered significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA).

RESULTS

In the course of a 14-year period, PLSVC was recognized in 32 out of 14,186 (0.22%) patients. CIED implantation was successfully completed with the left-side approach in 26 of 32 (81.3%) patients, and these 26 patients were included in our analysis. In two patients, lead positioning through PLSVC was not possible, so left-side approach was abandoned and pacemakers [single-chamber (VVI) and dual-chamber (DDD)] were implanted on the opposite (right) side without complications. In four CRT patients, it was not possible to implant left ventricle (LV) leads endovenously, so they were implanted subsequently, epicardially, using mini-thoracotomy approach. Limited availability of suitable tributaries due to thrombosis of coronary sinus or the unfavorable coronary venous anatomy were the reasons for transvenous approach failure. These six patients were excluded from the further analysis. There were 15 VVI and 6 DDD pacemakers, one single-chamber implantable cardioverter defibrillator (ICD-VR) and two dual-chamber implantable cardioverter defibrillators (ICD-DR), and two cardiac resynchronization therapy (CRT) devices implanted without complications. Of a total of 38 leads implanted through PLSVC and monitored in this study, two RV leads, one RA lead, and both CS were passive fixation leads, while all others were active fixation leads. Procedures were always started with standard length leads, and as needed, longer leads were used during the intervention. In seven cases the procedure was completed with a longer RV and in two cases with longer RA leads. Patient characteristics and indications for CIED implantation are presented in Table 1. The average implantation and fluoroscopy time in the group of patients with and without PLSVC and the existence of statistically significant differences in these parameters between the groups are shown in Table 2. For comparison, we used the mean values of these parameters obtained in patients without PLSVC who were implanted in our center in 2012. During the follow-up period 10 patients died and for statistical analysis we used the values of the parameters recorded at the last control if it was done at least one year after the implantation. The average follow-up period was 43.5 ± 29.9 months. No CIED related perioperative or late complications were noticed. We were monitoring 22 RV and 10 RA leads implanted through PLSVC, and its parameters were stable throughout follow-up period (presented in Tables 3 and 4). Four high-voltage (HV) leads implanted in one CRT-ICD, two dual-chamber ICDs, and one single-chamber ICD were observed. Mean values of HV leads' parameters did not change significantly at primo-implantation and at the time of the last checkup (HV impedance 60.5 ± 5 Ω and 63 ± 6.7 Ω, sense/pace impedance 609.5 ± 178.8 Ω and 400.3 ± 33.6 Ω, R wave 9.4 ± 4.7 V and 9.1 ± 2.6 V, threshold 0.9 ± 0.3 V / 0.4 ms and 0.7 ± 0.1 V / 0.4 ms). There were two LV leads implanted via coronary sinus. Baseline impedances were 936 Ω and 1050 Ω and at the last control 850 Ω and 965 Ω, while baseline thresholds were 1.7 V / 0.4 ms and 2.5 V / 0.4 ms and at the last control 1.5 V / 0.4 ms and 2 V / 0.4 ms.

DISCUSSION

While PLSVC is considered an uncommon venous anomaly, in specialized referral centers such as ours, where over 1000 CIED implantations are performed annually, it does

Table 1. Basic characteristics of patients with cardiac implantable electronic device leads implanted through persistent left superior vena cava

Patient	Age	Sex	Indication for CIED implantation	Device type
1	74	Male	Chronic AF with slow ventricular response	VVI
2	80	Female	CHB	VVI
3	81	Male	CHB	VVI
4	77	Female	Chronic AF with slow ventricular response	VVI
5	73	Female	CHB	VVI
6	69	Male	Chronic AF with slow ventricular response	VVI
7	72	Female	Chronic AF with slow ventricular response	VVI
8	66	Male	Chronic AF with slow ventricular response	VVI
9	73	Female	SND	VVI
10	75	Female	CHB	VVI
11	77	Male	AV block Mobitz II	VVI
12	73	Male	Chronic AF with slow ventricular response	VVI
13	79	Female	Chronic AF with slow ventricular response	VVI
14	56	Male	SND, paroxysmal AF	VVI
15	80	Female	SND, paroxysmal AF	VVI
16	38	Male	CHB	DDD
17	71	Male	CHB	DDD
18	62	Female	CHB	DDD
19	67	Female	SND	DDD
20	70	Female	SND	DDD
21	59	Male	CHB	DDD
22	68	Male	DCM, NYHA III, LBBB	CRT-ICD
23	62	Male	DCM, NYHA II, LBBB	CRT-P
24	44	Male	Sustained VT, NYHA II/III	ICD-VR
25	70	Male	DCM, NYHA II, non-sustained VT	ICD-DR
26	60	Male	Sustained VT, NYHA II, paroxysmal AF	ICD-DR

CIED – cardiac implantable electronic device; PLSVC – persistent left superior vena cava; SND – sinus node dysfunction; CHB – complete heart block; AF – atrial fibrillation; LBBB – left bundle branch block; VT – ventricular tachycardia; DCM – dilated cardiomyopathy; NYHA – New York Heart Association; ICD-VR – implantable cardioverter defibrillator; CRT – cardiac resynchronization therapy; VVI – single-chamber device; DDD – dual-chamber device; CRT-P – cardiac resynchronization therapy pacemaker

Table 2. Cardiac implantable electronic device implantation procedures in patients with and without persistent left superior vena cava

Parameter	The average CIED implantation time (min)		The average fluoroscopy time (min)		p
	With PLSVC	Without PLSVC	With PLSVC	Without PLSVC	
VVI	62.0 ± 37.9	31.2 ± 14.2	13.3 ± 16.8	2.4 ± 2.3	< 0.01
DDD	73.5 ± 37.1	38.4 ± 16.1	20.8 ± 22.8	3.4 ± 3.2	< 0.01
ICD-VR	120 ± 0	31 ± 8.6	35.7 ± 0	2 ± 1.6	< 0.01
ICD-DR	74 ± 18.3	37.8 ± 13.8	17.1 ± 9.9	3.6 ± 2.3	< 0.01
CRT-P	103.3 ± 19.3	63 ± 24.6	45.6 ± 13.4	14.8 ± 10.8	< 0.01
CRT-ICD	130 ± 50	59 ± 23	42.6 ± 19.6	11 ± 7.6	< 0.01

CIED – cardiac implantable electronic device; PLSVC – persistent left superior vena cava; ICD-VR – implantable cardioverter defibrillator; VVI – single-chamber device; DDD – dual-chamber device

Table 3. Right ventricle lead parameters after implantation and at the last follow-up

Parameters	N	Baseline		Follow-up		p
		$\bar{x}$	SD	$\bar{x}$	SD	
Impedance (Ω)	22	733	79.3	519.1	89.8	< 0.001
Sensing (mV)	22	11.3	6.7	10.8	3.6	0.945
Threshold (V / 0.4 ms)	22	1	0.2	0.8	0.4	0.007

Table 4. Right atrium lead parameters after implantation and at the last follow-up

Parameter	N	Baseline		Follow-up		p
		$\bar{x}$	SD	$\bar{x}$	SD	
Impedance (Ω)	10	656.7	151.2	518.2	164.2	0.002
Sensing (mV)	10	2.9	1.2	3.4	1.3	0.221
Threshold (V / 0.4 ms)	10	1.5	0.6	0.8	0.3	0.005

not even qualify as a rarity. The atypical venous anatomy may complicate the procedure, prolong duration and fluoroscopy time and it requires particular skill and experience of the physician [8]. To our best knowledge, our series of the patients with CIED lead(s) implanted through PLSVC, presented in this paper, is one of the largest reported.

The incidence of PLSVC was estimated at less than 0.5% in general population, as mentioned previously [1]. The true incidence of this congenital anomaly is unknown because it usually does not affect systematic venous return, so it has no physiological consequences. However, PLSVC may have significant clinical implications, especially when it drains in the left atrium creating left to right shunt, provoking possible hypoxemia, increasing the risk of paradoxical embolism and direct systemic effect of i.v. ordinated drugs [4, 5]. Also, it should always be thought of in the context of the association of PLSVC with congenital heart disease, as well as with extracardiac anomalies [2]. Because of all of the above, we believe that only large series, as shown in our study, with over 14,000 patients included, can give relevant estimate of the frequency of such anomalies. In our study, the incidence of PLSVC is 0.22% and we assert that this is a realistic assessment.

The implantation of CIED leads through PLSVC is challenging but feasible. Previous studies do not provide the information about duration and fluoroscopy time of CIED implantation through PLSVC. As expected, this study showed a significantly longer duration of the procedure and radiation exposure when implantation is performed through PLSVC for all types of CIED. Numerous factors have the potential to prolong the duration of X-ray exposure as well as the duration of the procedure itself, such as passing the lead by an unusual venous pathway, lead placement at the desired position, which always requires additional lead maneuvering, achieving lead stability and optimized values of its parameters. Many approaches for implanting and positioning of pacemaker/ICD leads have been described. Although, there are many approaches for RV lead implantation, in our center we use loop technique – making a loop in the RA before fixing the lead in the RV. Sometimes, during the procedure, it is necessary to

switch the standard-length lead (58 cm) with a longer one to facilitate lead placement in the RV. RA lead implantation also has its specificities in relation to routine procedures. After leaving the CS and entering the RA, the RA lead is typically directed towards the RA lateral wall. It is preferable to avoid fixing the electrode in that position due to the higher risk of lead displacement and cardiac perforation. The use of a curved stylet allows directing the lead towards the RA appendage, which is the preferred position for lead fixation [8].

However, implantation of the endocardial LV lead for CRT in the presence of the PLSVC remains very challenging. PLSVC can markedly increase the size of coronary sinus that makes LV lead placement difficult. On the other hand, increasing physician experience, cardiac imaging, and appropriate tools contribute to a positive outcome [13]. Nair et al. [14] showed that using the right-sided approach when RSVC is present makes it more likely that LV lead can be implanted using an endovascular approach. For this reason, some physicians decide to abandon the left-sided approach and implant the entire CRT system on the right side, while others use the right-sided approach to implant only the LV lead and then to tunnel it to the left prepectoral pacemaker pocket [8, 13]. Crossing to the other side and eventual tunneling that requires the application of analgosedation can significantly prolong the duration of these procedures. If LV lead implantation through PLSVC is not possible, it could be done epicardially, using mini-thoracotomy, as we did in four of our patients. Since 2005, a HEART team has existed in our institution with the idea of establishing a new protocol introducing a surgical approach into the standard therapy algorithm, following global trends. Until recently, LV lead implantation via lateral mini-thoracotomy was used as an alternative technique only when transvenous CRT was not possible, and nowadays we use this approach in CRT-non-responder patients who had the LV lead implanted in suboptimal CS tributary group. Therefore, we consider an LV lead implantation via mini-thoracotomy an elegant approach that does not depend on the anatomy of the coronary sinus, with significantly lower risk of phrenic nerve stimulation and lead dislodgement, without unnecessary prolonged radiation exposure, which all makes us often choose this technique when we encounter a problem like PLSVC.

In our study, no periprocedural complications were noticed in patients with CIED leads implanted through PLSVC. The absence of complications, within the certainly small number of cases for proper statistical prediction, could be explained by the experience and expertise of our operators and their increased caution on timely spotting this venous malformation.

During the follow-up period, no late complications were detected and there was no need to replace any lead implanted through PLSVC. Pacing parameters including impedance, sensing (of P and R waves), and threshold capture (for atrial RA, RV, and LV leads) were regularly checked by our physicians. All crucial lead parameters were stable during the follow-up period. Therefore, this is the very first study that provides long-term follow-up data of the CIED lead stability implanted through PLSVC.

CONCLUSION

The results of our study showed that the presence of PLSVC is not an obstacle for CIED implantation. The long-term follow-up proved the stability of CIED leads implanted through PLSVC. Longer implantation and fluoroscopy times are inherent to the procedure complexity. However, implantation of the endocardial LV leads for CRT in the presence of the PLSVC remains challenging and in some patients should be done epicardially.

Conflict of interest: None declared.

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Дугорочно праћење болесника са пејсмејкер електродама имплантираним кроз перзистентну леву горњу шупљу вену

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САЖЕТАК

Увод/Циљ Перзистентна лева горња шупља вена је најчешћа конгенитална малформација венског система грудног коша и често може компликовати уградњу електрода срчаних имплантабилних електронских уређаја.

Циљ овог рада је да се процени изводљивост и безбедност имплантације електрода срчаних имплантабилних електронских уређаја кроз перзистентну леву горњу шупљу вену, као и њена дугорочна ефикасност.

Методе Ово је ретроспективна, опсервациона студија, спроведена у терцијарном центру у периоду од јула 2005. до јула 2019. године међу болесницима којима су успешно имплантиране све предвиђене електроде срчаних имплантабилних електронских уређаја кроз перзистентну леву горњу шупљу вену.

Резултати Срчани имплантабилни електронски уређаји успешно су имплантирани у целости левостраним приступом код 26 од 32 (81,3%) болесника са перзистентном левом горњом шупљом веном. Просечно трајање имплантације износило је 62, 73,5, 120, 74,0, 103,3 и 130 минута, а просечно трајање флуороскопије износило је 13,3, 20,8, 35,7, 17,1, 45,6 и 42,6 минута за једнокоморске и двокоморске пејсмејкере, *ICD-VR*, *ICD-DR*, *CRT-P* и *CRT-ICD* уређаје, редом. Просечан период праћења је био 43,5 ± 29,9 месеци. Током периода праћења нису забележене компликације у вези са електродама срчаних имплантабилних електронских уређаја.

Закључак Резултати наше студије су показали да присуство перзистентне леве горње шупље вене није препрека за имплантацију срчаних имплантабилних електронских уређаја. Дугорочним праћењем је доказана стабилност електрода срчаних имплантабилних електронских уређаја имплантираних кроз перзистентну леву горњу шупљу вену.

Кључне речи: перзистентна лева горња шупља вена; срчани имплантабилни електронски уређај; електрода; имплантација

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Factors influencing mortality in prevalent hemodialysis patients with different types of heart failure – single-center experience

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SUMMARY

Introduction/Objective This retrospective longitudinal study aimed to analyze survival factors in prevalent hemodialysis (HD) patients with different heart failure (HF) phenotypes.

Methods Over 36 months, 96 patients were monitored, with 51 deaths recorded. Patients were categorized into HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and non-HF (no HF) groups. Demographic, clinical, and laboratory parameters were analyzed to identify survival predictors within each subgroup.

Results Survival curves did not differ among HF subgroups, and mortality was as follows: 42.9% for HFrEF, 52.4% for HFpEF, and 60.6% for no-HF patients. The main causes of death were COVID-19 infection (70%), followed by *de novo* cardiovascular diseases (myocardial infarction and cerebrovascular insult) (25%). Some demographic (age, male sex, HD vintage) and laboratory differences (anemia, lipids) between the surviving and deceased subgroups of patients have been found. Multivariate analysis identified distinct survival predictors: in HFrEF: pulse rate and interventricular septum thickness; in HFpEF: primary renal disease, cardiac history, and diuretic use; in no-HF: BMI, serum sodium, and HDL/LDL ratios.

Conclusion Our results led us to suspect that COVID-19 infection might have masked the expected impact of HF phenotype on patients' survival. Obtained findings contribute to the evolving understanding of HF in prevalent HD patients in the pandemic era. As HF, dialysis, and COVID-19 intertwine, further investigation is crucial to navigate this intricate finding and optimize patient care.

Keywords: heart failure; hemodialysis; mortality; risk factors

INTRODUCTION

Patients with end-stage renal disease undergoing maintenance hemodialysis (HD) frequently encounter an array of cardiovascular complications, further exacerbated by the coexistence of heart failure (HF) [1]. Consequently, the interplay between HD and HF warrants investigation, particularly in the context of mortality outcomes.

Three types of HF in the general population are recognized: HF with preserved ejection fraction (HFpEF), HF with reduced EF (HFrEF), and HF with moderately reduced EF [2]. Their clinical presentation and risk factors are similar, but the approach to treatment and response to treatment is different. Having in mind that HF is a poor predictor of HD patient outcome [3], timely identification of HF risk factors, and clinical presentation would be helpful in prevention and their management [4]. HFrEF is characterized by a compromised left ventricular ejection fraction (EF), often resulting from structural heart damage, myocardial infarction, or dilated cardiomyopathies. On the other hand, HFpEF, characterized by preserved EF, typically involves diastolic dysfunction and is associated with comorbidities such as hypertension, diabetes, and aging [4].

Mortality rates among patients with HF undergoing HD remain a subject of concern. The concomitant presence of both conditions introduces intricate hemodynamic alterations, electrolyte imbalances, and potential medication interactions, all of which contribute to elevated mortality risk [5, 6]. Understanding the differential impact of HFrEF and HFpEF on mortality in the context of maintenance HD is essential for tailoring effective interventions and optimizing patient care.

Existing research has primarily focused on overall mortality in HD patients without distinguishing between HFrEF and HFpEF subgroups, warranting further investigation into the unique contributors to mortality in each subgroup. Thus, the present study aimed to identify specific factors that contribute to mortality in prevalent HD population with different types of HF.

METHODS

Patients

This was a single-center retrospective longitudinal analysis of data from 96 prevalent patients treated with HD. The included patients

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were older than 18 years, with at least six months of HD treatment. Statins, aspirin, angiotensin-converting enzyme inhibitors (or angiotensin-receptor blockers), and beta-blockers were prescribed to all patients in accordance with current guidelines for secondary prevention of CV events independently of clinical evaluation, as well as anti-aggregation treatment and anticoagulants as needed. Parameter of anemia and mineral metabolism were controlled according to current KDIGO guidelines, which are adopted locally [7, 8]. Studied patients were all asymptomatic for chest pain and had no history of acute coronary syndrome in the previous three months. Exclusion criteria were the inability of the patients to provide signed written consent for participation in the study. According to the criteria of the American and European Society of Cardiology [2, 4] and based on signs and/or symptoms of HF, and left ventricular function indicators obtained by transthoracic echocardiography, patients were divided into the following groups: 1. those with HF and reduced EF – rEF (EF < 40%), plus moderately reduced HF marked as HFmrEF (EF = 40–50%) – 21 patients; 2. those with HF and preserved EF – HFpEF (EF ≥ 50%) – 42 patients; 3. those without overt HF – 33 patients. During the monitoring period (from March 2020 to April 2023), 51 patients died. In order to identify the factors that contributed to the mortality in the study population, we compared all the data reported in the methods below between deceased patients and survivors. For easier comparison, the basal groups of patients with HFrEF, HFpEF, and the group without HF were divided into two subgroups each i.e. those who survived and those who died, thus forming six subgroups marked with numbers 1–6.

The approval of the local ethics committee was obtained (number 110/21.1.2020) and written informed consent was obtained from all the participants.

Data collection

1. Demographic data: age, sex, renal disease, comorbidities (coronary artery disease, hypertension, diabetes mellitus, dyslipidemia, and peripheral obstructive arterial disease), residual diuresis, and body mass index (BMI) including history of coronary artery disease defined as prior revascularization (through angioplasty or coronary artery bypass). Also, each patient was physically examined and questioned for signs and/or symptoms of HF including edema of the lower extremities, (exertional) dyspnea graded by the New York Heart Association criteria (NYHA I-IV), and paroxysmal nocturnal dyspnea/orthopnea [9].

2. Dialytic data: duration of bicarbonate dialysis session (four hours three times a week), dialysis vintage, dialysis membrane (low- and high-flow polysulfone membrane, with a surface of 1.3–1.8 m^2), without change throughout the study period, single pool Kt/V [10], interdialytic weight gain, dialysis access, and systolic and diastolic blood pressure before HD session, volume status checked by bioimpedance spectroscopy, using the Body Composition Monitor – BCM (Fresenius Medical Care, Bad Homburg, Germany).

Measurements

All the measured parameters, i.e. laboratory data and transthoracic echocardiography characteristics, are described in detail in our previous work [11].

Outcomes

The main outcome of this study was all-cause and cardiovascular mortality during the 36 months of follow-up. The date and causes of death were recorded from the patient's medical files. Sudden cardiac death, heart failure, myocardial infarction, severe aortic stenosis, aortic dissection, ischemic stroke, and peripheral vascular ischemia were considered causes of cardiovascular death. Infection-related mortality included COVID-19 cases and sepsis. Also, the number and causes of hospitalizations were recorded from the patient's medical records.

Statistical analyses were performed using the IBM SPSS Statistics, Version 25.0 (IBM Corp., Armonk, NY, USA) and R software (version 3.6.1, R Core Team, 2019). Continuous variates with normal distribution were presented as mean ± SD and compared using the Student's t-test. Variables without normal distribution were presented as median with interquartile ranges and compared using the Mann–Whitney U test or for multiple comparisons Tukey post-hoc test. Categorical data were presented as the number of cases and percentages and compared using the χ^2 test. Cox multivariate logistic regression model including all significantly different characteristics in the univariate logistic regression models (at $p = 0.05$) as well as those predictors that are known to affect the patient's death were used to determine the independent association with all-cause mortality. Two-sided p-values < 0.05 were considered statistically significant.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

Study population

Differences in baseline characteristics between surviving and deceased patients at the entry of the study are presented in Table 1. Considering two subgroups with HFpEF, deceased patients were older, and there were more males. They had been on HD for a shorter time before the start of this study compared to patients from other groups, and had more frequent renal anemia compared to deceased persons without HF. In groups of survivors, more women were in the subgroup with HFrEF compared to the subgroup with HFpEF, and zero NYHA score was more common in HFpEF compared to no HF group. In the groups of non-survivors, the patients from the HFrEF group had

Table 1. Baseline characteristics of examined patients

Characteristics	Group 1 (HFrEF + HFmrEF)		Group 2 (HFpEF)		Group 3 (no HF)		p-value
	Survivors (N = 12 pts)	Deceased (N = 9 pts)	Survivors (N = 20 pts)	Deceased (N = 22 pts)	Survivors (N = 13 pts)	Deceased (N = 20 pts)	
Age, years	70 (61.2–76.5)	67 (52.5–75)	61.6 (52.7–71.2)	71 (61.2–81)	66 (59.2–73)	72 (65–77.5)	0.01
Sex, m/f	10/2	7/2	8/12	17/5	7/6	14/6	0.019
HD vintage, months	51 (30.2–103.2)	57 (35–224)	30.5 (15.2–63.2)	27.5 (17.75–52.5)	51.5 (32.7–82.2)	71 (28.5–130)	0.039
Co-morbidities, HTA/CVI DM2/tumor COPD/PVD IM/PCI/CABG	 2/- -/1 1/- -/-/1	 5/1 2/- -/-/1	 8/1 1/- 1/- 1/-	 9/1 4/2 2/2 8/-/5	 6/- -/1 - 1/-	 11/2 2/2 3/1 2/2/2	Non-significant
Renal anemia, yes	11	8	18	22	11	16	0.029
NYHA class: 1 2 3	 3 6 3	 1 5 3	 7 13 0	 6 10 6	 1 10 2	 3 13 4	0.021
EF %	46.33 ± 1.5	39.53 ± 5.26	59 ± 6.88	55 ± 4.53	59.12 ± 6.94	60.37 ± 5.39	0.025
Pre-dialysis BP Systolic, mmHg	155.5 (130–172.7)	155 (141.5–160.5)	148.5 (126.5–158)	146 (136.5–153.7)	145 (131–166.5)	140.5 (132.5–166.5)	Non-significant
Diastolic, mmHg	72.5 (68.5–79.7)	73 (68–95)	77 (64.7–81.7)	66.5 (59.5–77.0)	78 (72–85)	73 (64–88)	Non-significant
kT/V	1.05 (0.96–1.24)	1.41 (0.94–1.57)	1.1 (0.94–1.27)	1.03 (0.88–1.27)	1.18 (1.05–1.38)	0.96 (0.9–1.12)	Non-significant

HF – heart failure; rEF – reduced ejection fraction; pEF – preserved ejection fraction; HD – hemodialysis; HTA – hypertension; CVI – cardiovascular insult; DM2 – diabetes mellitus type 2; PVD – peripheral vascular disease; COPB – chronic obstructive pulmonary disease; IM – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery by-pass grafting; NYHA – New York Heart Association classification of heart failure;
Median (IQR), X ± SE, N – patients number;
Statistically significant differences:
age: group 2 survivors *vs.* deceased; sex: survivors group 1 *vs.* group 2; group 2 survivors *vs.* deceased; HD vintage: deceased group 1: group 2, group 2 *vs.* group 3; renal anemia: deceased group 2 *vs.* group 3; NYHA class 3: group 2 survived *vs.* deceased; EF: deceased group 1 *vs.* group 3

Table 2. Laboratory parameters of examined patients

Parameters	Group 1 (HFrEF + HFmrEF)		Group 2 (HFpEF)		Group 3 (no HF)		p-value
	Survivors (N = 12 pts)	Deceased (N = 9 pts)	Survivors (N = 20 pts)	Deceased (N = 22 pts)	Survivors (N = 13 pts)	Deceased (N = 20 pts)	
Leukocytes, $\times 10^9$/l	6.68 (5.75–8.81)	5.01 (3.62–7.23)	6.72 (5.28–8.16)	5.92 (5.20–7.58)	5.64 (5.28–7.37)	7.37 (5.99–8.73)	< 0.042
Hemoglobin, g/l	98 (93–103)	94 (86–120)	107 (89–121)	98 (84.2–110.5)	107 (94–120)	108 (97–125)	0.047
Platelets, $\times 10^9$/l	190 (176–203)	122.5 (106.7–182.2)	202 (162–222)	215 (176.7–255.2)	208 (127–229)	189 (156–247)	< 0.036
Sodium, mmol/l	139 (138–141.5)	137 (132–142)	138 (138–140)	138.5 (137–141)	138 (137–139.5	139 (138–141)	Non-significant
Calcium, mmol/l	2.15 (1.89–2.22)	2 (1.79–2.2)	2.16 (2.10–2.27)	2.13 (2.04–2.25)	2.15 (2–2.32)	2.16 (2.14–2.26)	Non-significant
Phosphate, mmol/l	1.31 (1.11–1.65)	1.17 (0.77–1.61)	1.76 (1.23–2.12)	1.38 (1.17–1.8)	1.31 (1.11–1.79)	1.35 (1.07–1.59)	Non-significant
iPTH, ng/ml	158.4 (51–404.8	133.4 (21.9–687.5)	418.3 (151.8–774.4)	163.3 (132–294.6)	438.4 (81.9–948.4)	319.2 (148.2–889.7)	Non-significant
CRP, mg/l	3.85 (1.36–7.57)	4.59 (1.72–15.94)	2.86 (1.37–5.40)	4.26 (3.14–16.61)	2.31 (1.11–5.88)	4.17 (2.76–21.63)	Non-significant
Total cholesterol, mmol/l	4.6 (3.85–5.66)	3.8 (3.74–5.62)	4.56 (3.96–5.27)	3.96 (3.52–5.24)	4.51 (3.92–5.009)	3.89 (3.61–5.28)	Non-significant
HDL-c, mmol/l	1.02 (0.84–1.33)	1.17 (0.92–1.47)	1.04 (0.84–1.65)	1.38 (0.94–1.92)	1.56 (1.25–2.01)	1.01 (0.63–1.54)	< 0.012
LDL-c, mmol/l	2.59 (2–2.93)	2.17 (1.96–3.43	2.41 (2.03–3)	1.89 (1.46–2.7)	2.06 (1.68–2.62)	2.35 (2.05–3.14)	Non-significant
HDL/LDL ratio	2.31 (1.7–3.23)	2.11 (1.6–2.39)	2.16 (1.91–2.75)	1.53 (0.98–2.29)	1.17 (0.65–1.94)	2.38 (2.06–3.55)	< 0.006
TG, mmol/l	1.65 (1.15–3.89)	1.39 (1.12–2.36)	1.96 (1.22–2.48)	1.2 (0.85–2.25)	1.09 (0.87–1.9)	1.72 (1.24–2.76)	Non-significant

PTH – parathyroid hormone, TG – triglyceride, HDL-c – high-density lipoprotein (LDL) cholesterol particles, LDL-c – low-density lipoprotein (LDL) cholesterol particles;
Median (IQR); statistically significant differences: leukocytes: deceased: group 1 *vs.* group 3, group 3: survived *vs.* deceased; hemoglobin deceased group 2 *vs.* group 3; platelets: group 1: survived *vs.* deceased, deceased: group 1 *vs.* group 2; group 1 *vs.* group 3; HDL-c: survived: group 1 *vs.* group 3; group 2 *vs.* group 3; group 3 survived *vs.* deceased; HDL/LDL ration: survived: group 1 *vs.* group 3, group 2 *vs.* group 3, deceased: group 2 *vs.* group 3; group 3: survived *vs.* deceased

Table 3. Number and causes of hospitalization and patients' death during the study period

Parameter	Group 1 (HFrEF + HFmrEF)		Group 2 (HFpEF)		Group 3 (no HF)		p
	Survivors (N = 12 pts)	Deceased (N = 9 pts)	Survivors (N = 20 pts)	Deceased (N = 22 pts)	Survivors (N = 13 pts)	Deceased (N = 20 pts)	
Hospitalization							Non-significant
0 1 2 ≥ 3	4 4 3 1	6 1 1 1	6 12 1 1	10 6 4 3	5 2 4 2	8 6 2 6	
Causes							Non-significant
Infection CVD others	6 1 1	1 2 0	10 3 1	5 4 2	5 3 0	7 5 0	
Death		9		22		20	
Causes							Non-significant
COVID-19 CVD Others		4 5		19 3		13 5 2	

CVD – cardiovascular diseases

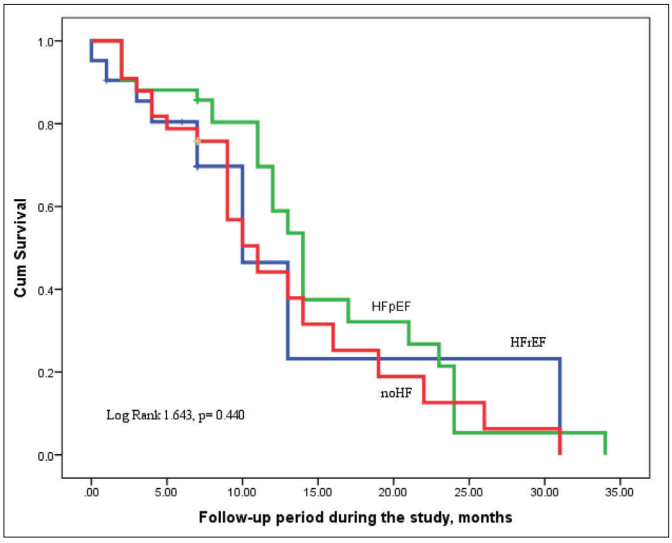

Figure 1. Survival plots for prevalent hemodialysis patients with heart failure (Kaplan–Meier analysis)

the lowest mean EF compared to the other two groups of patients. No other difference was found among subgroups regarding demographic, clinical, treatment, and ultrasound heart parameters except for the EF, which was the basis for patient grouping (data are not presented).

Laboratory analyses and lipid profile

Table 2 presents the results of laboratory analyses. When comparing survivors and deceased patients, those with HFrEF had higher platelet counts, while those without HF had lower leukocytes and serum sodium (both within normal limits). Minor differences, not statistically significant in iPTH and CRP were noted in both HFpEF and no HF subgroups. Also, deceased patients with HFrEF had the lowest leukocyte, hemoglobin, and platelet counts in comparison to other subgroups. Among survivors, patients with HFrEF had slightly lower phosphate and PTH compared to group 2 with HFpEF, but this difference was not statistically significant. Looking at lipids, in comparisons between survivors and deceased patients, group 3 had higher HDL-c levels, but a lower HDL/LDL ratio. On the other hand, survivors from group 2 showed a higher HDL/LDL ratio than deceased from the same subgroup.

Clinical outcome and survival analysis

No difference was found in the frequency and cause of hospitalizations between the examined groups of patients (Table 3). Throughout the 36 months of follow-up, 51 patients died. The frequency of COVID-19 infection being the cause of death (Table 3) was notably higher in comparison to cardiovascular diseases (CVD) across all groups of patients studied, i.e. 36 *vs*. 13 patients ($\chi^2 = 35.41$, $p < 0.001$).

No difference in patients' survival curves among the studied groups was found, as shown by Kaplan–Meier analysis (Figure 1). The medians for survival time – representing the point at which half of the patients were anticipated to remain alive – were as follows: 10 months (IQR 4.9–15.1) for HFrEF, 14 months (IQR 12.0–15.9) for HFpEF, and 11 months (IQR 7.39–14.61) for the no-HF group.

Mortality predictors were separately analyzed in each group using Cox regression analysis. Univariate Cox logistic regression analysis in patients with HFrEF identified the following mortality predictors: cardiovascular insult (CVI), pulse rate, and interventricular septum (IVS) thickness. However, multivariate analysis revealed only pulse rate and IVS thickness as independent predictors after adjusting for other variables in the model (Table 4). Each unit increase in the pulse rate correlated with a 187.47 times higher risk of mortality, though with considerable uncertainty due to a wide confidence interval. Similarly, IVS thickness showed a substantial risk increase, but with significant uncertainty.

For HFpEF patients, diabetes mellitus type 2 (DM2) and nephroangiosclerosis (as an underlying kidney disease), myocardial infarction, coronary artery bypass grafting, the use of diuretics, and the number of hospitalizations were identified by univariate analysis as significant predictors of mortality. Multivariate analysis retained only DM2, nephroangiosclerosis, and diuretic use as independent positive mortality predictors (Table 5). Although the wide confidence interval indicates some uncertainty in the estimate, the point estimate suggests a strong association between DM2, nephroangiosclerosis, and use of diuretics and mortality in patients with HFpEF.

Table 4. Mortality predictors selected with multivariable Cox regression analysis for patients from group 1 with heart failure with reduced ejection fraction

Parameter	Exp (B)	Sig	95% CI for Exp(B)	
			Lower	Upper
Pulse rate	187.470	0.027	1.839	19,110.495
IVS	8864.416	0.023	3.482	22,566,646.151

IVS – interventricular septum thickness

Table 5. Mortality predictors selected with multivariable Cox regression analysis for patients from group 2 with heart failure with preserved ejection fraction

Parameter	Exp (B)	Sig	95.0% CI for Exp(B)	
			Lower	Upper
DM2	15.366	0.007	2.091	112.930
Nscl	5.657	0.049	1.011	31.664
Diuretics, yes	4.043	0.044	1.036	15.777

DM2 – diabetes mellitus type 2; Nscl – nephroangiosclerosis

Table 6. Mortality predictors selected with multivariable Cox regression analysis for patients from group 3 with no heart failure

Parameter	Exp (B)	Sig	95% CI for Exp (B)	
			Lower	Upper
NYHA	2.055	0.031	2.055	3.953
Posterior wall	0.002	0.001	0.002	0.080
BMI, kg/m^2	1.271	0.006	1.271	1.511
Adipose tissue mass, kg	0.882	0.011	0.882	0.971

NYHA – New York Heart Association classification of heart failure; BMI – body mass index

In the case of patients with no HF, univariate Cox logistic regression analysis identified CVI, chronic obstructive pulmonary disease, IVS and posterior wall thickness, BMI, fat tissue, adipose tissue mass, sodium, HDL/LDL ratio, and number of hospitalizations as significant predictors of mortality. Multivariate analysis highlighted independent predictors for mortality to be NYHA class, BMI, posterior wall thickness, and adipose tissue mass after adjusting for other variables in the model (Table 6). Higher NYHA class correlated with a 2.05 times higher mortality risk, while each unit increase in BMI was associated with a 1.271 times higher risk. Conversely, each unit increase in adipose tissue mass is associated with a 0.882 times lower risk of mortality. Additionally, each unit increase in posterior wall thickness is associated with lower risk of mortality. However, the extremely small hazard ratio and wide CI indicate caution in interpreting this result.

DISCUSSION

In this single-center study, we aimed to examine the factors influencing the survival of prevalent HD patients with different HF phenotypes over a 36-month follow-up period. The key findings can be summarized as follows: 1) mortality rate among prevalent HD patients was high, with 53% of patients dying; 2) the survival rates of patients with two distinct HF phenotypes and those without HF were similar throughout the study; 3) COVID-19 infections emerged as a significantly greater risk factor for mortality compared to CVD; 4) *de novo* cardiovascular events contributed to a quarter of the recorded deaths, reaffirming the enduring significance of CVD as a mortality cause even during the pandemic; 5) analysis of laboratory and clinical parameters revealed noteworthy predictive associations with mortality: elevated pulse rate and specific cardiac structural parameters in patients with HFrEF, while primary kidney diseases, and diuretic usage in patients with HFpEF.

Our findings corroborate the elevated mortality observed in the studied population, aligning with conclusions drawn by other researchers. Comparing survival rates over two years, notable differences emerge when HF is present, with rates of 80% for patients without HF, and 33% for those with HF [12]. Regarding HF phenotypes, survival disparities have been reported. Among patients with HFpEF, a longer survival of 73% was noted, contrasting with HFrEF patients at 55% [12, 13, 14]. In the present study, mortality rates were 42.9% for HFrEF, 52.4% for HFpEF, and 60.6% for the no-HF patients. These outcomes, divergent from mortality analyses published so far, prompted us to investigate the underlying causes.

We conducted this study during the COVID-19 pandemic, and 70% of patients died due to COVID-19 infection equally distributed in all three groups of patients, compared to 25% who died due to *de novo* CVD (acute myocardial infarction, cerebrovascular insult). It is well known that COVID-19 infection has caused a substantial increase in mortality rates among the general population, and various patient populations, including those with cardiovascular diseases and patients with chronic kidney disease and on renal replacement therapy [15]. High mortality after the diagnosis of COVID-19 in HD patients was reported: the 28-day probability of death was 25%, but during the 90 days after diagnosis it reached 40.5%, emphasizing the increased vulnerability of HD patients due to a compromised immune system and the presence of numerous comorbidities [16, 17]. Our results led us to suspect that COVID-19 infection might have masked the impact of HF phenotype on patients' survival.

Our findings emphasize the ongoing significance of CVD in mortality, even beyond the context of the pandemic. Notably, 25% of the studied patients died of new cardiovascular events. Some differences in demographics and laboratory values between surviving and deceased patient subgroups could have influenced mortality. A higher prevalence of anemia was observed among deceased patients with HFpEF. This suggests a potential link between anemia, HF, and unfavorable outcomes, consistent with prior research [7]. Analyzing subgroups within HFrEF and HFpEF, deceased patients were older and with a higher proportion of males. Additionally, deceased patients with HFpEF had a shorter HD vintage. Patient age has consistently emerged as a mortality risk factor across studies, reflecting increasing mortality with age [5, 18]. Our observation of higher mortality among male patients with shorter HD vintage contrasts with findings by Sumida et al. [19]. They reported an inverse relationship between patient mortality and prolonged HD duration in a Japanese registry cohort. These disparities underscore the intricate

and multifaceted nature of factors contributing to patient outcomes, influenced in part by the size of the analyzed sample.

The observed associations between laboratory and clinical parameters with survival outcomes align with prior research. For instance, regardless of the limitations in interpretation and the uncertainty of the results, elevated pulse rate and cardiac structural parameters in HFrEF patients as positive predictors of mortality highlight the potential significance of both cardiac and hemodynamic factors in this cohort which is well-known from previous studies [14, 20]. The impact of underlying kidney disease (diabetic kidney disease and nephroangiosclerosis, to be more precise), and the use of diuretics (which reduce the risk of death) in patients with HFpEF on survival outcomes is consistent with the complex interaction between kidney function, cardiovascular health, and survival observed by other authors [14, 21, 22]. Additionally, the impact of metabolic parameters, serum sodium level, and lipid ratios on survival outcomes among patients with no HF offers further insights into the intricate finding of determinants in this cohort.

It is essential to acknowledge the limitations of our study, including the small sample size and the single-center design, which may limit the generalizability of our findings. Nevertheless, our analysis provides valuable insights into the complex of factors influencing survival outcomes in prevalent HD patients with different HF phenotypes. These findings pave the way for further research, potentially in multicenter studies, to validate and expand upon our observations, ultimately leading to a more comprehensive understanding of the predictors driving survival in this complex clinical scenario.

CONCLUSION

In this study of prevalent hemodialysis patients with diverse HF phenotypes, we analyzed survival dynamics. During the pandemic, COVID-19 emerged as a prominent cause of mortality, potentially obscuring expected differences in HF subtypes. While survival rates between the HFrEF, HFpEF, and no-HF subgroups showed no significant disparities, multivariable Cox regression unveiled independent predictors specific to each group that included pulse rate and cardiac parameters in HFrEF, kidney diseases in HFpEF, and metabolic factors in no-HF patients. As we interpret these results in the pandemic context, we emphasize the significance of ongoing research in the interplay of HF, dialysis, COVID-19, and survival, to guide enhanced patient care strategies. By combining personalized treatment plans, multidisciplinary collaboration, patient education, and ongoing research, healthcare providers can strive to improve outcomes and enhance the quality of life for these patients.

Conflict of interest: None declared.

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Фактори који утичу на смртност код превалентних болесника лечених хемодијализом са различитим типовима срчане инсуфицијенције – искуство једног центра

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САЖЕТАК

Увод/Циљ Ова ретроспективна студија са дужим праћењем имала је за циљ да анализира факторе преживљавања код превалентних болесника лечених хемодијализом са различитим фенотиповима срчане инсуфицијенције (СИ).

Методе Током 36 месеци, праћено је 96 болесника, а забележен је 51 смртни случај. Према типу СИ болесници су подељени у групе: СИ са смањеном ејекционом фракцијом (СИрЕФ), СИ са очуваном ејекционом фракцијом (СИоЕФ) и без СИ. Анализирани су демографски, клинички и лабораторијски параметри како би се идентификовали предиктори преживљавања унутар сваке подгрупе.

Резултати Криве преживљавања нису се значајно разликовале међу испитаним групама, а број умрлих је био следећи: 42,9% за СИрЕФ, 52,4% за СИоЕФ и 60,6% за болеснике без СИ. Главни узроци смрти били су инфекција ковидом 19 (70%), а затим *de novo* кардиоваскуларне болести (инфаркт миокарда и цереброваскуларни инсулт) (25%). Подгрупе преживелих и умрлих болесника разликују се по старости, полу, трајању хемодијализе и анемији и профилу липида. Мултиваријантна анализа идентификовала је предикторе преживљавања: код СИрЕФ брзину пулса и дебљину интервентрикуларног септума; код СИпЕФ примарно обољење бубрега, претходне срчане болести и употребу диуретика; код групе без СИ индекс телесне масе, натријум у серуму и однос *HDL*/*LDL* липида.

Закључак Добијени налази доприносе разумевању СИ код превалентних болесника лечених хемодијализом у ери пандемије. Како се СИ, дијализа и ковид 19 преплићу, даље истраживање је кључно за објашњење ове замршене интеракције и оптимизацију бриге о болесницима.

Кључне речи: срчана инсуфицијенција; хемодијализа; морталитет; фактори ризика

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Efficacy of combined use of *Tetradium ruticarpum* (A. Juss.) patch and Chinese massage (tuina) for the treatment of insomnia in elderly chronic heart failure patients

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SUMMARY
Introduction/Objective The objective of the paper was to evaluate the efficacy of *Tetradium ruticarpum* (A. Juss.) patch (TRP) in combination with Chinese massage (tuina) for the treatment of insomnia in elderly patients with chronic heart failure (CHF).
Methods A cohort of 320 elderly CHF patients with comorbid insomnia, treated at the Zhejiang University of Traditional Chinese Medicine Affiliated Wenzhou Hospital from January 2019 to July 2022, were enrolled and equally divided into four groups (80 patients per group). The control group received standard pharmacological intervention with eszopiclone. Patients in the TRP group received TRP alone, while those in the tuina group received tuina therapy alone. Patients in the combined treatment group received both TRP and tuina therapy. All treatments lasted 14 days. Sleep quality was assessed at baseline and then on days 7 and 14 after treatment using the Pittsburgh Sleep Quality Index Scale (PSQI).
Results There were significant reductions in total PSQI scores in all groups on day 7 compared to baseline ($p < 0.05$). On day 14, the combined treatment, tuina, and TRP groups showed significantly reduced total PSQI scores relative to baseline, while a reversal of this trend was seen in the control group ($p < 0.05$). The combined treatment group had the lowest total PSQI scores on both days 7 and 14.
Conclusion The combined use of tuina and TRP may be effective in alleviating insomnia in elderly CHF patients. It resulted in consistent and sustained efficacy, potentially reducing the likelihood of drug resistance.
Keywords: Chinese massage (tuina); *Tetradium ruticarpum* (A. Juss.) patch; chronic heart failure; insomnia

INTRODUCTION

The prevalence of chronic heart failure (CHF) among the elderly population in China exceeds four million [1]. The combination of advanced age and CHF precipitates a marked decline in sleep quality [2]. CHF contributes to sleep disturbances through symptoms such as chest tightness and breathlessness which interfere with the ability to lie down comfortably, leading to nocturnal discomfort and sedentary breathing [3]. Additionally, the reduced mobility associated with CHF exacerbates psychological distress which often manifests as anxiety and depression, leading to further deterioration in sleep quality [4]. During the protracted course of coronary heart disease (CHD), these physiological and psychological factors become compounded, thereby exacerbating insomnia and significantly decreasing the quality of life of the patient. Notwithstanding its negative impact, insomnia often receives less attention than the primary cardiac condition. This has resulted in paucity of diverse and effective therapeutic options for management of insomnia.

Traditional Chinese Medicine (TCM) emphasizes holistic regulation of bodily functions and seeks to re-establish equilibrium within the internal environment. This systemic approach offers potential benefits for managing insomnia, particularly in the elderly population. Recent empirical studies have highlighted the efficacy of Tuina in combination with other treatments in improving sleep quality, alleviating depressive symptoms, reducing TCM symptom scores, and enhancing overall quality of life in patients with insomnia [5, 6]. Furthermore, evidence suggests that TRP, a traditional *warm-natured* TCM modality, may be applied to *Yongquan* acupoints in the treatment of insomnia in the elderly, and it results in markedly fewer side effects than Western medications [7, 8]. However, there is a discernible gap in clinical research regarding the effectiveness of combined application of tuina and TRP in the treatment of insomnia in elderly CHF patients.

Therefore, the current study was aimed at investigating the clinical efficacy of an integrated intervention with tuina and TRP in a cohort of elderly CHF patients afflicted with insomnia, with eszopiclone as a pharmacological benchmark. The study was an attempt to carry out a comprehensive evaluation of the therapeutic impact of TCM modalities on sleep disturbances in elderly CHF patients with insomnia.

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METHODS

Clinical participates

This study enrolled 320 CHD patients with concomitant insomnia who were examined at the Zhejiang University of TCM Affiliated Wenzhou Hospital between January 1, 2019 and July 13, 2022. All subjects provided informed consent and agreed to participate in the study after being informed of its nature, potential risks, and benefits. This study was approved by the medical ethics committee of our hospital (approval number: WZY-2-23-KT-022-01). A strict selection process was designed to ensure the homogeneity of the study population in order to accurately assess the effects of the proposed TCM intervention on sleep quality in elderly CHD patients.

Inclusion criteria

All participants were confirmed to have CHD as per the criteria set out in the 2018 edition of Chinese Guidelines for the Diagnosis and Treatment of Heart Failure, as published by the Cardiovascular Disease Branch of the Chinese Medical Association [9]. Insomnia diagnosis was established in accordance with the parameters stipulated in the 2017 edition of the Chinese Guidelines for the Diagnosis and Treatment of Insomnia in Adults, as authorized by the Neurology Section of the Chinese Medical Association [10]. Eligible participants were those who exhibited a New York Heart Association (NYHA) functional classification of I–III, thereby indicating acceptable cardiac function.

Exclusion criteria

All patients with cardiac function class IV were excluded from this study. Moreover, patients with a history of malignancy, psychiatric disorders, and poorly-controlled common chronic diseases [e.g., type 2 diabetes mellitus (DM), hypertension, etc.], were excluded from the study.

Grouping and treatment

Grouping

A cohort of 320 patients diagnosed with CHD and comorbid insomnia was assigned to four groups: combined treatment group, tuina group, TRP group, and control group, with 80 subjects in each group.

Treatments

Patients in the control group received pharmacological intervention for insomnia in the form of estazolam (license: H11020891). The administration protocol involved an oral dose of 1 mg of eszopiclone given at bedtime. In the TRP group, a traditional acupoint application method was utilized to address insomnia symptoms. Specifically, 9 g of TRP was finely ground with an adequate volume of white vinegar to produce a paste which was uniformly spread out on oil paper to a thickness of approximately 1 cm. This preparation was applied bilaterally to the *Yongquan* acupoints at 20:00 hours, and it was allowed to remain in place for a duration of 12 hours each night. The tuina group underwent therapeutic Chinese massage, which was carried out daily for 20 minutes.

The acupoints and meridian areas for Chinese massage (tuina) were: (a) the temples, along with the *feng chi* and sleeping acupoints; (b) the area along the arch of the eyebrow from the *yin-tang* to the temples; (c) the area along the sides of the nose from the *yin-tang* down through the *yangbai* acupoints and back to the temples; (d) the area from the *yin-tang* to the *bai-hui* acupoints on the scalp, and (e) the areas around the eyes, forehead and cheeks, and the sides of the ears in the hairline zone. The other acupoints used were the abdominal *zhong wan, oihai*, and *guan yuan* acupoints, as well as the bladder meridian, the governing vessel, and the heart *shu*, liver *shu*, gallbladder *shu*, spleen *shu*, stomach *shu*, and kidney *shu* acupoints.

The combined treatment group received a synergistic intervention comprising the TRP acupoint application and tuina as detailed above. The intervention period for all the groups was set at 14 days. The study meticulously outlined the treatment modalities to ensure a standardized approach across all the participants, in order to allow for reliability in the evaluation of the efficacy of the TCM interventions for insomnia in patients with CHD.

Data collection and follow-up

Cardiac function

Pre-developed questionnaires were applied for collection of clinical data from medical records. The data comprised gender, age, height, weight, history of chronic diseases, and cardiac function indicators. The height and weight of each of the subjects were used to calculate the body mass index (BMI) by dividing body weight (in kg) with the square of height in meters (m^2). The histories of previous chronic diseases such as hyperlipidemia, myocardial infarction, cardiac arrhythmia, DM, primary hypertension and stroke, were determined based on the diagnostic certificates in medical records and the history of previous medications and treatments taken. If these could not be determined, the patient's primary healthcare physician was consulted for clarification. Cardiac function was assessed using the NYHA classification, six-minute walk distance test (6MWD), left ventricular ejection fraction (LVEF) measured using cardiac ultrasound, and calculated metabolic equivalents (MET) [11, 12].

Sleep quality

Sleep quality was quantitatively assessed at baseline, on the seventh day, and at the culmination of the 14-day treatment period, using the PSQI. This self-administered assessment measures seven components of sleep: latency, use of sleep medication, sleep quality, efficiency, disturbances, duration, and daytime dysfunction. Each component was

scored on a scale in which scores ranged from 0 (no sleep difficulty) to 3 (severe sleep difficulty), yielding a composite score between 0 and 21. The higher the score, the poorer the sleep quality [13].

Statistical analysis

All analyses were performed using IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables consistent with normal distribution are presented as mean ± standard deviation. Inter-group comparisons for the variables across the four groups were conducted using ANOVA, with post-hoc pairwise comparisons performed via the Least Significant Difference method. Categorical variables are depicted as frequencies, and were compared amongst groups using the χ^2 test; inter-group differences were assessed by comparing the categories with the highest and lowest frequencies. The χ^2 test yielded values and p-values. Multifactorial logistic regression was employed for determination of the association between the treatment regimen and sleep improvement. This yielded odds ratios (ORs), 95% confidence intervals, and p-values. Statistical significance was inferred at $p < 0.05$.

This study was approved by the Medical Ethics Committee of Zhejiang University of TCM Affiliated Wenzhou Hospital (WZY-2-23-KT-022-01).

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

Comparison of baseline characteristics amongst the four groups of patients

Results of comparison of baseline characteristics of patients amongst the four groups are presented in Table 1. There were no significant differences in gender, age, ethnic distribution, BMI levels, and the history of various chronic conditions such as hyperlipidemia (HTG), previous myocardial infarction (MI), arrhythmia, DM, and essential hypertension, amongst the four groups ($p > 0.05$). However, the frequency of stroke history, a factor closely linked to insomnia, was significantly higher in the control group than in the TRP group ($p = 0.027$). No significant differences were observed in stroke history among the other groups ($p > 0.05$). This uneven distribution of stroke history may potentially influence the validity of the outcomes of this study.

Table 1. Comparison of baseline characteristics of the four groups of patients*

Group	n	Male (n)	Age (years)	Han nationality (n)	BMI (kg/m^2)	Hyperlipidemia (n)
Combination therapy	80	49	68.1 ± 6.1	73	21.5 ± 1.8	33
Tuina	80	41	67.3 ± 6.0	76	21.2 ± 1.9	30
TRP	80	43	68.1 ± 5.7	70	21.1 ± 1.9	37
Control	80	48	68.4 ± 5.5	76	20.9 ± 1.8	29
F/χ^2		1.625	0.554	2.818	1.640	1.651
p		0.202	0.646	0.093	0.180	0.199
Group	n	MI (n)	Arrhythmias (n)	Type 2 DM (n)	Hypertension (n)	Stroke (n)
Combination therapy	80	41	12	27	33	9
Tuina	80	43	16	30	37	12
TRP	80	37	10	21	33	7
Control	80	46	17	29	41	17
F/χ^2		2.028	2.183	2.331	1.609	4.902
p		0.154	0.140	0.127	0.205	0.027

TRP – *Tetradium ruticarpum* (A. Juss.) patch; DM – diabetes mellitus; BMI – body mass index; MI – myocardial infarction;

*normally-distributed continuous variables are expressed as mean ± standard deviation, and differences amongst the groups were determined with ANOVA; categorical variables are expressed as frequencies, and differences between the groups were determined using the χ^2 test (i.e., comparison of the group with the highest frequency and the group with the lowest frequency)

Comparison of baseline cardiac function among the four groups of patients

As shown in Table 2, there were no significant differences in NYHA classification, 6MWD results, LVEF, and MET levels among the four groups. These findings indicate that cardiac function, a critical factor that affects sleep, was comparably distributed across the study groups, which shows that the results of this study are reliable. Furthermore, all subjects had adequate cardiac function, which helps minimize risks when implementing sleep improvement interventions.

Table 2. Comparison of baseline cardiac function among patients in four groups

Group	n	NYHA I–II stage (n)	6MWD (m)	LVEF (%)	MET
Combination therapy	80	62	321.7 ± 30.6	43.5 ± 3.1	2.6 ± 0.4
Tuina	80	66	318.0 ± 29.5	44.5 ± 3.2	2.5 ± 0.3
TRP	80	60	326.8 ± 29.1	43.9 ± 3	2.7 ± 0.4
Control	80	71	323.3 ± 27.5	43.8 ± 3	2.7 ± 0.3
F/χ^2		0.181	1.266	1.485	2.226
p		0.671	0.286	0.219	0.085

TRP – *Tetradium ruticarpum* (A. Juss.) patch; NYHA – New York Heart Association; 6MWD – six-minute walk distance test; LVEF – left ventricular ejection fraction; MET – metabolic equivalents

Comparison of PSQI scores among the four groups of patients

Table 3 shows that there were no significant differences in total PSQI scores and sub-scores in the seven dimensions among the four groups at baseline ($p > 0.05$). This indicates that the initial sleep conditions were similar across

Table 3. Comparison of the Pittsburgh Sleep Quality Index Scale subscales for patients in four groups*

Group	Sleep time	Drugs	Sleep quality	Sleep efficiency	Sleep disorders	Sleep duration	Daytime dysfunction	Total score
Baseline								
Combination therapy	1.9 ± 0.8	2.0 ± 0.7	2.1 ± 0.1	2.2 ± 0.3	1.7 ± 0.1	2.1 ± 0.9	2.1 ± 0.8	14.1 ± 2
Tuina	2 ± 0.7	1.9 ± 0.5	2 ± 0.7	2.1 ± 0.7	2 ± 0.6	2 ± 0.8	2.2 ± 0.7	14.1 ± 2
TRP	2.1 ± 0.1	2.2 ± 0.2	2.2 ± 0.8	2 ± 0.6	1.8 ± 0.3	2.1 ± 0.1	2 ± 0.6	14.3 ± 1.7
Control	1.9 ± 0.6	2 ± 0.7	2 ± 0.6	2.2 ± 0.6	1.8 ± 0.7	2.0 ± 0.3	2 ± 0.8	13.9 ± 1.8
F	1.130	1.885	2.192	1.913	2.278	0.837	1.658	0.564
p	0.337	0.132	0.089	0.127	0.080	0.474	0.176	0.639
Day 7 of treatment								
Combination therapy	0.6 ± 0.5	0.7 ± 0.5	0.6 ± 0.5	0.7 ± 0.6	0.6 ± 0.5	0.7 ± 0.5	0.7 ± 0.5	4.5 ± 1.4
Tuina	0.9 ± 0.7	1 ± 0.7	1 ± 0.4	0.9 ± 0.7	0.9 ± 0.8	1 ± 0.8	0.9 ± 0.7	6.7 ± 1.9
TRP	1.2 ± 0.7	1.1 ± 0.7	1 ± 0.2	1.1 ± 0.3	1 ± 0.7	0.9 ± 0.7	1 ± 0.8	7.2 ± 2.2
Control	0.8 ± 0.6	1.1 ± 0.6	0.9 ± 0.7	0.9 ± 0.9	1 ± 0.8	1.1 ± 0.7	1 ± 0.7	6.9 ± 1.6
F	10.060	6.112	5.148	5.687	6.240	5.109	5.030	36.636
p	< 0.001	< 0.001	0.002	0.001	< 0.001	0.002	0.002	< 0.001
Day 14 of treatment								
Combination therapy	0.7 ± 0.5	0.6 ± 0.5	0.7 ± 0.6	0.7 ± 0.5	0.6 ± 0.6	0.6 ± 0.5	0.6 ± 0.5	4.5 ± 1.4
Tuina	1 ± 0.7	1 ± 0.5	0.9 ± 0.8	1 ± 0.5	1 ± 0.3	1 ± 0.6	1 ± 0.7	6.9 ± 1.8
TRP	1 ± 0.6	1.1 ± 0.8	1 ± 0.7	1.1 ± 0.7	1.1 ± 0.6	1 ± 0.7	1 ± 0.6	7.2 ± 1.6
Control	2 ± 0.4	2.1 ± 0.3	1.9 ± 0.8	2.1 ± 0.4	2.0 ± 0.5	1.9 ± 0.8	1.9 ± 0.7	13.9 ± 1.8
F	64.971	68.309	52.285	75.236	69.383	52.182	59.998	474.276
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

TRP – *Tetradium ruticarpum* (A. Juss.) patch;

*normally-distributed continuous variables are expressed as mean ± standard deviation, and differences amongst groups were compared with ANOVA

all the groups, thereby enhancing the comparability of outcomes in subsequent studies on mitigation of insomnia using TCM.

On the seventh day of treatment, significant variations were observed in the total PSQI scale scores and sub-scores in the seven dimensions among the four groups, with the combined treatment group having the lowest total score and sub-scores ($p < 0.05$). These results indicate differences in efficacies of the various treatment regimens, with the combined treatment group exhibiting the highest efficacy.

On the 14th day of treatment, the differences in total PSQI scale scores and sub-scores in the seven PSQI dimensions amongst the groups were further amplified ($p < 0.05$). The combined treatment group maintained the lowest total score and sub-scores, while the score of the control group rebounded to baseline levels, with total score and sub-scores being the highest amongst the four groups ($p < 0.05$). These findings suggest that the efficacy of treatment was least in the control group on the 14th day of treatment.

Comparison of PSQI total scores at the three time points among the four groups

There were distinct changes in total scores on the PSQI for each study group during the treatment course. All the four groups had significantly lower PSQI total scores on the seventh day of treatment, when compared to baseline, indicating the effectiveness of the various therapies administered ($p < 0.05$). However, on the 14th day of treatment, the total PSQI score of the control group was significantly rebounded to the baseline level. In contrast, the total PSQI scores for the combined therapy group, the Chinese massage (tuina) group, and the TRP group were significantly reduced on day 14, relative to the respective baseline levels ($p < 0.05$). These findings suggest that therapeutic efficacy in the control group was significantly attenuated on day 14, while the other three groups sustained their levels of efficacy, as shown in Table 4.

Table 4. Comparison of Pittsburgh Sleep Quality Index Scale total scores for patients at the three time points*

Group	PSQI total scores				
	Baseline	Day 7 of treatment	Day 14 of treatment	F	p
Combination therapy	14.1 ± 2	4.5 ± 1.4†	4.5 ± 1.4†	935.070	< 0.001
Tuina	14.1 ± 2	6.7 ± 1.9†	6.9 ± 1.8†	399.757	< 0.001
TRP	14.3 ± 1.7	7.2 ± 2.2†	7.2 ± 1.6†	389.285	< 0.001
Control	13.9 ± 1.8	6.9 ± 1.6†	13.9 ± 1.8	423.606	< 0.001

PSQI – Pittsburgh Sleep Quality Index Scale; TRP – *Tetradium ruticarpum* (A. Juss.) patch;

*normally-distributed continuous variables are expressed as mean ± standard deviation, and differences amongst groups were determined using ANOVA;

†$p < 0.05$ *vs.* baseline

Multifactorial logistic analysis of the total PSQI scores of the four groups after treatment

As depicted in Table 5, after adjusting for gender, age, ethnicity, body mass index, history of previous diseases, and cardiac function indices, multifactorial analysis revealed

Table 5. Multifactorial logistic analysis of the comparison of Pittsburgh Sleep Quality Index Scale total scores after treatment among patients in the four groups*

Group	B	SE	Wald χ^2	p	OR	95% CI
Day 7 of treatment						
Combination therapy	-1.523	0.364	17.509	< 0.001	0.218	0.107–0.445
Tuina	0.542	0.756	0.515	0.473	1.720	0.391–7.567
TRP	0.212	0.652	0.106	0.745	1.237	0.344–4.442
Control	—	—	—	—	—	—
Day 14 of treatment						
Combination therapy	-2.236	0.457	23.909	< 0.001	0.107	0.044–0.262
Tuina	-4.233	0.791	28.656	< 0.001	0.015	0.003–0.068
TRP	-5.306	1.121	22.411	< 0.001	0.005	0.001–0.045
Control	—	—	—	—	—	—

TRP – *Tetradium ruticarpum* (A. Juss.) patch;

*multifactorial logistic regression was adjusted for gender, age, ethnicity, body mass index, past medical history, and cardiac function indicators

that the combined treatment group had significantly lower total PSQI scores than the control group on day 7 of treatment ($p < 0.05$). In contrast, the tuina and TRP groups did not exhibit statistically significant differences in total PSQI scores, when compared to control group ($p > 0.05$). These findings suggest that the combined treatment group outperformed, while the tuina and TRP groups showed comparable efficacy to the control group. Furthermore, multifactorial analysis indicated that on day 14 of treatment, the PSQI total scores were significantly lower in the combination therapy group, the tuina group, and the TRP group than in the control group ($p < 0.05$). These findings, in addition to the preceding results, suggest that sleep improvement efficacy remained satisfactory in the combined treatment group, the Tuina group, and the TRP group at day 14. In contrast, therapeutic efficacy was markedly decreased in the control group.

Side effects of the four groups after treatment

During the treatment period of all subjects, only one patient in the TRP group developed a mild rash, while two patients in the control group were accompanied by drowsiness and one patient developed dizziness. Patients in the combination therapy group and the tuina group did not experience any adverse effects.

DISCUSSION

CHF, a prevalent disease in the elderly population, is a common cardiac insufficiency condition due to several factors such as coronary artery disease, arrhythmia, and heart valve disease [3]. Although insomnia is not a symptom of CHF, it may be a resultant condition which further exacerbates the physiological and psychological states of CHF patients. This negative impact on CHF treatment and quality of life of patients underscores the need for effective treatment for insomnia. Modern medications such as eszopiclone and zolpidem offer reliable sedative effects. However, these drugs are associated with risks such as respiratory depression, particularly in CHF patients, in addition to the likelihood of increased drug resistance after long-term use [14]. In contrast, TCM offers benefits in the treatment of insomnia due to its unique properties [15].

The present study has demonstrated that the combined use of Chinese massage (tuina) and TCM-based relaxation practices (TRP) significantly mitigated insomnia, when compared to eszopiclone. Furthermore, with extended regular use, tuina and TRP, individually and in combination, maintained their effectiveness, unlike eszopiclone, which showed waning response over time. These findings are consistent with published data, an indication of the potential benefits of TCM in the management of insomnia in CHF patients [5–8].

Advancements in contemporary medicine have resulted in the extraction of evodiamine, the bioactive constituent of TRP. Subsequent research revealed its diverse biological potential: it was shown to effectively mitigate inflammation, malignant tumors, metabolic disorders, and cognitive impairments, and some preliminary data on the underlying molecular mechanisms are also available [16, 17, 18]. However, the specific mechanism behind anti-insomnia effect of the TRP was unknown, thereby highlighting an area of focus in future basic medical investigations. It has been reported that dehydroevodiamine and hortiamine, extracts from TRP, are able to potentially inhibit potassium channels in the myocardium in cellular and animal experiments, resulting in altered excitatory processes in the myocardium, which induces severe arrhythmias including tip-twisting ventricular tachycardia and ventricular fibrillation [19]. In contrast, another study showed that rutaecarpine (another TRP extract) is a promising cardiovascular protective alkaloid [20]. In the present study, only one patient was found to have a mild rash with the application of TRP and no patients with arrhythmia or blood pressure abnormalities were noted. The appearance of the rash may be related to the topical application of TRP, which also resulted in a very low intake of dehydroevodiamine and hortiamine, which avoided cardiac arrhythmia. The safety of the topical application of TRP has also been supported by another clinical study [21].

Chinese massage (Tuina), an integral part of external treatments in TCM, employs a plethora of techniques on various human acupoints to facilitate meridian flow and enhance internal organ functions, thereby aiding the treatment of diseases [22]. Tuina exhibits a broader spectrum of application, when compared to TR, which accounts for its benefits in diverse conditions affecting the motor, respiratory, neurological, digestive, and urinary systems [23]. This study not only confirmed the therapeutic effect of Tuina in insomnia, but also underscored the enhanced efficacy of combining Tuina with TRP in the management of insomnia. Furthermore, the research team exploited the application of tuina and TRP to abdominal acupuncture points and meridians associated with gastrointestinal function post-surgery [24, 25]. Thus, these findings may potentially expand the clinical application of combined therapy involving tuina and TRP.

Limitations of the study

A major limitation of this study is its small sample size, primarily due to limitations such as a lack of funding. A small sample size can potentially affect the statistical reliability as well as the robustness of the conclusions, but these findings provide a valuable basis for further, more extensive studies. Therefore, it is recommended that future studies use larger sample sizes and long-term follow-up to validate these findings.

CONCLUSION

The combination of Tuina and TRP holds promise as an effective therapeutic approach for alleviating insomnia in elderly CHF patients. This TCM technique exhibited sustained efficacy, and it potentially reduced the onset of drug resistance. A broader application of this TCM regimen in the CHF patient population may substantially enhance sleep quality, mental health, immune function, and overall quality of life, thereby boosting the confidence of patients in overcoming the disease.

Conflict of interest: None declared.

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Ефикасност комбиноване употребе фластера *Tetradium ruticarpum* (*A. Juss*.) и кинеске масаже (туина) за лечење несанице код старијих болесника са хроничном срчаном инсуфицијенцијом

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САЖЕТАК

Увод/Циљ Циљ рада био је да се процени ефикасност фластера *Tetradium ruticarpum (A. Juss.)* (ТРП) када се користи у комбинацији са кинеском масажом (туина) за лечење несанице код старијих болесника са хроничном срчаном инсуфицијенцијом.

Методе Кохорта од 320 старијих болесника са хроничном срчаном инсуфицијенцијом и коморбидном несаницом који су били на лечењу у болници Венџоу, придруженој болници Универзитета Џећанг у оквиру Универзитета традиционалне кинеске медицине, од јануара 2019. до јула 2022. године, била је уписана и подељена у четири једнаке групе (80 болесника у свакој групи). Контролна група је примила стандардну фармаколошку интервенцију са есзопиклоном. Болесници у групи ТРП примали су само ТРП, док су они у групи туина примали само терапију туина. Болесницима у групи комбинованог третмана дате су и ТРП и туина терапије. Сви третмани су трајали 14 дана. Квалитет спавања је процењен на почетку, а затим седмог и 14. дана после третмана коришћењем Питсбуршке скале индекса квалитета сна (ПСКС).

Резултати Било је значајног смањења укупних резултата ПСКС у свим групама седмог дана, у односу на почетну линију ($p < 0,05$). Дана 14, комбиновани третман, туина и ТРП групе показале су значајно смањене укупне резултате ПСКС у односу на почетне вредности, док је преокрет овог тренда примећен у контролној групи ($p < 0,05$). Група комбинованог третмана имала је најниже укупне резултате ПСКС и седмог и 14. дана.

Закључак Комбинована употреба туина и ТРП-а може бити ефикасна у ублажавању несанице код старијих болесника са хроничном срчаном инсуфицијенцијом. То је резултирало доследном и трајном ефикасношћу, чиме је смањена вероватноћа резистенције на лекове.

Кључне речи: кинеска масажа (туина); фластер *Tetradium ruticarpum (A. Juss.)*; хронична срчана инсуфицијенција; несаница

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Erectile dysfunction in ankylosing spondylitis – associations with disease-related parameters

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SUMMARY

Introduction/Objective Patients with ankylosing spondylitis (AS) often experience chronic musculoskeletal pain, fatigue, and stiffness, which may contribute to psychological distress and sexual dysfunction. This study aims to assess prevalence of erectile dysfunction (ED) in patients with AS and identify potential associations between clinical parameters related to AS with the presence of ED.

Methods Forty consecutive male patients with AS (mean age 42.8 ± 8.9 years) and 60 healthy men (mean age 38.9 ± 10.9 years) were included. All subjects filled out the International Index of Erectile Function (IIEF) questionnaire, as well as the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI). In patients with AS disease activity was evaluated using the Ankylosing Spondylitis Disease Activity Score (ASDAS) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), functionality using the Bath Ankylosing Spondylitis Functional Index (BASFI), and quality of life using the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire.

Results ED was significantly more frequent in patients with AS compared to controls (52.5%: 25%, p = 0.049). AS patients with ED had more severe symptoms of depression, than AS patients without ED (p = 0.034). According to ASQoL scores, patients with AS and ED had a worse quality of life, compared to patients with AS without ED (p = 0.022). The increase in one unit of ASQoL increased the odds of having ED for 17.5% (p = 0.035).

Conclusion ASQoL score, as a measure of quality of life, was the only independently associated parameter with the presence of ED. It is necessary to raise awareness of ED in patients with AS.

Keywords: ankylosing spondylitis; erectile dysfunction; ASQoL; depression; IIEF

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, inflammatory, autoimmune disease that dominantly affects younger men [1]. AS belongs to the group of spondyloarthropathies (SpA). Prevalence of the disease is believed to be 0.1–1.4% [2]. There is a strong association between human leukocyte antigen (HLA) B27 and AS. The onset of the disease is insidious and usually presented with bilateral sacroiliitis and inflammatory lower back pain (BP) (improved by exercise and not relieved by rest). Progressively, inflammation and ankylosis of the axial joints may result in dorsal kyphosis. Patients with AS may also have enthesitis (inflammation of insertions of tendons and ligaments to the bone and an asymmetrical oligoarthritis (especially on lower extremities). Extra-articular manifestations of AS include iridocyclitis, inflammatory bowel disease, and psoriasis [3]. The Assessment of SpondyloArthritis International Society (ASAS) criteria are widely used for the classification of AS. When a patient with at least three months of BP and age less than 45 years at disease onset has verified sacroiliitis on X-ray or MRI, one of the following criteria is necessary for classifying the patient as having axial spondylarthritis: inflammatory BP, arthritis, enthesitis, uveitis, dactylitis, psoriasis, inflammatory bowel disease, good response to nonsteroidal anti-inflammatory drugs (NSAID), family history for SpA, HLA-B27, or elevated C-reactive protein (CRP). Additionally, if patient is HLA-B27-positive and has not verified sacroiliitis on X-ray or MRI, it is necessary to have two of the features listed above in order to be classified as AxSpA (non-radiographic AS) [4]. Management of AS includes combination of non-pharmacological and pharmacological treatment. The non-pharmacological treatment includes physical therapy, regular exercises, education and lifestyle modification. Pharmacological treatment of AS with axial predominance includes NSAID, biologic agents such as tumor necrosis factor-alpha (anti-TNFα) inhibitors and anti-interleukin 17a (anti-IL17a) antibodies and recently added Janus kinase inhibitors (JAKi). When patient has peripheral joints affected sulfasalazine, methotrexate and leflunomide may be used [1].

Patients with AS often experience musculoskeletal pain, fatigue, stiffness, and low self-confidence. The chronicity of the disease may lead to psychological disturbances as well as sexual dysfunction. Beside the effort to combat AS by treating physical symptoms of the disease, it is important not to overlook other

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associated conditions, like depression, anxiety, or erectile dysfunction (ED) [5]. ED is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis sufficient for satisfactory sexual performance. It has a negative impact on both the patient's quality of life (QoL) and his relation with the sexual partner [6].

Some studies have shown that the prevalence of ED is higher among male patients with AS than in healthy males [7, 8]. According to the literature, morning stiffness, disease activity, and depression are associated with ED [9]. However, some studies did not find a clear association between AS and ED [10]. There are laboratory and imaging-based methods used for assessment of ED. Nevertheless, self-reported questionnaires are important tools in diagnosing and classifying ED in the clinical practice. The aim of this study was to determine prevalence of ED in patients with AS and to find potential association between clinical parameters related to AS and the presence of ED.

METHODS

This observational cross-sectional study was approved by the institutional Ethics Committee. The study included 40 consecutive male patients with AS (mean age 42.8 ± 8.9 years) and 60 healthy men (mean age 38.9 ± 10.9 years), who signed inform consent to participate in the study. Patients with the AS were recruited during their regular visit at the hospital. They were matched with healthy controls by age, education, and socioeconomic status. Excluding criteria were previous pelvic radiation or surgeries of the pelvis, penile deformities, as well as unregulated cardiovascular and endocrine diseases such as hypertension and diabetes mellitus.

All of the subjects enrolled in the study filled out the International Index of Erectile Function (IIEF-15), the Beck's Anxiety Inventory (BAI) and the Beck's Depression Inventory (BDI) questionnaires. IIEF-15 is a multidimensional self-assessment questionnaire with 15 questions, divided into five domains of sexual function (erectile and orgasmic functions, sexual desire, satisfaction with intercourse, and overall sexual satisfaction). There are six questions in the domain related to erectile function [11]. The answers were scored 0–5. IIEF score 0–10 is categorized as severe ED, 11–16 as moderate, 17–21 as mild to moderate, and 22–25 as mild ED. Subjects with IIEF score above 25 are considered as having normal erectile function. BDI is a useful tool for the assessment of depressive symptoms in everyday practice. The inventory consists of 21 questions. Answers to each question are scored 0–3, with the overall score ranging 0–63. The cut-off value for clinically significant symptoms of depression is 17. BAI is self-reported questionnaire with 21 questions related to anxiety symptoms. The answers are scored on a four-point scale from 0 (not at all) to 4 (severely). Total BAI scores are classified as follows: minimal anxiety (0–7), mild anxiety (8–15), moderate anxiety (16–25), and severe anxiety (30–63) [12].

Disease activity was evaluated using the Ankylosing Spondylitis Disease Activity Score (ASDAS). This score includes patient estimation of morning stiffness, BP, global disease activity, number of swollen and painful joints, as well as biohumoral markers of inflammation [CRP or erythrocyte sedimentation rate (ESR)]. The three cut-offs for staging the activity of the AS were the following: < 1.3 between "inactive disease" and "low disease activity," < 2.1 between "low to moderate disease activity" and "high disease activity," and >

3.5 between "high disease activity" and "very high disease activity" [13]. In addition, patients answered six questions for calculating Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). These questions were related to major symptoms of the AS: fatigue, spinal pain, arthralgia or arthritis, enthesitis, morning stiffness duration and morning stiffness severity. Scores of 4 and greater suggested active disease [14]. To assess the functional status of the AS patients, the Bath Ankylosing Spondylitis Functional Index (BASFI) questionnaire was used. The BASFI score ranges 0–10 points. Higher score indicates a higher degree of functional limitations [15]. Ankylosing Spondylitis QoL (ASQoL) is disease-specific questionnaire used to evaluate QoL in patients with AS. It consists of 18 questions with dichotomous answers (yes or no). The questionnaire is related to the impact of disease on sleep, mood, motivation, coping, activities of daily living, independence, relationships, and social life with a total score of 0–18. Lower ASQoL scores represent a better QoL [16]. Numerical rating scale (NRS) was used for the assessment of BP and BP at night (BP night). The 11-point numeric scale ranges from 0, representing one extreme of the pain (i.e. no pain), to 10, representing the other extreme of the pain (i.e. pain as bad as you can imagine or the worst pain imaginable) [17]. Other relevant clinical and demographic data (duration of the disease, CRP, medication) about the patients with the AS were obtained from medical records.

IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Categorical variables were presented as numbers or percentages and compared using χ^2 test. Continuous variables were expressed as mean with the standard deviation and depending on the normality of the distribution, independent t-test or Mann–Whitney test was performed. The univariate and multiple logistic regression model were used to predict statistically significant and independent parameters of the AS associated with the presence of the ED. Values $p < 0.05$ where considered to be statistically significant.

RESULTS

This study included 40 male patients with AS and 60 healthy males in the control group. The age of the patients with AS varied 21–64 years and 18–68 years in the control group. There was no statistically significant difference in the mean age between these two observed groups (Table 1). ED of any degree was significantly more present in patients with AS (21/40, 52.5%) comparing with the control group (15/60, 25%) ($p = 0.049$). The mean value of IIEF score in the group with AS was significantly lower than in

the control group (p = 0.035). BAI and BDI scores were higher in the group with the AS but without statistical significance. The mean duration of the disease was 10 ± 7.5 years. Anti-TNFα antibodies were used as part of the treatment in 77.5% of the patients with AS (Table 1).

Table 1. Clinical and demographic data on patients with ankylosing spondylitis and healthy controls

Parametrs	AS (n = 40, 100%)	Control (n = 60, 100%)	p
Age (years)	42.8 ± 8.9	38.9 ±10.9	0.065
ED	21 (52.5%)	15 (25%)	0.049
IIEF	22.3 ± 8.9	25.7 ± 7.5	0.035
IIEF grade			0.016
none	19 (47.5%)	45 (75%)	
mild	13 (32.5%)	10 (16.7%)	
moderate	3 (7.5%)	0 (0%)	
severe	5 (12.5%)	5 (8.3%)	
BAI	10.3 + 12.5	9.2+10.1	1
BDI	7.6 ± 7.4	6 ± 6.1	0.289
Duration of the disease (years)	10 ± 7.5	-	NA
CRP (mg/L)	6.8 ±10.3	-	NA
ASDAS	2.26 ± 1.2	-	NA
BASDAI	3.2 ± 2	-	NA
BASFI	3.43 ± 2.2	-	NA
ASQoL	5.9 ± 5.2	-	NA
BP	3.8 ± 2.7	-	NA
BP night	3.5 ± 2.7	-	NA
anti-TNFα	31 (77.5%)	-	NA

AS – ankylosing spondylitis; ED – erectile dysfunction; IIEF – International Index of Erectile Function; BAI – Beck Anxiety Inventory; BDI – Beck Depression Inventory; CRP – C reactive protein; ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; ASQoL – Ankylosing Spondylitis Quality of Life; BP – back pain; TNFα – tumor necrosis factor alpha

Table 2. Erectile dysfunction in patients with ankylosing spondylitis and control group with erectile dysfunction

Parameters	AS (n = 21, 100%)	Control (n = 15, 100%)	p
Age (years)	42.8 ± 9.2	39.4 ± 11.9	0.338
IIEF score	16.1 ± 8.2	16.4 ± 10.3	0.357
IIEF grade			0.292
mild	13 (61.9%)	10 (66.7%)	
moderate	3 (14.3%)	0 (0%)	
severe	5 (23.8%)	5 (33.3%)	
BAI	14.2 ± 15.6	17.9 ± 14.2	0.119
BDI	10 ± 8.1	11.9 ± 6	0.327

AS – ankylosing spondylitis; ED – erectile dysfunction; IIEF – International Index of Erectile Function; BAI – Beck Anxiety Inventory; BDI – Beck Depression Inventory

The mean age of group with AS and ED was 42.8 ± 9.2 years and 39.4 ± 11.9 years in the control group with ED. There was no significant difference in IIEF scores between these groups. BAI and BDI scores were higher in the control group, with no statistical significance (Table 2).

Patients with AS were divided into two groups based on the presence of ED and comparisons were made between those groups. There was no statistically significant difference in terms of age and duration of the disease among the groups (Table 3). According to the BDI, the group with AS

Table 3. Erectile dysfunction vs. without erectile dysfunction in patients with ankylosing spondylitis

Parameters	AS with ED (n = 21)	AS without ED (n = 19)	p
Age (years)	42.8 ± 9.2	42.7 ± 9	0.980
IIEF score	16.1 ± 8.2	29.1 ± 1.3	0
BAI	14.2 ± 15.6	6 ± 5.9	0.117
BDI	10 ± 8.1	5 ± 5.7	0.034
Duration of the disease (years)	9.21 ± 6.9	10.9 ± 8.2	0.714
CRP (mg/l)	7.4 ± 12	6.1 ± 8.3	0.714
ASDAS	2.4 ± 1.2	2.1 ± 1.17	0.578
BASDAI	3.1 ± 2	3.3 ± 2.2	0.763
BASFI	3.8 ± 2.3	3 ± 2	0.286
ASQoL	7.7 ± 5.4	4 ± 4.2	0.022
BP	4.1 ± 2.75	3.5 ± 2.6	0.470
BP night	3.7 ± 2.8	3.2 ± 2.8	0.576
anti-TNFα	16 (76.2%)	15 (78.9%)	1

AS – ankylosing spondylitis; ED – erectile dysfunction; IIEF – International Index of Erectile Function; BAI – Beck Anxiety Inventory; BDI – Beck Depression Inventory; CRP – C-reactive protein; ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; ASQoL – Ankylosing Spondylitis Quality of Life; BP – back pain; TNFα – tumor necrosis factor alpha

Table 4. Correlation of the clinical and demographic data of patients with the ankylosing spondylitis and erectile dysfunction with the International Index of Erectile Function

Parameters	AS (n = 40, 100%)	Spearman's ρ	p
Age (years)	42.8 ± 8.9	-0.47	0.773
BAI	10.3 ± 12.6 (0–54, med = 6)	-0.324	0.042
BDI	7.6 ± 7.4 (0-30, med = 6)	-0.430	0.006
Duration of the disease (years)	10 ± 7.5	0.061	0.707
CRP	6.8 ± 10.3	-0.035	0.832
ASDAS	2.26 ± 1.2	-0.132	0.416
BASDAI	3.2 ± 2	-0.008	0.961
BASFI	3.43 ± 2.2	-0.310	0.051
ASQoL	5.9 ± 5.2	-0.428	0.006
BP	3.8 ± 2.7	-0.124	0.447
BP night	3.5 ± 2.7	-0.160	0.323

AS – ankylosing spondylitis; ED – erectile dysfunction; BAI – Beck Anxiety Inventory; BDI – Beck Depression Inventory; ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; ASQoL – Ankylosing Spondylitis Quality of Life; BP – back pain

Table 5. Univariate and multivariate logistic regression of correlated parameters of ankylosing spondylitis and erectile dysfunction

Parameters	B	Wald	p	B (exp)
Univariate				
ASQoL	0.161	4.437	0.035	1.175
BAI	0.073	3.370	0.066	1.076
BDI	0.113	3.869	0.049	1.120
Multivariate				
ASQoL	0.161	4.437	0.035	1.175

ASQoL – Ankylosing spondylitis quality of life; BAI – Beck Anxiety Inventory; BDI – Beck Depression Inventory

and ED was likely to be more depressed than the group with AS without ED (p = 0.034). The same observation was made about anxiety symptoms and BAI in the groups with and without ED in patients with AS, but this observation was not statistically significant. Parameters reflecting disease activity (ASDAS, BASDAI, CRP), patient functionality (BASFI), as well as values of the NRS for BP and BP night were higher in the patients with AS and ED (Table 3). However, these findings were not statistically significant. The QoL of the group with AS and ED seemed worse than the QoL of the group with AS and without ED according to ASQoL scores (p = 0.022) (Table 3). The biologics were used in 76.2% of patients with AS and ED and in 78.9% of patients with AS and without ED, respectively (p = 1).

The scores for anxiety and depression assessment (BAI, BDI) as well as score for quality of life (ASQoL) showed negative correlation with the IIEF score (Table 4). Univariate logistic regression showed that BDI and ASQoL scores were associated with the presence of ED in patients with AS. However, in multivariate logistic regression analysis only ASQoL sustained itself as independent parameter associated with the presence in patients with AS (Table 5). The increase in one unit of ASQoL score increased the odds of having ED by 17.5% (p = 0.035).

DISCUSSION

This study found that more than half of included patients with AS had some grade of ED (52.5%). The inflammation as underlying pathological mechanism in AS may contribute to the atherosclerosis, which is strongly associated with the risk of ED [18]. In addition, there were studies about the role of high levels of proinflammatory cytokine TNFα in the upregulation of phosphodiesterase type 5, which resulted in decreased levels of pro-erectile mediators and potential onset of ED [19, 20]. However, most of the patients with AS and ED in this study were treated with anti-TNFα therapy implicating the possible significance of other risk factors for the development of ED. The mean CRP levels were higher in the group of patients with AS and ED, but without significant difference. Although the CRP and ESR are serological markers widely used to estimate the degree of inflammation, it is hard to judge inflammation over using them in spondyloarthropathies [21]. The inflammatory process could disturb the balance of male sexual hormones and perhaps could lead to the low testosterone level that could possibly lead to ED. In one study on 35 patients with AS and 104 healthy controls, Nisihara et al. [22] showed no difference in free and bioavailable testosterone in patients with AS comparing to healthy controls.

The chronic inflammation as well as anatomical and physiologic impairments in patients with AS have great impact on QoL. In our study, there was no statistically significant difference between parameters related to disease activity (ASDAS, BASDAI) and functionality (BASFI) among patients with and without ED. Despite that, mean ASDAS and BASFI scores were higher in the group with ED. The negative correlation between BASDAI and BASFI with the IIEF score was found in the meta-analysis of 39 studies [23]. However, Pirildar et al. [24] reported that only morning stiffness is associated with the ED. In our study, patients with AS and ED had higher scores on NRS for BP as well as for BP night than patients without ED. The patients with AS may have limited mobility of the intervertebral joints of the lower back and combined with BP could experience discomfort during the sexual intercourse, which may contribute to ED.

The age of the patients and the duration of the disease were similar among groups with and without ED. Santana et al. [21], as well as several other authors, did not find correlation between the age of patients and the duration of the disease with ED [25]. However, Dhakad et al. [26] in their study reported that the patients with AS and ED had a longer duration of the disease comparing to those without ED. Also, in the same study, the older age was a risk factor for ED. Even though our study had not reported the association between the age of the patients with AS and ED, knowing that the AS is the disease of the predominantly younger males, the impact of the age on the ED may be neglected.

The anxiety and depression were shown to be associated with ED. Chronic inflammation, pain, fatigue, and stiffness contribute to the onset of these conditions. Furthermore, disabilities and deformities in patients with AS may lead to state of being handicapped. Altogether, psychogenic status of patients with AS could be altered and lead to the onset of ED [25]. BAI, BDI, and ASQoL scores showed negative correlation with IIEF score in our study, which was also shown in the study by Santana et al. [21]. That study reported that problems with emotional health were present in 20% of patients with AS. One study which included 117 patients with AS and mean duration of the disease of 10 years showed that the symptoms of clinical depression were present in 49.5% [27]. The mean BDI and ASQoL scores in our study in patients with AS and ED were higher than in the group without ED. The symptoms of depression might be associated with the sexual dysfunction due to low QoL patients reported. However, in our study, BDI did not sustain itself as statistically independent parameter associated with ED.

While the previous parameters about disease activity (ASDAS, BASDAI) and functionality (BASFI) provide important information about the degree of disabilities and impairment experienced by patients, they do not inform us clearly about the impact of the condition on QoL [28]. ASQoL is made to concern the impact of the disease from the patient's perspective (rather than a clinical one) [29]. Sexual function is recognized as an important part of QoL. In our study, ASQoL was shown to be the independent parameter associated with the presence of ED. Patients with AS and ED had reported lower QoL than patients without ED. Similar results in ASQoL in patients with AS and ED were reported by Erdem et al. [25]. Van der Meer et al. [30] showed that the presence of extra-articular manifestations is associated with poorer QoL and reduced spinal mobility. Our results suggested that patients with ASQoL score of five or more points should be encouraged to talk

about this segment of life because the odds of having ED are higher than 50%.

The study lacked data on lipid status and history of smoking of the patients and healthy controls.

CONCLUSION

In our study, the prevalence of ED in patients with AS was higher than in the healthy controls, as reported in the literature. It is well known that patients with chronic rheumatic inflammatory diseases have more chance of developing ED, but the direct connection between AS and ED is still being researched. Rheumatologists should be aware of ED in patients with AS and accordingly to values of the associated parameters should make referral to urologist if appropriated.

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Conflict of interest: None declared.

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Параметри болести повезани са еректилном дисфункцијом код болесника са анкилозирајућим спондилитисом

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САЖЕТАК

Увод/Циљ Болесници са анкилозирајућим спондилитисом (АС) често имају укоченост и болове у мишићно-скелетном систему, што је праћено хроничним умором. Ове тегобе доприносе настанку психолошких сметњи и сексуалне дисфункције.

Циљ ове студије био је да испита учесталост еректилне дисфункције (ЕД) код оболелих од АС и да идентификује могућу повезаност клиничких параметара који се односе на АС са присуством ЕД.

Методе У студију је било укључено 40 мушкараца оболелих од АС (просечне старости 42,8 ± 8,9 година) и 60 здравих мушкараца (просечне старости 38,9 ± 10,9 година). Сви учесници студије су попунили Интернационални упитник за процену еректилне функције, Бекову скалу за процену анксиозности и Бекову скалу за процену депресивности. За процену активности АС код оболелих коришћени су скорови *ASDAS* и *BASDAI*. Функцијска способност је процењивана употребом индекса *BASFI*, док је квалитет живота евалуиран употребом упитника *ASQoL*.

Резултати ЕД је значајно више присутна код оболелих од АС у поређењу са контролном групом (52,5%: 25%, $p = 0,049$). Болесници са АС и ЕД имају озбиљније симптоме депресивности у односу на болеснике са АС који немају ЕД ($p = 0,034$). Према скору *ASQoL*, оболели од АС са ЕД имају лошији квалитет живота у поређењу са оболелим од АС који немају ЕД ($p = 0,022$). Пораст скора *ASQoL* за јединичну вредност повећава шансу за присуство ЕД за 17,5% ($p = 0,035$).

Закључак Скор *ASQoL*, као мера процене квалитета живота оболелих од АС, показао се као једини параметар који је независно повезан са присуством ЕД. Потребно је подићи свест о присуству ЕД код оболелих од АС.

Кључне речи: анкилозирајући спондулитис; еректилна дисфункција; Упитник о квалитету живота болесника са анкилозирајућим спондилитисом (*ASQoL*); депресија; Интернационални упитник за процену еректилне функције (*IIEF*)

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Functional results of patients with ankle syndesmosis injuries treated with the dynamic fixation (the syndesmosis TightRope® suture button) compared to the rigid fixation

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SUMMARY

Introduction/Objective Sprains account for 85% of all ankle injuries. Syndesmosis injuries occur in 1–18% of patients with ankle sprains and are more common in contact sports involving forced foot dorsiflexion.

Methods In our study, we compared 30 patients treated with dynamic fixation for acute syndesmotic injury with patients treated with rigid fixation. The criteria for comparison were: American Orthopedic Foot and Ankle Society (AOFAS) Ankle Hindfoot Scale, visual analogue scale (VAS), EuroQol five-dimension questionnaire (EQ-5D), range of motion, complications and reoperations.

Results The mean AOFAS score for patients treated with rigid fixation was 88.6, while the mean score for patients treated with dynamic fixation was 91.6. The mean VAS score for rigid fixation was 83.5, while it was 85.8 for dynamic fixation. Infection as a complication of rigid fixation was present in two patients (11.8%), while it was absent in the dynamic fixation group. The need for implant removal occurred in two patients treated with rigid fixation (11.8%) and in one patient treated with dynamic fixation (7.7%).

Conclusion Based on our results and the results reported by other authors, we prove that there is a lower incidence of problems related to implants and the need for the implant removal with dynamic fixation, based on the results of AOFAS score, we notice better and faster recovery with dynamic fixation as well.

Keywords: ankle syndesmosis injuries; dynamic fixation; rigid fixation; AOFAS score

INTRODUCTION

The talocrural joint is the supporting joint consisting of the articular surfaces of the distal tibia and fibula as well as the talus in its superior, medial and lateral aspects. The morphology of these surfaces forms a hinge-type synovial joint with one axis of movement (bimalleolar axis) which enables dorsiflexion and plantar flexion of the foot in the sagittal plane. The normal range of motion of plantar flexion is 23–56° and of dorsiflexion 11–33° [1]. Passive ankle stability depends on joint surface contour, joint capsule, collateral ligament and retinaculum integrity. Muscles provide dynamic stability of the ankle. Based on the functional relationship with the rest of the body, it is not surprising that ankle injuries are among the most common ones. Sprains account for 85% of all ankle injuries [2, 3]. Syndesmosis injuries occur in 1–18% of patients with ankle sprains and are more common in contact sports involving forced foot dorsiflexion [4]. Also, these injuries are associated with 23% of all ankle fractures [5].

Syndesmotic ligaments (talofibular ligaments) are composed of three separate parts. The anterior talofibular ligament is the weakest of all synesmotic ligaments and is the first to be injured when the fibula rotates around its longitudinal axis [6]. It consists of three parts, the upper which is the shortest, the medial which is the strongest and the lower which is the longest and thinnest. The posterior talofibular ligament is a strong, compact ligament whose lower edge literally forms the labrum for the lateral ridge of the trochlea of the talus. And the interosseous tibiofibular ligament, which consists of a network of pyramidal fibers composed of fibrous and adipose tissue [7].

The aim of this study is to present the functional outcome of patients with ankle syndesmosis injury treated with rigid or Tigh-rope fixation.

METHODS

In our study, we had 30 patients, of whom 18 were women and 12 men. The patients we included in the study were physically active and recreationally engaged in sports. The diagnosis of syndesmosis injury was made on the basis of clinical examination, X-ray and NMR. In our study, we compared patients treated with dynamic (ArthrexTighRope) fixation for acute syndesmotic injury with patients treated with rigid fixation. This study was retrospective and included patients who were treated in the

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Institute for Orthopedic Surgery "Banjica" in the period from 01 January 2016 to 01 January 2020. The inclusion criterion for our study was a syndesmosis injury which was proven intraoperatively. The exclusion criteria were open fracture and polytrauma. The criteria for comparison were: American Orthopedic Foot and Ankle Society (AOFAS) Ankle Hindfoot Scale, visual analogue scale (VAS), EuroQol five-dimension questionnaire (EQ-5D), range of motion, complications and reoperations.

Rigid and dynamic fixation of syndesmosis was performed in the operating room under radiographic control. The operations were performed according to AO principles. Antibiotics and thromboprophylaxis were given according to the Institute protocol. Patients were advised non-weight-bearing walking for six weeks with the present immobilization until the removal of the sutures (two weeks). Full weight-bearing was allowed after six weeks. After removing the sutures, the patients were referred to physical therapy. Regular visits occurred after the second, sixth, 12th, 24th week. We performed the assessment minimum six months after the injury.

To describe the results we obtained, we did the comparison with the healthy side and presented the results using the AOFAS score, which is a clinical score that evaluates the function of the ankle and foot before and after treatment, with a maximum score of 100 corresponding to normal ankle function. Through the EuroQol five-dimension questionnaire (EQ-5D), patients described the possibility of performing daily activities. This questionnaire contains five characteristics: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each of these characteristics has five levels: no problems, slight problems, moderate problems, serious problems and extreme problems. 5Q-5D can be used as a quantitative measure of treatment outcome assessed by the patient himself/herself. To monitor the subjective experience of symptom severity, we used VAS, which is used to quickly classify symptom severity and control of the disease or condition. We tested the range of motion by comparing the injured and healthy foot, and the results were expressed as a percentage relative to the uninjured side.

The study has been approved by competent Ethics Committee, and conforms to the legal standards. The Decision Number of the Ethics Committee is i-97/30.

RESULTS

Thirty patients were included in our study, of whom 13 were treated with dynamic fixation and 17 with rigid fixation (RF), aged 40–60 with a mean value of 49.3 ± 5.4 (RF 49.5 ± 5.4, dynamic fixation (DF) 49.0 ± 5.5, 0.795) of whom 18 were women (60%). RF was used in 10 (58.8%), DF in eight (61.5%), p = 0.880. The minimum follow-up period from the intervention was two years. We classified the fractures according to the AO classification. We had B1 type fractures in 11 (36%) patients – RF was used in nine (52.9%), DF in two (15.4%), B2 type fractures in nine (30%) patients – RF in five (29.4%), DF in four (30.8%), B3 type fractures in seven (23.3%) patients – RF in two (11.8%), DF in five (38.5%), C1 type fractures in two patients (6.7%), RF in 0 (0%), DF in two (15.4) %) and C3 type in one (3.3%) patient; RF in one (5.9%), DF in zero (0%) (Table 1).

In our study, the occurrence of infection as a complication was present in two (6.7%) patients. Both patients were treated with rigid fixation (11.8%), while in dynamic fixation we did not have this complication (0%). We had implant removal in three (10%) patients, of which two (11.8%) had rigid fixation and one (7.7%) had dynamic fixation (Table 2).

Table 1. Demographic characteristics of study population

Patient characteristics	Total n = 30	Rigid fixation n = 17	Dynamic fixation n = 13	p-value
Age, mean ± sd	49.3 ± 5.4	49.5 ± 5.4	49 ± 5.5	0.795
Gender, female, n (%)	18 (60)	10 (58.8)	8 (61.5)	0.880
Type of bone fracture, n (%)	B1	11 (36.7)	9 (52.9)	2 (15.4)
	B2	9 (30.0)	5 (29.4)	4 (30.8)
	B3	7 (23.3)	2 (11.8)	5 (38.5)
	C1	2 (6.7)	0 (0.0)	2 (15.4)
	C3	1 (3.3)	1 (5.9)	0 (0.0)

Table 2. Complications

Complications	Total n = 30	Rigid fixation n = 17	Dynamic fixation n = 13	p-value
Infection, n (%)	2 (6.7)	2 (11.8)	0 (0.0)	0.492
Screw removal, n (%)	3 (10)	2 (11.8)	1 (7.7)	1.000

We demonstrated that patients in the group in which syndesmosis was treated with dynamic fixation had better AOFAS scores and modified visual analog scales based on the EQ-5D-5L questionnaire.

The mean value of AOFAS score was 89.9 ± 13.9 (RF 88.6 ± 17.1, DF 91.6 ± 8.4, p = 0.572). The mean value of VAS scale was 84.5 ± 19.6 (RF 83.5 ± 21.7, DF 85.8 ± 17.2, p = 0.762), with a value of 1 indicating the worst and 100 the best result.

Also, by analyzing the modified EQ-5D-5L questionnaire, we obtained better results in most individual parameters in the group of patients treated with dynamic fixation compared to those treated with rigid fixation. The results are shown in Figures 1 and 2, as well as in Tables 3 and 4.

DISCUSSION

Since dynamic fixation of syndesmosis is a relatively new technique, the current literature on this topic consists mainly of studies with small samples, such as ours. In our study, the minimum follow-up period was two years from the intervention. The most common fracture types according to the AO classification were B1 and B2. Surgical treatment of syndesmosis injury is an imperative in treatment, to prevent ankle instability and secondary osteoarthritis. Standard treatment involves the use of trans-syndesmotic screws. While the new technique is the use of dynamic fixation (The syndesmosis TightRope® suture button)

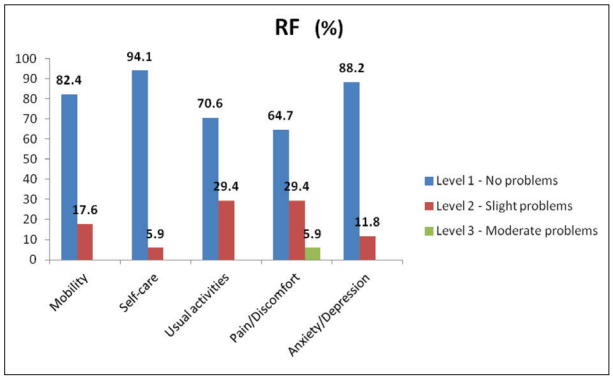

Figure 1. Rigid fixation (RF)

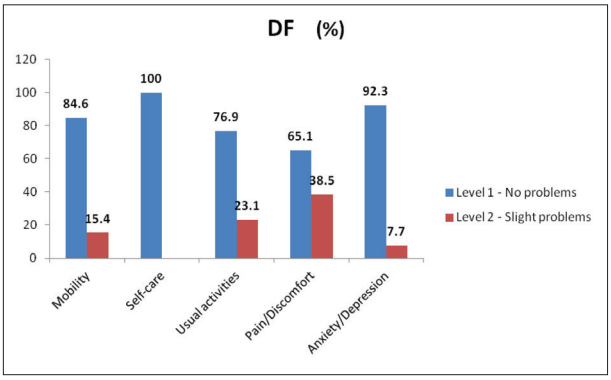

Figure 2. Dynamic fixation (DF)

Table 3. EuroQol five-dimension questionnaire (EQ-5D) results

Type of fixation	Mobility		Self-care		Usual activities		Pain/discomfort			Anxiety/depression	
	Level 1	Level 2	Level 1	Level 2	Level 1	Level 2	Level 1	Level 2	Level 3	Level 1	Level 2
RF, n (%)	14 (82.4)	3 (17.6)	16 (94.1)	1 (5.9)	12 (70.6)	5 (29.4)	11 (64.7)	5 (29.4)	1 (5.9)	15 (88.2)	2 (11.8)
DF, n (%)	11 (84.6)	2 (15.4)	13 (100)	0 (0.0)	10 (76.9)	3 (23.1)	8 (61.5)	5 (38.5)	0 (0.0)	12 (92.3)	1 (7.7)

RF – rigid fixation; DF – dynamic fixation

Table 4. Comparison of quality of life between patients treated with different procedures

Score	Total n = 30	Rigid fixation n = 17	Dynamic fixation n = 13	p-value
VAS, mean ± sd	84.5 ± 19.6	83.5 ± 21.7	85.8 ± 17.2	0.762
AOFAS, mean ± sd	89.9 ± 13.9	88.6 ± 17.1	91.6 ± 8.4	0.572

VAS – visual analogue scale; AOFAS – American Orthopedic Foot and Ankle Society score

which is a permanent stabilization system composed of a nonabsorbable suture. A drill hole is made through all four cortices in a parallel manner along the transmalleolar axis, 1–2 cm above the ankle joint. A needle containing the pull-through suture is advanced through the drilled hole from a lateral approach. The suture pulls the oblong button longitudinally across the hole until it can be flipped and attached to the medial tibial cortex. The suture is tightly tied by hand to stabilize compression. In cases of Maisonneuve fracture, two TightRope® sutures may be placed. The procedure requires anatomic fibular alignment, and thus associated fibular fractures usually undergo simultaneous reduction and internal fixation [8]. In their work, Westermann et al. [9] demonstrated that dynamic fixation allows more movement and better self-centering of syndesmosis, which proves better anatomical reduction of syndesmosis. In their study, Qamar et al. [10] presented 16 patients with tibiofibular syndesmosis injury treated with dynamic fixation, with a follow-up period of two years. The average AOFAS score was 86.88 ± 11.49. Thornes and McCartan [8] in a similar study showed a mean AOFAS score of 93 with TightRope® compared to the use of a transsyndesmotic screw whose mean AOFAS score was 83. Colcuc et al. [11] have proven in their study that dynamic fixation has a lower complication rate and earlier return to sports activities and their conclusion is that this method is especially recommended for highly active patients. Some authors showed that the use of rigid fixation is associated with a higher reoperation rate compared to dynamic fixation, mainly due to screw removal [12]. Routine screw removal is also associated with a wound infection rate of 5–9% [13]. One of the advantages of dynamic fixation is that it does not require implant removal [12]. Some studies show osteolysis, an implant slippage, and tibial drill-hole enlargement with the use of dynamic fixation [14, 15]. Better AOFAS results when using dynamic fixation compared to a rigid type, indicate a higher level of satisfaction and functionality in patients treated with dynamic type of fixation, which suggests that dynamic fixation is a valid option in the treatment of these injuries. Benedikte et all. showed that five years after syndesmotic injury which was treated with either dynamic or rigid fixation, they found better AOFAS and OMA scores and they also found lower incidence of ankle osteoarthritis, in the dynamic fixation group [16–27]. Based on our results and the results of the above authors, we prove that there is a lower incidence of problems related to implants and the need for the implant removal with dynamic fixation, based on the results of AOFAS score, we notice better and faster recovery with dynamic fixation as well. However, we believe that it is desirable to do a randomized controlled trial with more parameters in the outcome reports in order to determine the long-term effects of the dynamic fixation method.

Infection rate of patients who undergo surgical treatment of ankle fracture is 1–8%.

Predisposing factors for occurrence of infection are: patient age, high-energy injuries, smoking, diabetes, open fracture, compromised soft tissue sheath, alcoholism [28, 29, 30].

CONCLUSION

Since our results show reduced incidence of infections in patients treated with dynamic fixation, a study that would show whether the use of dynamic fixation has an effect on reducing the incidence of infection in all operated

ankles, should also be considered. The dynamic fixation system has a similar treatment result compared to rigid fixation. The rate of implant removal and infection is lower compared to the group treated with synedsmotic screw. Dynamic fixation is a modern and promising technique for surgical repair of ankle syndesmosis injury and can eventually replace traditional fixation with a trans-syndesmotic screw. In addition, there is a need for studies on the long-term effects of the TightRope® system.

Conflicts of Interest: None declared.

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Функционални резултати пацијената са повредом синдесмозе скочног зглоба лечених динамичком фиксацијом (*tight-rope*) у поређењу са ригидном фиксацијом

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САЖЕТАК

Увод/Циљ Уганућа чине 85% свих повреда скочног зглоба. Синдесмотске повреде се јављају код 1–18% пацијената са уганућем скочног зглоба и чешће су у контактним спортовима који укључују форсирану дорзифлексију стопала.

Методе У нашој студији поредили смо 30 пацијената који су лечени динамичком фиксацијом због акутне синдесмотске повреде са пацијентима који су лечени ригидном фиксацијом. Критеријуми за поређење били су: скор Америчког удружења за стопало и скочни зглоб, визуелна аналогна скала, упитник *EuroQol* са пет димензија, опсег покрета, компликације и реоперације.

Резултати Средња вредност скора Америчког удружења за стопало и скочни зглоб за пацијенте третиране ригидном фиксацијом била је 88,6, док је средња вредност за пацијенте третиране динамичком фиксацијом била 91,6. Средња вредност визуелне аналогне скале била је 83,5 код ригидне фиксације, док је код динамичке фиксације била 85,8. Инфекција као компликација ригидне фиксације била је присутна код два пацијента (11,8%), док је код динамичке фиксације нисмо имали. Потребу за уклањањем имплантата имали смо код два пацијента лечена ригидном фиксацијом (11,8%) и код једног пацијента леченог динамичком фиксацијом (7,7%).

Закључак На основу наших резултата и резултата наведених аутора, показали смо да је мања инциденца проблема везаних за имплантате и потреба за њиховим уклањањем код динамичке фиксације. Резултати скора Америчког удружења за стопало и скочни зглоб показали су бољи и бржи опоравак код динамичке фиксације.

Кључне речи: повреде синдесмозе; динамичка фиксација; ригидна фиксација; скор Америчког удружења за стопало и скочни зглоб

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Efficacy observation of acupoint application combined with psychological intervention in elderly patients with mild liver-qi stagnation depression

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SUMMARY

Introduction/Objective The objective was to propose a safer and more effective treatment method for mild liver-qi stagnation syndrome depression in elderly patients.

Methods A total of 70 elderly patients were recruited from the outpatient or inpatient departments of our hospital between July and December 2022 and were randomly divided into two groups, with 35 in each. The control group received sertraline, and the observation group received acupuncture point application combined with psychological intervention. The course of treatment was 10 days for four consecutive courses of treatment. Following courses 1, 2, and 4, the patients' Hamilton Depression Scale (HAMD-24) scores were compared. Statistical analysis was performed using the paired t-test and the χ^2 test.

Results After the end of courses 1, 2, and 4, the traditional Chinese medicine syndrome scale and total HAMD-24 scores were lower in the observation group than in the control group ($p < 0.01$, $p < 0.05$).

Conclusion The acupoint application combined with psychological intervention has a rapid and significant effect and fewer adverse effects in liver-qi depression.

Keywords: depression; acupoint application; psychological intervention; liver qi stagnation type

INTRODUCTION

With the aging population in China, the elderly account for a huge proportion of the total population. Widowhood, living alone and illness among the elderly are gradually increasing, enhancing their risk of mental health disorders, with depression particularly prominent [1]. Depression not only reduces the quality of life and happiness index of the elderly but also forms a vicious cycle with physical diseases such as hypertension, coronary heart disease, and cancers, and even leads to disability or death, thus bringing a heavy burden to families and society [2, 3]. Severe depression poses a risk of self-harm and suicide [4]. Sertraline is the most commonly used antidepressant treatment in clinics, and its efficacy has been confirmed. However, sertraline tablets can cause a variety of adverse reactions, such as dizziness, fatigue and dry mouth, with high incidences. In addition, the patients' compliance is low, and the therapeutic difficulty is high [5]. Acupoint application is adopted in traditional Chinese medicine (TCM) and is highly safe and generally does not induce side effects. Moreover, the drugs used are low-cost, contributing to suitability for long-term use and easy promotion. On this basis, the present study compares the clinical efficacy of acupoint application combined with psychological intervention in treating the elderly with mild depression due to liver-qi stagnation syndrome, to identify a safer and more effective therapeutic method.

METHODS

General data

Through a randomized controlled trial, a total of 70 elderly patients with depression due to liver-qi stagnation syndrome were recruited from the outpatient or inpatient departments of Jiangxi Provincial Institute of Traditional Chinese Medicine between July and December 2022. They were divided into two groups using a random number table, with 35 patients in each group. The entire intervention process for the observation group was conducted in our hospital.

This study was based on the sample size calculation formula for comparing means between the two groups: power (1-βerrprob) = 0.90, with alpha = 0.05. The sample size ratio in the two groups was 1:1. Based on a previous study, the effect size (δ) was set as 1.6 and the standard deviation (σ) as 2.15 [6]. The results showed that the sample size of the observation group should be 28 and that of the control group also 28, with a total sample size of 56. The loss to follow-up rate was calculated at 20%, meaning at least 35 patients were required for both the control group and the observation group, totaling 70 patients.

Diagnostic criteria

The TCM diagnosis was based on the diagnostic criteria for depression of liver-qi stagnation

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syndrome in the *Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine* [7]. The psychiatric symptoms included the following: (1) depression, fatigue and weakness; (2) suicidal thoughts/behavior and sense of despair; (3) anxiety and irritability; (4) inhibition of thought; and (5) slowness of movements. The physical symptoms were as follows: (1) dull complexion; (2) sternocostal fullness; and (3) dark purplish tongue with ecchymosis and white coating as the main symptom. Western medicine diagnosis was based on the diagnostic criteria for single or repeated episodes of depression in the *Chinese Classification and Diagnostic Criteria of Mental Disorders* published in 2001 [8].

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) according to the doctor's diagnosis, the total Hamilton Depression Scale (HAMD-24) score was > 8 and < 20, and the condition was diagnosed as depression of liver-qi stagnation syndrome in TCM; (2) patients aged 60–80 years; (3) patients willing to voluntarily participate in the trial and able to understand the scale content and fully cooperate with the treatment; and (4) patients and their families who provided informed consent. The exclusion criteria included the following: (1) patients diagnosed with severe psychiatric disorders by a specialist, and with recent self-harm or suicidal tendencies; (2) patients with severe internal diseases (doctor-diagnosed diseases that can affect emotions, such as coronary heart disease, cirrhosis, asthma); (3) patients with alcohol or drug dependency within one year [8]; (4) patients undergoing antidepressant treatment in the last month; and (5) patients who did not sign the informed consent form or who could not cooperate with the treatment.

Therapeutic methods

Control group

Sertraline was given orally at a regular dose of 50 mg/tablet once a day, in the morning or evening, before or after meals. The initial dose of 50 mg/day was adjusted according to the changes in the condition, with a maximum of 200 mg/day. The interval between dose adjustments was less than one week. The onset of the effect occurred within seven days, but it took longer to fully exert its effect. The patients' reactions were observed 2–3 weeks after administration to adjust any medical advice, and the adverse reactions were recorded [9]. The therapeutic drug and its dose were adjusted by a psychiatrist based on the condition, and the occurrence of adverse reactions was recorded.

Observation group: acupoint application

Based on the clinical symptoms of the patients, acupoints were selected by local acupoint selection, distant acupoint extraction and syndrome differentiation-based acupoint selection, including *shenmen*, double *shenshu*, double *ganshu*, double *pishu*, double *zusanli*, double *xinshu* and double *taichong*. The medicines for acupoint application were composed of *Codonopsis pilosula* (200 g), *Astragalus membranaceus* (300 g), *Ligusticum wallichii* (200 g), *Rhizoma atractylodis* (150 g), borneol (200 g), *Euphorbia kansui* (100 g), *Asarum heterotropoides* (100 g), and white mustard seed (100 g), which were crushed into a powder and well mixed with Vaseline to make a 2 × 2 cm medicine cake with a thickness of 0.5 cm. It was applied for 3–4 hours per day, with 10 days as a course of treatment for four consecutive courses of treatment. The patients were followed up every 10 days to assess their TCM syndrome and HAMD scores [10].

Psychological intervention

In terms of cognitive intervention, by communicating with the patients and their family members, they were helped to correctly and rationally understand possible discomforts and therapeutic measures, correct their misconceptions about depression, master coping skills, reduce their cognitive misunderstandings, and improve their adaptability. The onset, outcome, and prognosis of depression were introduced, and health manuals relevant to the disease were distributed and carefully interpreted. Health classes, knowledge lectures and health consultations were organized to provide the patients with a comprehensive understanding of the disease and its treatment [11]. For the psychological intervention, guidance was conducted through adopting targeted intervention plans to help the patients establish correct cognitive patterns and to guide them to engage in relaxation training. The patients were encouraged to communicate with other patients with good recovery, and those who were undergoing psychological intervention were asked to share their recovery experience.

In terms of family intervention, full use was made of the family and social support systems. Family members were encouraged to participate in the rehabilitation treatment of the patients, providing psychological support and life assistance and encouraging them to communicate more to obtain spiritual help and support from their families, to stimulate their confidence in life and their attachment to their families, and establish confidence in overcoming the disease. The patients were also encouraged to communicate with people around them and participate in group activities, and were assisted in cognitive reconstruction. In addition, the inner world of the patients was empathized with and the information conveyed by them was more accurately grasped, especially meaningful emotional messages implicit in language. The elderly should recognize that excessive worry and fear can only accelerate aging. They should be open-minded, try to look on the bright side and respect others' values, outlooks on life, and lifestyles. Many elderly people develop depression due to loneliness, meaning they can tend to shut themselves off at home and become unwilling to communicate with others. Children should encourage the elderly to participate in group activities, which can help alleviate this unhealthy psychology [12].

Evaluation criteria

The HAMD-24 scale was used to assess the depression status of the two groups before and after treatment [13]. A higher score indicated worse psychiatric symptoms. The TCM efficacy was evaluated with reference to the evaluation criteria for efficacy in the depression of heart and spleen deficiency syndrome proposed in the *Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine* [7]. Here, 'cured' meant the symptoms and signs had disappeared, or had essentially disappeared, and the syndrome score had decreased by > 90%; 'remarkably effective' meant the clinical symptoms and signs were improved significantly and the syndrome score had decreased by > 70%; 'effective' meant the clinical symptoms and signs were improved and the syndrome score had decreased by > 30%; and 'invalid' meant the symptoms and signs were not improved significantly or were aggravated and the syndrome score had decreased by < 30%. The formula for the TCM syndrome integral was (pre-treatment score – post-treatment score) / pre-treatment score × 100%.

Statistical analysis

All the data were statistically analyzed using SPSS Statistics, Version 16.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov method was used for the test of normality. The measurement data conforming to the normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and analyzed using the paired t-test. The enumeration data were expressed as *n* (%) and analyzed using the χ^2 test. A p-value of < 0.05 was considered statistically significant.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Jiangxi Provincial Institute of Traditional Chinese Medicine (batch number: 20220520). Written informed consent was obtained from all participants.

RESULTS

There were 16 men and 19 women in the observation group, and 14 men and 21 women in the control group. The mean age in the observation group was 67 ± 7 years and the course of the disease was 47 ± 6 days. In the control group, the mean age was 69 ± 5 years and the course of the disease was 49 ± 5 days. Overall, the participants were aged 58–82 years, with a minimum medical history of 14 days and a maximum of 68 days. There were no statistically significant differences in the basic data (e.g. gender) between the two groups (all $p > 0.05$), indicating comparability, as shown in Table 1.

Following treatment, the total effective rate of TCM syndrome in the observation group was higher than that in the control group. The total effective rate was 97.2% in the observation group and 91.4% in the control group, with a statistically significant difference ($p < 0.05$), as shown in Table 2.

No statistically significant difference was found in the HAMD-24 score between the two groups before treatment ($p > 0.05$), indicating comparability. After each course of treatment, the HAMD-24 score was improved. However, after four courses of treatment, the observation group had a significantly lower HAMD-24 score compared with the control group, with 8.73 ± 6.21 in the former and 16.23 ± 6.26 in the latter, presenting a statistically significant difference ($p < 0.05$) (Table 3).

Adverse reactions

Adverse reactions are defined as symptoms that do not occur before taking medication but do occur after taking medication. Compared with the control group, the incidence of adverse reactions in the observation group was lower, with an overall incidence of 2.9% in the latter and 91.4% in the former, indicating a statistically significant difference ($p < 0.05$), as shown in Table 4.

DISCUSSION

From a holistic perspective, TCM holds that depression is an emotional disease that can be classified into the category of 'depression syndrome,' with liver-qi stagnation syndrome and liver-kidney yin deficiency syndrome as the most common forms. Acupoint application therapy is a TCM treatment method that involves external treatment through applying medicines on certain acupoints to treat diseases through the interaction of medicines and acupoints [14]. As a unique external treatment for internal diseases in TCM, acupoint application acts on the outermost layer of the skin of the meridian system, stimulating acupoints and meridian qi. Through the body surface-acupoint-meridian-visceral system, the medicines are delivered from the surface to the interior through the skin, and to the viscera along the meridians, exerting dual therapeutic effects to regulate the qi, blood, yin and yang of the viscera, and ultimately achieving the goal of treating depression [15].

In the present study, *Codonopsis pilosula* was used in the application. This is the principal medicine that can benefit qi, nourish blood, and promote fluid production, and is compatible with *Astragalus membranaceus*, which has the function of warming and replenishing qi. *Ligusticum wallichii* can promote blood circulation, dissipate blood stasis, dissolve lumps and promote qi circulation, *Rhizoma atractylodis* is fragrant and can eliminate dampness and invigorate the spleen, whereas borneol can not only promote the percutaneous absorption of medicines but also prevents local skin infections. The warm acrid mobile and penetrating medicines, *Euphorbia kansui*, *Asarum heterotropoides*, and white mustard seed, were used to drive away the cold in the body, thereby regulating, mobilizing and improving

Table 1. Comparison of general data between the two groups of depressed patients

Group	n	Gender (n)		Age (n)			Course of disease (days)		
		Male	Female	Minimum	Maximum	Average ($\bar{x} \pm s$)	Shortest	Longest	Average ($\bar{x} \pm s$)
Observation group	35	16	19	61	82	67±7	14	68	47±6
Control group	35	14	21	58	80	69±5	17	63	49±5

Table 2. Comparison of efficacy in traditional Chinese medicine syndrome between the two groups [n (%)]

Group	n	Cured	Remarkably effective	Effective	Invalid	Total effective rate %
Observation group	35	15 (42.9)	17 (48.6)	2 (5.7)	1 (2.8)	97.2%
Control group	35	11 (31.4)	14 (40)	7 (20)	3 (8.6)	91.4%

Comparison of total effective rate between the two groups, $p < 0.05$

Table 3. Comparison of HAMD-24 score between the two groups before and after treatment ($\bar{x} \pm s$)

Group	n	Before treatment	After 1 course of treatment	After 2 courses of treatment	After 4 courses of treatment
Observation group	35	34.03 ± 8.43	27.33 ± 8.05	19.03 ± 7.88	8.73 ± 6.21
Control group	35	33.17 ± 7.06	28.76 ± 8.55	24.63 ± 8.35	16.23 ± 6.26

Compared with the same group before treatment, $p < 0.05$;
compared with the control group at the same time point, $p < 0.05$

Table 4. Comparison of adverse reactions between the two groups [n (%)]

Group	n	Sleep disorders	Dry mouth	Weakness	Dizziness	Others	Overall incidence %
Observation group	35	0 (0)	0 (0)	0 (0)	1 (2.9)	0 (0)	1 (2.9)
Control group	35	18 (51.4)	6 (17.1)	4 (11.4)	2 (5.7)	2 (5.7)	32 (91.4)

the physiological functions of the heart, spleen and kidney, and revitalizing the body's positive qi [16].

The results showed that after four courses of TCM acupoint application, the patients' depressive state could be significantly improved, suggesting that acupoint application can activate the aforementioned medicines through meridian acupoints and regulate body function, thereby effectively improving depression and other relevant symptoms in elderly patients. Compared with the control group, the incidence of adverse reactions in the observation group was lower, which indicated that acupoint application combined with psychological intervention therapy has high safety. Zhang and Zhao [17] used acupoint application combined with psychological intervention to treat patients with post-stroke depression, also revealing that the HAMD score of the observation group was significantly lower than that of the control group, which confirms the scientificity, effectiveness and practicality of our experiment.

Psychological intervention refers to conducting targeted psychological interventions through formulating intervention plans based on the characteristics of patients using psychological methods and techniques adopted by medical staff. Psychological intervention is not only an effective measure to improve medical quality, promote rehabilitation and reduce complications, but is also an effective means to establish a good doctor–patient relationship [18]. Psychological intervention during acupoint application refers to the process of step-by-step influencing the psychological activities, personality traits or psychological problems of patients under the guidance of psychological theory, leading to changes towards the expected goals [19]. The patient's body and mind should be relaxed to improve the therapeutic effect of this therapy.

Most studies have only adopted psychological intervention, without taking other measures, and have not used psychological intervention combined with drug therapy [20, 21, 22]. However, drug therapy, such as that using sertraline, has many side effects and is not tolerated by some elderly patients with stroke, meaning their treatment has to be stopped. As a result, the patients have poor medication compliance, and the drug efficacy is difficult to maintain. Although the final intervention effect is significant, there are adverse reactions that harm physical health and are prone to recurrence. We not only strengthened the therapeutic effect but also ensured its safety by adding an acupoint application. The final results also showed that the incidence of adverse reactions in the observation group was significantly lower than that in the control group.

Acupoint application combined with psychological intervention is a novel treatment method for liver-qi stagnation syndrome-induced depression. Acupoint application therapy combines the advantages of acupuncture and drug therapy. It not only has none of the disadvantages of internal medication, which can damage the spleen and stomach, but also integrates the characteristics of acupuncture to stimulate meridian qi movement, especially helpful for the elderly, young and weak. In addition, the medicines used are mostly common low-cost Chinese herbal medicines, thereby reducing the economic burden on patients and saving a large amount of medicinal material. Acupoint application therapy directly stimulates acupoints through medication and causes a significantly higher local drug concentration than with other areas through percutaneous absorption. The drugs penetrate into the meridians through the skin pores and move along them, thereby achieving the effects of regulating qi activity as well as yin and yang.

During psychological intervention, fully communicating with patients and discussing matters with them can help them change their misconceptions about certain points, thereby reducing the impact on their moods and emotions. It can help patients re-establish their own behavioral perspectives and values, and view problems and surrounding behaviors correctly and rationally. The combination of acupoint application and psychological intervention not only fully reflects the characteristics of TCM in China but also has the high safety of external application and no systemic adverse reactions.

This study also has some limitations. First, the sample size is relatively small and the samples were selected from a single hospital, leading to relatively low result representativeness. Second, only one type of patient group was studied, meaning the results cannot be generalized to all patients with depression. Therefore, in future research, we will consider enlarging the sample size, selecting participants from multiple sources, and expanding the sample type to explore whether this method can be applied to patients with other types of depression.

CONCLUSION

The combination of acupoint application and psychological intervention effectively alleviates the depressive state of patients with depression, with few side effects, low cost, high patient compliance, and high efficacy. Moreover, it makes full use of TCM, leverages the advantages of unique TCM treatment without toxic side effects, and has no adverse effects on the environment. When treating patients with depression, it can improve their emotional state.

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Посматрање ефикасности примене акупунктурних тачака у комбинацији са психолошком интервенцијом код старијих пацијената са благом депресијом повезаном са *qi* стагнацијом јетре

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САЖЕТАК

Увод/Циљ Циљ овог истраживања био је да се предложи безбеднији и ефикаснији начин лечења благе депресије повезане са *qi* стагнацијом јетре код старијих болесника.

Методе Укупно 70 старијих болесника из амбулантних и болничких одељења наше болнице у периоду од јула до децембра 2022. године насумично је подељено у две групе, са по 35 пацијената у свакој групи. Контролна група је добијала сертралин, док је посматраној групи примењена акупунктурна терапија у комбинацији са психолошком интервенцијом. Третман је трајао 10 дана у оквиру четири узастопна циклуса лечења. После првог, другог и четвртог циклуса упоређивани су резултати болесника на Хамилтоновој скали депресије (*HAMD*-24). Статистичка анализа је спроведена коришћењем *t*-теста за зависне узорке и теста χ^2.

Резултати На крају првог, другог и четвртог циклуса, Скала синдрома традиционалне кинеске медицине и укупни резултати *HAMD*-24 били су нижи у посматраној групи у поређењу са контролном групом ($p < 0,01$, $p < 0,05$).

Закључак Примена акупунктурних тачака у комбинацији са психолошком интервенцијом има брз и значајан ефекат са мање нежељених ефеката код депресије повезане са *qi* стагнацијом јетре.

Кључне речи: депресија; примена акупунктурних тачака; психолошка интервенција; *qi* стагнација јетре

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The effects of web-based progressive muscle relaxation exercise on perceived stress and anxiety levels of nursing students who were in clinical practice for the first time – a randomized controlled trial

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SUMMARY

Introduction/Objective It is reported that during the education process, uncontrollable long-term stress affects professional identity development and health of nursing students negatively.The effects of web-based progressive muscle relaxation exercises on perceived stress and anxiety levels of nursing students who were in clinical practice for the first time were analyzed in the present study.

Methods The present study used a randomized controlled design.The study was carried out at a state university in Turkey. A total of volunteering 66 nursing students (36 in the control and 30 in the intervention group) in clinical practice for the first time who were studying during the 2021–2022 academic year were included in the sample. Intervention group students performed 36 sessions of progressive muscle relaxation exercise three days a week for 12 weeks. The data were collected by using the Sociodemographic Characteristics Form, State-Trait Anxiety Inventory (STAI), and Perceived Stress Scale (PSS).

Results In comparing post-test mean scores of intervention and control group, PSS and STAI total mean scores of the intervention group were found to be statistically significantly lower than those of the control group ($p < 0.05$).

Conclusion Progressive muscle relaxation exercise was found to reduce perceived stress and anxiety in nursing students who were in clinical practice for the first time.

Keywords: anxiety; nursing student; stress; progressive muscle relaxation; randomized controlled study

INTRODUCTION

Nursing education consists of two complementary parts: theoretical and clinical. Clinical education, an essential component, helps students acquire skills such as effective communication, problem-solving, clinical decision-making, and critical thinking. It also allows students to observe and adapt to the harmonious collaboration of various professionals. It also includes multiple difficulties that may lead to stress and anxiety in students [1]. In clinical education, students may experience anxiety and stress due to unfamiliar environments, the need to communicate with various healthcare professionals, fear of making mistakes and harming patients, lack of practical interpersonal communication skills, self-confidence, information, and skills [2]. Stress and anxiety can be both positive and negative emotions. Moderate levels can motivate students and enhance their performance [3]. High levels of stress and anxiety can negatively impact students' physical and psychological health, as well as their academic, clinical, and overall performance [2, 3]. Literature reports that the first clinical practice is the stage that causes the most stress and anxiety in the clinical education process [4, 5]. It is also stated that nursing students managing their stress and anxiety more effectively will result in more effective clinical training [6].

Studies in literature have examined the effects of music therapy, progressive muscle relaxation (PMR) exercises, cognitive therapy, emotional freedom technique, breathing exercises, mind-clearing, and aromatherapy methods on decreasing stress and anxiety levels in nursing students [7, 8, 9]. One preferred method for reducing stress and anxiety is PMR exercise because it is easy, inexpensive, reliable, and helps cope with academic stress [10]. Different studies suggest PMR exercises throughout nursing courses to increase student satisfaction, reduce anxiety and stress, and promote positive perspectives [3, 11, 12]. PMR exercises are performed to enable self-relaxation by helping individuals feel the difference between tension and relaxation in their bodies. PMR exercises decrease muscle tension, leading to less stress and anxiety, and provide a feeling of deep rest, refreshment, and rebirth [13].

It is reported that during the education process, uncontrollable long-term stress negatively affects professional identity development and the health of nursing students [14]. Nursing students are affected by numerous academic,

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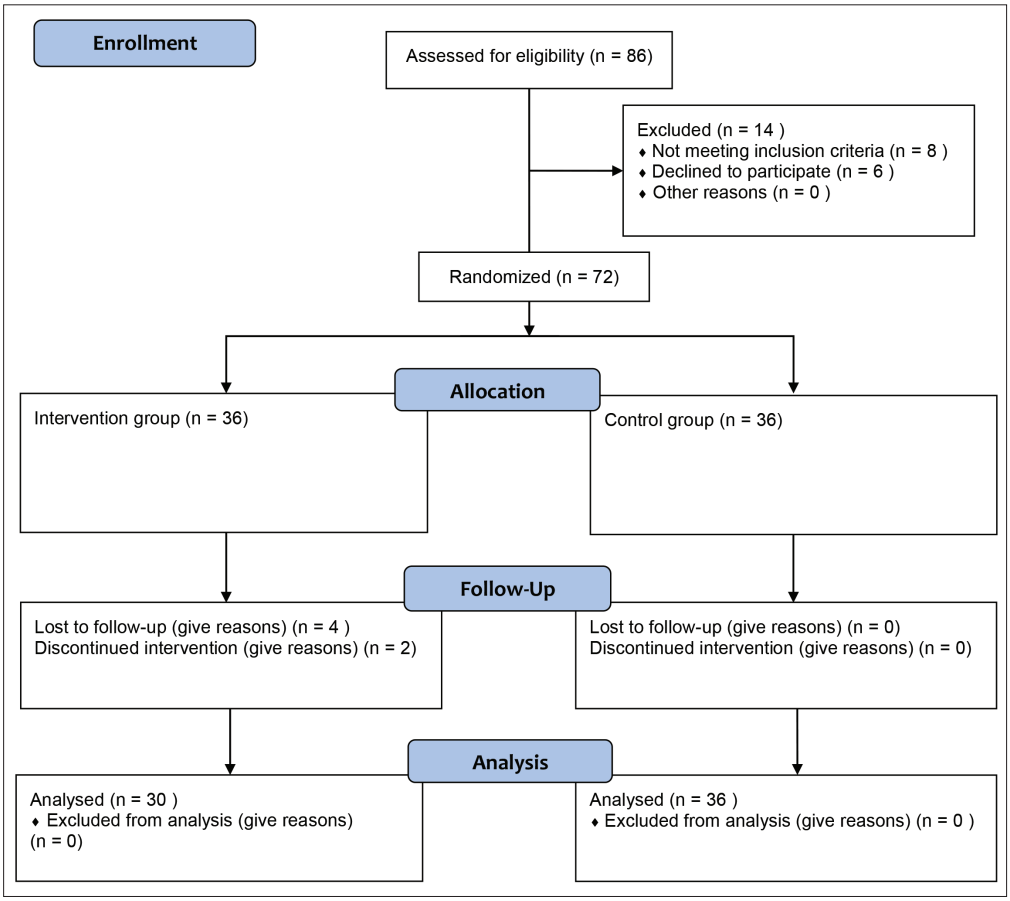

Figure 1. Enrollment process

social, and psychological stressors. Additionally, the pandemic has introduced many new challenges that may have further increased students' stress levels [15, 16]. Students are concerned that they will not be able to develop clinical skills due to problems in nursing education, most of which consist of clinical practice [17].

The stress and anxiety levels of nursing students at the beginning of their educational process, who have limited professional knowledge and skills, should be examined, especially as they transition from online to face-to-face clinical practice due to the COVID-19 pandemic. This study will contribute to understanding students' potential stress and anxiety regarding their first clinical practice, offer solutions to mitigate this stress and raise educators' awareness. It is believed that using relaxation therapy can enhance students' satisfaction with clinical practice, foster a positive perspective, and reduce stress. Therefore, the aim of this study is to analyze the effects of web-based PMR exercises on the perceived stress and anxiety levels of nursing students during their first clinical practice.

Study hypotheses

H_0– Web-based PMR exercise does not affect the perceived stress and anxiety levels of nursing students who experience clinical practice for the first time.
H_1– Web-based PMR exercise affects the perceived stress and anxiety levels of nursing students who experience clinical practice for the first time.

METHODS

This study was designed as randomized parallel study with a pre-test, mid-test, and post-test control group. Clinical trial registration was done (ClinicalTrials.gov.:NCT05312749).

Population and sample of the study

The study included 300 second-year nursing students at a state university in Turkey during 2021–2022. In total, 86 students were reached, and 72 (36 intervention, 36 control) were sampled. The study was completed with 66 students (36 control, 30 intervention), as six did not participate regularly. Inclusion criteria: aged over 18, second-year student, no psychiatric history. Exclusion criteria: first-, third-, or fourth-year student, prior clinical practice, relaxation exercises. Post hoc power analysis with G-Power 3.1.9.4 showed an effect size of 0.156 and a power of 0.88 at a 95% confidence interval, indicating sufficient sample size.

Randomization

Students were randomly assigned student numbers during university enrollment. For this study, odd-numbered students were in the intervention group, and even-numbered students were in the control group, ensuring equal numbers (1:1 ratio). In total, 72 students were distributed accordingly (Figure 1).

Data collection tools

The study collected data using the Sociodemographic Characteristics Form, State-Trait Anxiety Inventory (STAI), and Perceived Stress Scale (PSS).

Sociodemographic Characteristics Form: The form included questions about students' demographics, feelings about clinical practice, willingness to choose nursing, love for the profession, and previous hospital experience.

STAI: Öner and Le Compte [18] adapted the STAI for Turkish, ensuring its validity and reliability. The STAI has two parts: the State Anxiety Inventory (SAI) and the Trait Anxiety Inventory, each with 20 items. This study used the SAI, which measures state anxiety at a specific time. Scores range from 20 to 80, with higher scores indicating higher anxiety. The Cronbach α level for the SAI was 0.94–0.96. This study's pre-test and post-test Cronbach α values were 0.918–0.941.

PSS: Eskin et al. [19] validated the Turkish version of the PSS-14. This 14-item scale has two factors: "insufficient self-efficacy" and "perceived stress," with a five-Likert-type range. Scores range from 0 to 56, with higher scores indicating higher stress levels. Scores between 0–35 are normal, while 35–56 indicate high stress. The original Cronbach α was 0.84; in this study, it ranged from 0.765 to 0.842.

Pre-application

Five students tested the survey questions for clarity, finding all questions clear and sufficient. Their data should have been included in the research.

Progressive muscle relaxation exercise CD

The "Relaxation Exercises CD" by the Turkish Psychologists Association, featuring a 30-minute session with instructions and river sounds, was used [3, 20]. PMR exercises were performed three times a week for 12 weeks (36 sessions total) to reduce anxiety and stress in nursing students during their first clinical practice.

WhatsApp group

A WhatsApp group was created to share information and manage the study. The CD was converted to a WhatsApp-compatible format and shared as a voice recording.

Progressive Relaxation Exercise Application Record Chart

This chart was created for students to record their sessions and for researchers to track them, covering seven days a week for 12 weeks.

Application of progressive relaxation exercise

Before starting the exercise training, an online Zoom meeting was held. A researcher explained the exercises' definition, aim, benefits, and techniques. Steps were demonstrated, practiced, and checked for correctness. Following the audio recording commands, students were instructed to perform the exercises for 30 minutes in the evening three days a week for 12 weeks. Daily reminders were sent at 8 p.m. through WhatsApp. Students shared confirmation messages in the group about their practice. Weekly calls checked for any problems.

Fundamentals of nursing course

The university offers theoretical courses and lab applications in the first year, preparing students for clinical practice. In the second year's first semester, students take the "Fundamentals of Nursing" course that lasts for 28 hours (two hours per week for 14 weeks) with about 100 students. Students engage in 112 lab and clinical practices (eight hours per week) alongside theoretical courses to apply their knowledge. Active learning methods like group discussions, reflection, problem-based learning, and case analysis are used in the course.

Clinical practice

The laboratory application lasted four weeks, and the clinical application lasted eight weeks, totaling 12 weeks for the PMR exercise. Initially, students practiced nursing skills in the laboratory, focusing on infection control, drug administration, nutrition, and urinary interventions on simulation models. In the fifth week, students started clinical practice. The lecturer explained the responsibilities at the clinic, and students met the clinic team, adapted, and informed patients. Students were at the clinic from 8:00 a.m. to 4:00 p.m. once a week for eight weeks, participating in patient care and treatment practices.

Control group

After collecting the pre-test data, no interventions were given to these students. The same forms were distributed online as mid-test, and post-test surveys.

Data collection

After collecting pre-test data using the Sociodemographic Characteristics Form, STAI, and PSS forms, the intervention group was taught PMR exercises. These were performed three days a week for four weeks alongside laboratory practices. In the fifth week, students started clinical practice and continued the exercises. Both groups filled out mid-test forms before clinical practice in the fifth week and post-test forms in week 12. Forms had to be completed within five minutes; otherwise, they were deemed invalid.

Data assessment

Socio-demographic characteristics were summarized with frequency and percentage. Group homogeneity was analyzed using the χ^2 test. The independent t-test compared the groups' mean ages. Intragroup comparisons of STAI

Table 1. Sociodemographic characteristics of students (n = 66)

Variables		Groups				Test value and significance
		Intervention		Control		
		N	%	n	(%)	
Gender	Female	23	76.7	26	72.2	$\chi^2 = 0.169$ p = 0.681
	Male	7	23.3	10	27.8	
Type of family	Nuclear	22	73.3	32	88.9	$\chi^2 = 2.662$ p = 0.103
	Extended	8	26.7	4	11.1	
Place of living	Dormitory	23	76.7	29	80.6	$\chi^2 = 0.576$ p = 0.750
	Family home	6	20	5	13.9	
	Peer home	1	3.3	2	5.6	
Feeling fearful about clinical practice	Yes	26	86.7	26	72.2	$\chi^2 = 2.043$ p = 0.153
	No	4	13.3	10	27.8	
Feeling nervous about clinical practice	Yes	26	86.7	34	94.4	$\chi^2 = 1.198$ p = 0.274
	No	4	13.3	2	5.6	
Feeling curious about clinical practice	Yes	20	66.7	25	69.4	$\chi^2 = 0.058$ p = 0.809
	No	10	33.3	11	30.6	
The state of choosing nursing department willingly	Yes	20	66.7	25	69.4	$\chi^2 = 0.058$ p = 0.809
	No	10	33.3	11	30.6	
The state of loving nursing profession	Yes	27	90	34	94.4	$\chi^2 = 0.462$ p = 0.497
	No	3	10	2	5.6	
Previous hospital experience (hospital attendant, patient, etc.)	Yes	19	63.3	21	58.3	$\chi^2 = 0.171$ p = 0.679
	No	11	36.7	15	41.7	
Feeling ready for clinical practice	Yes	7	23.3	15	41.7	$\chi^2 = 2.475$ p = 0.116
	No	23	76.7	21	58.3	
Sufficiency of theoretical knowledge	Yes	5	16.7	5	13.9	$\chi^2 = 0.098$ p = 0.754
	No	25	83.3	31	86.1	
Continuous variables		**X ± SD**	Min–max	**X ± SD**	Min–max	
Age		19.93 ± 0.944	18–22	19.75 ± 1.42	18–23	t = 0.775 p = 0.441

and PSS scores used repeated measurements ANOVA for normal distributions and the Friedman test for non-normal distributions. The dependent t-test analyzed normally distributed groups, while the Wilcoxon test analyzed non-normal groups. Between-group comparisons used the independent t-test for normal distributions and the Mann–Whitney U test for non-normal distributions. Multiple linear regression analyzed the effect of progressive relaxation exercises on stress and anxiety.

Ethical considerations

The university's ethics committee approved the study on September 16, 2021 (2021/09-45). The study followed the Declaration of Helsinki principles and obtained written consent. After data collection, PMR exercises were taught to three willing control group students, and the CD was shared with them for ethical equality.

Clinical trial registration was done (ClinicalTrials.gov.: NCT05312749). The CONsolidated Standards Of Reporting Trials checklist for randomised controlled trials was used in this study.

RESULTS

In the intervention group, 76.7% were female, 73.3% had a nuclear family, 76.7% lived in a dormitory, 86.7% had fears about clinical practice, 86.7% felt nervous, and 66.7% felt curious. Additionally, 66.7% chose nursing willingly, 90% loved nursing, 63.3% had hospital experience, 76.7% did not feel ready for clinical practice, 83.3% lacked theoretical information, and the mean age was 19.93 ± 0.944. In the control group, 72.2% were female, 88.9% had a nuclear family, 80.6% lived in a dormitory, 72.2% had fears about clinical practice, 94.4% felt nervous, and 69.4% felt curious. Furthermore, 69.4% chose nursing willingly, 94.4% loved nursing, 58.3% had hospital experience, 58.3% did not feel ready for clinical practice, 86.1% lacked theoretical information, and the mean age was 19.75 ± 1.42. Both groups are homogeneous in sociodemographic characteristics (Table 1).

In the intervention group, statistically significant differences were found in PSS and STAI pre-test, mid-test, and post-test scores ($p < 0.05$). Differences in insufficient self-efficacy perception were between pre-test and post-test scores ($p < 0.05$). Differences in perceived stress were between pre-test, mid-test, and post-test scores ($p < 0.05$). SAI differed between pre-test, mid-test, and post-test scores ($p < 0.05$). No statistically significant differences were found in the control group in the PSS factors pre-test, mid-test, and post-test scores. Statistically significant differences were found between both groups in post-test insufficient self-efficacy perception, pre-test stress perception, pre-test and post-test PSS, and post-test SAI scores ($p < 0.05$) (Table 2).

Table 2. Comparison of intragroup and between groups of perceived stress scale and factors and state anxiety inventory scores of nursing students

Perceived stress scale factors		Groups		Test value and significance between groups
		Intervention	Control	
		X ± SD	X ± SD	
Insufficient self-efficacy perception	Pre-test[1]	13.47 ± 5.09	12.92 ± 3.73	t = 0.492 p = 0.625
	Mid-test[2]	11.73 ± 4.82	11.39 ± 5.09	t = 0.280 p = 0.780
	Post-test[3]	9.43 ± 5.03	12.72 ± 3.07	**t = -3.054 p = 0.003**
	Difference	1 > 3[x]	None	
Intragroup test value and significance		**F = 6.072 p = 0.004**	Friedman = 4.491 p = 0.106	
Stress perception	Pre-test[1]	17.07 ± 5.47	13.72 ± 5.34	**t = 2.506 p = 0.015**
	Mid-test[2]	14.50 ± 4.22	14.64 ± 4.70	U = 481.50 p = 0.448
	Post-test[3]	12.83 ± 4.97	13.83 ± 4.29	U = 475.50 p = 0.402
	Difference	1 > 2, 1 > 3[x]	None	
Intragroup test value and significance		**F = 8.296 p = 0.001**	Friedman = 0.645 p = 0.724	
Total Perceived Stress Scale	Pre-test[1]	30.53 ± 8.02	26.64 ± 5.90	**t = 2.270 p = 0.027**
	Mid-test[2]	26.23 ± 7.72	26.03 ± 7.04	U = 510.50 p = 0.703
	Post-test[3]	22.26 ± 8.99	26.56 ± 6.04	**U = 293.00 p = 0.001**
	Difference	1 > 2, 1 > 3, 2 > 3[y]	None	
Intragroup test value and significance		**Friedman = 23.248 p = 0.001**	Friedman = 1.206 p = 0.547	
State Anxiety Inventory	Pre-test[1]	47.23 ± 9.88	41.11 ± 8.96	t = 2.638 p = 0.010
	Mid-test[2]	40.63 ± 8.84	41.92 ± 7.45	t = -0.640 p = 0.524
	Post-test[3]	38.73 ± 8.19	45.50 ± 9.03	**t = -3.160 p = 0.002**
	Difference	1 > 2, 1 > 3[y]	3 > 1[y]	
Intragroup test value and significance		Friedman = 16.167 p = 0.001	Friedman = 6.048 p = 0.049	

*p < 0.05
x – dependent groups t test; y – Wilcoxon test

Multiple linear regression analysis showed a significant positive effect of PMR on insufficient self-efficacy perception (β = -0.357, p < 0.003), perceived stress (β = -0.277, p < 0.024), and state of anxiety (β = -0.367, p < 0.002) (Table 3).

DISCUSSION

Clinical teaching environments are crucial for nursing students to develop professional knowledge and skills, but they also create significant anxiety and stress. This study analyzed the effects of PMR exercises on nursing students' perceived stress and anxiety levels before their first clinical practice. Unlike previous studies, this research examined the additional stress and anxiety caused by the COVID-19 pandemic, such as close contact with patients and infection risk, alongside the usual anxiety of first clinical practice. The results showed that PMR exercises significantly decreased stress and anxiety levels. Therefore, hypothesis 1 was accepted, indicating that these exercises effectively reduce stress and anxiety in nursing students.

Nursing students experience various stress levels during clinical practices [21, 22]. This study found high rates of fear, nervousness, and curiosity about clinical practice, with moderate stress and anxiety levels before starting clinical practice. Bahçecioğlu Turan et al. [5] also found moderate anxiety among nursing students during the COVID-19 pandemic. These findings align with existing literature, indicating that moderate anxiety and stress reflect students' need for support. Recognizing and addressing students' anxiety before clinical practice can help create a less traumatic experience and a positive learning environment. Hamadi et al. [23] reported increased stress among nursing students during the COVID-19 pandemic, leading to more use of stress-coping strategies. This study supports PMR exercises as an effective, cost-free coping method. The study's timing during the COVID-19 pandemic is significant. The pandemic likely influenced the finding that perceived stress levels remained the same while anxiety levels decreased in the intervention group. This highlights the importance of PMR exercises in reducing stress and anxiety among nursing students during challenging times.

This study found a significant decrease in anxiety levels of intervention group nursing students. It is essential to provide intervention strategies to manage nursing students' stress and anxiety levels before the first clinical practice. In the literature, it is recommended to try different methods as intervention programs so that during clinical practices nursing students can manage their stress and anxiety [24]. In this study, PMR exercises were applied as an intervention program because they are the most efficient and effective therapy for psychosomatic disorders like anxiety and stress [25]. This is because, in a relaxed state, the body generates natural chemicals to repair damage and eliminate toxins. Additionally, relaxation nurtures internal abilities, increases capacity to think and innovate, and empowers psychological and mental strength, increasing useful output and self-confidence [26].

Various studies have demonstrated the effectiveness of PMR exercises in reducing anxiety levels among nursing students. For instance, research by, İnangil et al. [3], Korkut et al. [27] and Pelit-Aksu et al. [20] reported significant reductions in anxiety and stress levels both before and during clinical practice. Similarly, Ayed [11], Toqan et al. [28] and Torabizadeh et al. [9] highlighted the effectiveness of PMR exercises, particularly in managing anxiety within psychiatric and intensive care settings. These findings align

Table 3. Regression analysis results regarding the effects of progressive muscle relaxation exercise on anxiety and perceived stress levels

Dependent variable	Model	Variables	B	S.Error	β	t	p
Insufficient self-efficacy perception	1	Fixed	9.433	0.795		11.860	**0.001***
		Progressive muscle relaxation exercise - intervention	3.289	1.077	-0.357	3.054	**0.003***
	R = 0.357, R^2 = 0.127						
	F = 9.327, p = 0.003*						
Stress Perception	1	Fixed	12.833	0,841		15.253	**0.001***
		Progressive muscle relaxation exercise - intervention	1.000	1.139	-0.109	0.878	0.383
	R = 0.109, R^2 = 0.012						
	F = 0.771, p = 0.383						
Perceived Stress Scale	1	Fixed	22.267	1.373		16.215	**0.001***
		Progressive muscle relaxation exercise - intervention	4.289	1.859	-0.277	2.307	**0.024***
	R = 0.277, R^2 = 0.077						
	F = 5.320, p = 0.024*						
State Anxiety Inventory	1	Fixed	38.733	1.581		24.495	**0.001***
		Progressive muscle relaxation exercise - intervention	6.767	2.141	-0.367	3.160	**0.002***
	R = 0.367, R^2 = 0.135						
	F = 9.988, p = 0.002*						

with our study, supporting the notion that PMR exercises can help reduce pre-clinical practice anxiety, thereby fostering a more positive learning environment. Given the heightened stress and anxiety during the COVID-19 pandemic, the use of these exercises emerged as an economical and effective intervention. The present study aligns with other studies, showing that intervention group students used relaxation techniques more and integrated them into their lives. PMR helped students learn to stretch and relax muscle groups, reducing stress and anxiety by alleviating muscle tension. This study contributes to the literature by enhancing nursing students' psychological health with an economical, web-based method, avoiding pharmacological approaches.

Limitations of the study

The leakage of information from students with previous clinical experiences and from intervention groups to control groups may have influenced the study results. Other limitations include conducting the study in a single school and not comparing it with different education curricula. Additionally, PMR exercises were not applied to the control group after completing the study.

CONCLUSION

PMR exercises significantly decreased perceived stress and anxiety in nursing students. These results suggest PMR can reduce stress and anxiety during clinical practice. It is recommended to assess students for anxiety, identify those at risk, and implement measures to reduce anxiety before clinical practice. This method is crucial for nurses, especially during disasters like COVID-19 pandemic, to healthily cope with anxiety.

PMR can be recommended as a supportive treatment for nursing students in clinical practice. It can serve as a stress management tool. Future studies should include more students and be conducted in universities with different curricula. A qualitative study could also better understand nursing students' experiences with interventions to reduce stress.

Conflict of interest: None declared.

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Ефекти прогресивне релаксације мишића путем интернета на перципирани стрес и нивое анксиозности код студената сестринства током првог искуства у клиничкој пракси – рандомизована контролисана студија

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САЖЕТАК

Увод/Циљ Пријављено је да током образовног процеса неконтролисани дуготрајни стрес негативно утиче на здравље и развој професионалног идентитета студената на студијама сестринства. У овој студији анализирани су ефекти онлајн вежби прогресивне релаксације мишића на нивое перципираног стреса и анксиозности код студената Факултета медицинских сестара који су први пут били у клиничкој пракси.

Методе Ова студија је користила рандомизовани контролисани дизајн. Спроведена је на државном универзитету у Турској. У узорак је укључено укупно 66 студената сестринства (36 у контролној и 30 у студијској групи) који су први пут били на клиничкој пракси, а студирали су током школске 2021–2022. Студенти у студијској групи одрадили су 36 сесија вежби прогресивног опуштања мишића три пута недељно током 12 недеља. Подаци су прикупљени коришћењем Обрасца социодемографских карактеристика, Инвентара анксиозности као стања и особина и Скале перципираног стреса.

Резултати Поређењем средњих резултата после теста студијске и контролне групе, укупни средњи резултати Скале перципираног стреса и Инвентара анксиозности као стања и особина у студијској групи били су статистички значајно нижи од оних у контролној групи ($p < 0,05$).

Закључак Утврђено је да вежбе прогресивног опуштања мишића смањују перципирани стрес и анксиозност код студената сестринства који су први пут били у клиничкој пракси.

Кључне речи: анксиозност; студенти сестринства; стрес; прогресивна релаксација мишића; рандомизована контролисана студија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Sociodemographic and socioeconomic predictors of unmet healthcare needs of adolescents and young adults in Serbia – a part of the national research

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SUMMARY

Introduction/Objective Recognizing the reasons for the unmet health needs of adolescents and young adults is important for identifying the barriers in solving certain health problems, as well as for monitoring the availability, level of use and implementation of healthcare. The aim of this study was to establish the socio-demographic and socio-economic parameters associated with unmet healthcare needs of adolescents and young adults in Serbia.

Methods This cross-sectional study is a part of the 2019 Population Health Survey of Serbia, carried out by Statistical Office of the Republic of Serbia in cooperation with the Dr. Milan Jovanović Batut Institute of Public Health of Serbia and the Ministry of Health of the Republic of Serbia, on a stratified two-stage sample. The survey included 1519 respondents, aged 15–24 years. The instruments and methodology of the European Health Survey – third wave (EHIS-wave 3) were used. Factors associated to unmet healthcare needs were examined using logistic regression and the χ^2 test.

Results Unfulfilled health needs were present in 4.1% of respondents, and the dominant reasons were finances (44.4%) and long waiting times (34.9%), distance from health institutions was recorded in 1.6% of respondents, while 19.5% of respondents stated several reasons. Multivariate analysis revealed that significant parameters of unmet healthcare needs include age, region, marital, and employment status.

Conclusion The results of this research can give a new direction in creating strategies and defining preventive programs to reduce inequality in the health of adolescents and young adults improve the health of future young generations.

Keywords: healthcare; health services' needs; adolescents; young adults; health surveys; Serbia

INTRODUCTION

A society's systematic, all-encompassing efforts to maintain and enhance its members' health are known as healthcare. The healthcare system consists of institutions, laws, and other regulations in the field of health, as well as organizations responsible for health insurance. Its main goals are the prevention of diseases and health disorders, the improvement and restoration of health and it is responsible for implementation of programs and services for individuals, families, and society. This system is society's response to unforeseen events that threaten health, and its availability depends on both individual and systemic factors [1, 2, 3]. The extent to which health services will be used depends on the number of services offered, the speed of development of health technologies, and on their accessibility and affordability [3, 4]. The unfulfilled need for medical care is one of the most important indicators of disparities in healthcare access, implementation, and utilization. An unmet need for healthcare is present in an individual who has recognized the need for specific medical care, but does not obtain it. Research has shown that unmet needs for medical treatment have an impact on one's health and life quality [5]. They can also raise one's chance of dying or being linked to a wide range of psychological and psychosomatic disorders [3]. Certain socio-demographic and socio-economic factors, such as age, gender, education level, inadequate financial status, unemployment, and the distance of settlements from urban centers, are all associated with unmet healthcare needs [3, 6, 7]. Research of EU Statistics on Income and Living Conditions conducted in 2022 shows that 4.1% of individuals 16 years of age and older in the EU reported having an unfulfilled need for healthcare and that the two most typical causes of unfulfilled medical needs were poor financial situation and long waiting [6]. The most precious part of any society are children and adolescents; therefore, their health is a priority task of every society. The United Nations Global Strategy for Women's, Children's and Adolescent Health (2016–2030) supports the goal of providing adolescent health more attention [8]. Since its founding in 1948, the World Health Organization (WHO) has considered that having good health was a basic right, irrespective of ethnicity, faith, financial or social standing, opinions on politics, and has repeatedly confirmed its commitment to enhance the health of vulnerable categories of the population and recognized the reasons for unmet

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healthcare needs and reduced them to a minimum [9]. Many countries are making efforts to reduce the prevalence of unfulfilled medical needs through a system of universal health coverage for every individual, which is the goal of modern global health policy. Research and improvements in understanding the unfulfilled health needs of adolescents are important above all from the aspect of health preservation and prevention of chronic diseases, because they can lead to the formation of healthy generations in the future, and therefore to a more favorable economic aspect for the society [10, 11].

The aim of this research is to identify the relationship between socio-demographic and socio-economic determinants of health and unmet healthcare needs of adolescents and young adults in Serbia. This research is the first study on the unmet healthcare needs of adolescents in this country, carried out on a nationwide representative sample.

METHODS

This study was done as an analytical, cross-sectional, nationwide research on a sample that was representative of the population of the Republic of Serbia and the population from the territory of the Autonomous Province of Kosovo and Metohija was excluded. The research was a part of the 2019 Serbian National Health Survey carried out by the Statistical Office of the Republic of Serbia in cooperation with the Dr. Milan Jovanović Batut Institute of Public Health of Serbia and the Ministry of Health of the Republic of Serbia, from October to December of 2019. The instruments and methodology of the European Health Survey – third wave (EHIS-wave 3) were used in this study [12]. EHIS-wave 3 recommendations are also used to compute sample size (https://ec.europa.eu/eurostat/documents/3859598/8762193/KS-02-18-240-EN-N.pdf/5fa53ed4-4367-41c4-b3f5-260ced9ff2f6).

The sample of this study included 1519 adolescents (15–19 years old) and young adults (20–24 years old). The study used a two-stage random stratified sampling. The sample was selected in order to get ratings that were statistically credible for Serbia overall and for each of the regions separately: Belgrade, Vojvodina, Šumadija and West Serbia, and South Serbia and East Serbia. The research was conducted through interviewing in person and self-completed questionnaires [13].

In this study, the dependent variable was the unmet need for healthcare. The socio-economic status factors (household wealth, employment status, and educational attainment) and demographic factors (gender, age, marital status, and region of living) were the independent variables.

IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA) was used to conduct the statistical analysis. Using the χ^2 test, the differences between the groups, with categorical variables, were compared. Univariate and multivariate logistic regression were used to evaluate the risk (OR (odds ratio)) with a 95% confidence interval. A statistically significant outcome was defined as one with a probability of less than 5% ($p < 0.05$).

Ethical standards have been harmonized with the international Declaration of Helsinki, as well as the legislation of the Republic of Serbia. In order to respect the privacy of the research subjects and the confidentiality of the information collected about them, all necessary steps were taken in accordance with the General Data Protection Regulation. Research participants were provided with a document outlining the subject matter and objectives of the study [13].

RESULTS

In this research, data from 1519 respondents aged 15–24 years (52.2% male and 47.8% female) were analyzed. The average age of the respondents was 19.6 ± 2.8 years. The largest percentage of respondents completed secondary education (59.6%), 33.2% completed elementary school, while the least number of them had higher education (7.2%). In relation to work status, the largest percentage were students/inactive (61.4%), the unemployed accounted for 22.7%, while the percentage of employed was 15.9%. Regarding financial status, most of the respondents belonged to the poorest class (25.2%), and the lowest percentage to the wealthiest class (14.8%). The average number of household members was 4.7 (± 1.9), the lowest percentage consisted of a single-person households (0.7%), followed by couples without children (1.4%), households with one parent under 25 years of age (7.6%), households with couples with at least one child under the age of 25 (39.5%), and other households made up almost one-half of the surveyed households. The largest percentage of respondents (92%) had never been married or cohabiting, 7.6% were married or cohabiting, and 0.4% were divorced or had ended a cohabiting relationship. The majority of responders were from the region of Šumadija and West Serbia (34.3%), followed by Belgrade (23.8%), Vojvodina (21.7%), and the lowest number of respondents were from the regions of South and East Serbia (20.1%).

Unmet healthcare needs were present among 4.1% of respondents, and the dominant reasons were finances (44.4%) and long waiting time (34.9%). The problem of the distance from the healthcare facility was the reason for unmet healthcare needs among 1.6% of the respondents, while 19.5% of the respondents mentioned several reasons.

The χ^2 test's findings indicated that the highest percentage of unfulfilled needs (39.7%) was among respondents from the Belgrade region, and the lowest from Šumadija and West Serbia (7.9%). There was a statistically significant difference in distribution of unmet health needs between the regions, showing the greatest risk in Belgrade (Pearson χ^2 square = 22.540, df = 3, p = 0.000). Distribution of unmet health needs was significantly different in relation to marital status, showing greater risk among married and cohabiting (continuity correction = 5.295, df = 1, p = 0.021). Unfulfilled needs were recorded in a higher percentage among men (60.3%), in the younger age group (57.1%), with a completed secondary level of education (61.9%), the poorest (52.4%), and among inactive respondents/students

Table 1. The correlation of sociodemographic and socioeconomic parameters with unmet healthcare needs (χ^2 test)

Sociodemographic and socioeconomic parameters	Total respondents (%)	Unmeet healthcare (%)		Pearson χ^2 (continuity correction) / df / p
		Yes	No	
Gender				
Female	47.8	39.7	51.9	1.411/1/0.235
Male	52.2	60.3	48.1	
Age group				
15–19	49.5	57.1	49.2	1.231/1/0.267
20–24	50.5	42.9	50.8	
Region				
Belgrade	23.8	39.7	23.1	22.540/3/0.000*
Vojvodina	21.7	30.2	21.4	
Šumadija and West Serbia	34.3	7.9	35.4	
South and East Serbia	20.1	22.2	20.1	
Educational level				
Higher	7.2	4.8	7.3	0.618/2/0.734
Secondary	59.6	61.9	59.5	
Primary	33.2	33.3	33.2	
Marital status				
In marriage / cohabiting	7.6	15.9	7.2	5.295/1/0.021*
Unmarried	92.4	84.1	92.8	
Economic status				
Wealthy class	32.3	30.2	32.3	0.460/2/0.794
Middle class	19.5	17.5	19.6	
Poor class	48.3	52.4	48.1	
Employment status				
Employed	15.9	22.2	15.6	5.347/2/0.069
Unemployed	22.7	30.2	22.3	
Inactive/student	61.5	47.6	62.1	

*Statistically significant ($p < 0.05$)

(47.6%). However, no statistically significant difference was observed in the distribution of unmet health needs in relation to these socio-demographic and socio-economic parameters (Table 1).

When looking at the individual impact of socio-demographic and socio-economic indicators (univariate approach), region and marital status contribute significantly to the explanation of unmet healthcare needs. Those living in Šumadija and West Serbia had an 87% lower chance of having unmet needs compared to those living in the Belgrade region (OR = 0.13; 95% CI = 0.05–0.35; p = 0.00). Singles were 59% less likely to have unfulfilled healthcare needs than cohabiting individuals (OR = 0.41; 95% CI = 0.21–0.84; p = 0.01). When looking at the joint influence of socio-demographic and socio-economic indicators (multivariate approach), age, region, marital status, and employment status contributed significantly to the explanation of unmet healthcare needs. Those aged 20–24 years were 59% less likely to have unmet needs than those aged 15–19 years (OR = 0.41; 95% CI = 0.21–0.79; p = 0.01). Those living in Šumadija and West Serbia had a 90% lower chance of having unmet needs in comparison to those who resided in the Belgrade region (OR = 0.10; 95% CI = 0.04–0.28; p = 0.00). Those living in South and East Serbia had a 56% lower chance of having unmet needs compared to those who lived in the Belgrade region (OR = 0.44; 95% CI = 0.22–0.92; p = 0.03). Singles were 62% less likely to have unmet needs than cohabiting individuals (OR = 0.38; 95% CI = 0.17–0.86; p = 0.02). Inactive students were 54% less likely to have unmet needs in comparison with employed population (OR = 0.46; 95% CI = 0.21–0.99; p = 0.05) (Table 2).

DISCUSSION

According to this study, waiting, finances, and distance are the primary barriers preventing adolescents and young adults from receiving the necessary medical care. The results show a statistically significant relationship between unmet healthcare needs and region, marital status, age, and employment status.

A major public health problem is represented by socio-demographic and socio-economic inequalities in the accessibility of medical care because they are reflected in the health status of the population. They have not been given enough attention in public health policies and have not been studied enough in countries in transition, including Serbia. According to the WHO, every person should have access to the best medical care, despite their ethnicity, religion, political affiliation, or socio-economic background. In this regard, the WHO has developed Sustainable Development Goal 3 for equal access to healthcare [14].

In the last 20 years, unfulfilled health needs have doubled in many European Union (EU) countries [3]. In the EU in 2022, the proportion of unmet healthcare needs varied from 0.2% in Cyprus to 13.1% in Greece [6]. In Russia in 2018, failure to receive healthcare was recorded in 34.7% of cases [14]. In the Republic of Serbia, there were several studies on unmet health needs, nevertheless, not enough research has been done on the unfulfilled needs for healthcare in adolescents and young adults.

In this research the following were the main barriers to receiving the necessary healthcare: lack of funds (44.4%), long waiting time for appointments or medical exams (34.9%), the distance to a healthcare facility (1.6%), or issues with transportation. In neighboring countries such as Montenegro, Macedonia, Croatia, and Slovenia, similar obstacles to access to healthcare are cited as in Serbia [3]. The national research from 2013 showed results which indicate that the main factor for not meeting health needs is of a financial nature, and this is stated by every fourth citizen of Serbia (24.8%), followed by waiting lists and the distance from health institutions [15]. Also, data from the study from 2014 showed that the most frequent cause of unfulfilled healthcare requirements was financial (36.6%) [16].

Regarding reasons linked to the organization and operating of health services (finances, distance or waiting lists), the share varied from 0.1% in Cyprus to 9.1% in Estonia. Waiting lists as a reason for unfulfilled healthcare needs were

Table 2. Influence of sociodemographic and socioeconomic indicators on unmet healthcare needs (logistic regression)

Sociodemographic and socioeconomic parameters	Univariate model		Multivariate model	
	OR (95% CI)	p	OR (95% CI)	p
Gender				
Female	1		1	
Male	1.411 (0.843–2.362)	0.190	1.477 (0.860–2.539)	0.158
Age group				
15–19	1		1	
20–24	0.726 (0.436–1.208)	0.217	0.410 (0.213–0.790)	0.008*
Region				
Belgrade	1		1	
Vojvodina	0.824 (0.445–1.525)	0.537	0.657 (0.345–1.251)	0.201
Šumadija and West Serbia	0.131 (0.050–0.345)	0.000*	0.104 (0.039–0.279)	0.000*
South and East Serbia	0.646 (0.330–1.267)	0.204	0.444 (0.216–0.916)	0.028*
Educational level				
Higher	1		1	
Secondary	1.606 (0.488–5.287)	0.436	0.982 (0.284–3.401)	0.977
Primary	1.551 (0.454–5.293)	0.484	0.796 (0.202–3.131)	0.744
Marital status				
In marriage / cohabiting	1		1	
Unmarried	0.414 (0.205–0.837)	0.014*	0.377 (0.165–0.862)	0.021*
Economic status				
Wealthy class	1		1	
Middle class	0.957 (0.449–2.040)	0.909	1.079 (0.496–2.352)	0.847
Poor class	1.169 (0.657–2.080)	0.596	1.422 (0.751–2.694)	0.280
Employment status				
Employed	1		1	
Unemployed	0.948 (0.466–1.930)	0.883	0.893 (0.415–1.922)	0.773
Inactive	0.539 (0.281–1.033)	0.062	0.458 (0.212–0.990)	0.047*

*Statistically significant ($p < 0.05$)

expressed in most European countries, including Serbia [6]. The proportion of individuals who faced financial obstacles to receiving healthcare in 38 selected European countries in 2018 ranged from 0.1% in Austria to 13.7% in Albania, while in Korea 2.5% of people included a financial barrier [17]. Similar results were obtained in a study in Italy, where the primary cause for unfulfilled needs was economic reasons, followed by the distance and waiting. Another important result of this study was the evidence of an increase in the gradient from north to south for all considered barriers [18]. In Serbia, respondents from the Šumadija and West Serbia regions have significantly less unfulfilled health needs compared to the Belgrade region. Contrary to this, in research by Popović et al. [16], which included the elderly population, it was observed that the smallest percentage of unfulfilled health requirements occurred in the Belgrade region; however Vojvodina was listed as the region with the most of unmet health needs. In a previous study the most unrealized healthcare needs were detected in the northern region – Vojvodina (39.5%), and the least in the central region – Šumadija and West Serbia (20.3%) [16].

Regarding the marital status, those who are not married or cohabiting had less unfulfilled needs than those who were married or cohabiting, while the study by Popović et al. [16] point out that divorced people have more unmet health needs than married. The research conducted in South Korea also revealed that younger people had more unfulfilled healthcare needs than older respondents [19], while in the study by Mitrašević et al. [3], there were more unfulfilled needs in the category of citizens aged 60–69 years. A previous study carried out in Serbia showed that it was more common for women to have unfulfilled needs compared to males, and that the lowest degrees of education, employment, and economic standing had a significant influence on whether or not healthcare demands were met, which was not the case in our research [3]. In many member states of the EU, age played an important role in the existence of unfulfilled needs for healthcare. In the EU, notably in Greece and Romania, younger people reported fewer unmet needs in 2022 compared to older people. In Denmark, France, Sweden, Germany, Luxembourg, Norway, Switzerland, and Belgium, opposite results were obtained [6]. In South Korea, in 2017, 9.5% of respondents had unmet healthcare needs [19].

In 2022, the share of unmet health needs was higher among people with lower education. This was indeed noticeable in Greece and Romania. In Spain, Lithuania, and the Netherlands, the group of individuals with the greatest percentage of unmet needs comprised those with a secondary education level, while in Estonia the opposite results were obtained [6]. A study conducted in Iran showed that unemployed people were 1.7 times more probable to have unmet needs, which is the opposite of our results [7].

Bismarck's "classical" model (1883) is in force in Serbia, which represents mandatory health insurance, or the so-called "social health insurance." The healthcare system in Serbia is financed from contributions for statutory health coverage, within which 97% of inhabitants are covered by it in the area of healthcare interventions, including preventative ones, but only around 3% of people have insurance for emergency medical care [3, 20, 21]. Given that the healthcare system of Serbia has undergone reform in the last ten years, it is essential to observe the unfulfilled healthcare needs at the national level [20]. The theory says that access to health services is free in most countries, but practice does not confirm this. Health inequalities arise because of variations in opportunities, situations, and living conditions between geographic regions and demographic groups. Generally speaking, possibilities and resources to do actions that promote health increase with one's socioeconomic status [22].

A persistent concern for health policy is the disparity in socio-economic status [23]. This was also shown in our study, which confirmed that individuals with better financial situation have greater access to healthcare and use the

services of private practice more, unlike those who belong to the poorest population. Adolescent health is influenced by many factors that are associated with determinants of health that include socio-economic status [24].

Public health and healthcare are the responsibility of EU member states. Chapter 28 of the EU membership negotiations, which Serbia has not yet opened, addresses this area, containing EU legislative and strategic acts. In 2019, a report on Serbia's progress in the EU accession process concluded that the country had achieved moderate preparedness in the areas of consumer protection and health. However, more active participation from Serbian institutions is needed to create the conditions for further progress [25].

CONCLUSION

The results of this research show that the main obstacles that cause unmet health needs among adolescent and young adults are finances, waiting time, and distance. Our study revealed the significant association between region, marital status, age and employment status with unmet healthcare needs. Policies aimed at addressing unfulfilled healthcare requirements ought to take a multifaceted strategy, concentrating on removing obstacles that restrict access to healthcare for the general and vulnerable populations.

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Социодемографски и социоекономски предиктори неостварених здравствених потреба адолесцената и младих одраслих у Србији – део националног истраживања

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САЖЕТАК

Увод/Циљ Препознавање разлога неостварених здравствених потреба адолесцената и младих одраслих важно је како би се сагледале препреке које стоје на путу решавања одређених здравствених проблема, као и како би се пратили доступност, степен коришћења и спровођења здравствене заштите.

Циљ истраживања је био утврђивање социодемографских и социоекономских фактора који су повезани са неоствареним здравственим потребама адолесцената и младих одраслих у Србији.

Методе Ова студија пресека је део Националног истраживања здравља становништва Србије 2019. године, које је спровео Републички завод за статистику, у сарадњи са Институтом за јавно здравље Србије „Др Милан Јовановић Батут" и Министарством здравља Републике Србије, на стратификованом двостепеном узорку. Истраживањем је обухваћено 1519 испитаника, узраста 15–24 године. У студији су коришћени инструменти и методологија трећег таласа Европског здравственог истраживања. Одређени фактори повезани са неоствареним потребама здравствене заштите испитани су коришћењем логистичке регресије и χ^2 теста.

Резултати Неостварене здравствене потребе биле су присутне код 4,1% испитаника, а доминантни разлози били су финансије (44,4%) и дуго чекање (34,9%). Удаљеност од здравствених установа забележена је код 1,6% испитаника, док је 19,5% испитаника навело више разлога. Мултиваријантна анализа показује да су значајни индикатори неостварених потреба за здравственом заштитом: животна доб, регион, брачни статус и радни статус.

Закључак Резултати овог истраживања могу дати нови правац у креирању стратегија и дефинисању превентивних програма за смањење неједнакости у здрављу адолесцената и младих одраслих и унапређење здравља будућих младих генерација.

Кључне речи: здравствена заштита; потребе за здравственим услугама; адолесценти; млади одрасли; истраживања здравља; Србија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Epidemiological characteristics of infections caused by bacteria *Clostridioides difficile* toxins

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SUMMARY

Introduction/Objective *Clostridioides difficile* is one of the most common infectious agents and an important cause of infections among hospitalized patients, often resulting in severe and potentially fatal outcomes.

The objective of this study was to determine demographical characteristics (age and sex distribution) and outcomes among hospitalized patients with *Clostridioides difficile* infection, and to analyze differences in toxin A, toxin B or toxin A/B prevalence among hospitalized patients with *Clostridioides difficile* infection.

Methods Retrospective descriptive analysis of 200 patients hospitalized at the Institute for Pulmonary Diseases of Vojvodina, Serbia, from 2015 to 2018 was performed. The data were obtained using a standardized "Active surveillance of *Clostridioides difficile*" questionnaire. A non-parametric χ^2 test and binominal logistic regression was used to validate all hypotheses: focusing on higher infection rates and mortality in the elderly compared to younger populations, and the predominance of diagnostic methods isolating both toxins A and B.

Results There are statistically significant differences in the distribution of infection cases among age groups, particularly with a higher prevalence in individuals aged 66 and older, ($p < 0.001$). There is a statistically significant difference in the frequency of respondents in relation to the detection of toxins. Percentage of representation of toxins is 61.5%.

Conclusion The results show that the most common diagnostic method is the detection of toxins A and B, rather than isolating either toxin independently. However, the study suggests that certain diagnostic methods should be supplemented by other newer diagnostic methods.

Keywords: *Clostridioides difficile* infections; hospital infections; preventive measures

INTRODUCTION

Clostridioides difficile (*C. difficile*) represents a significant public health issue exacerbated by the widespread use of antibiotics. Although it is an anaerobic gram-positive bacterium that is found both in the intestinal flora and soil, it also poses a significant risk of infection among both healthy individuals and hospitalized patients [1]. In the United States of America, around half a million new infections are reported each year, while approximately 14,000 deaths are caused by this pathogen [2]. Upon entering the gastrointestinal tract, *C. difficile* transitions from a spore form to an active vegetative state, which leads to the appearance of infection. What makes this bacterium particularly dangerous are the toxins it secretes, namely toxin A and toxin B. Toxin A enhances the cytotoxic effect of toxin B. These toxins synergistically destroy intestinal epithelial cells and significantly disrupt the intestinal barrier [3]. It is believed that asymptomatic colonization of patients admitted to the health care facility shows a prevalence rate ranging from 0.6% to 13% [4]. Today, three types of antibiotics are most often used in the treatment of this infection: vancomycin, metronidazole, and fidaxomicin. Fidaxomicin has been proved to be the most effective in managing recurrent infection [4]. Resistance to these treatments often leads to pseudomembranous colitis, characterized by severe intestinal damage, diarrhea, and potentially fatal outcomes [5, 6]. Certain studies show the key role of disrupted intestinal microbiota in facilitating *C. difficile* growth. In addition to the bacterial microflora of the intestine, it is important to emphasize that the disturbed fungal microflora also leads to a significant worsening of the clinical picture in people infected with this bacterium [7]. Besides causing pseudomembranous colitis in humans, this bacterium also exhibits pathogenicity in various animal species causing similar disease profiles. However, bacteriophage therapy offers a targeted alternative, leveraging virus specificity against bacterial strains to effectively mitigate infection [8]. Moreover, in the case of the bacterium *C. difficile*, it was discovered that plasmids can affect both pathogenic potential and antibiotic susceptibility, impacting the regulation and production of its toxins. The research objectives of these studies were to detect a potential change in the genome of this bacterium that would lead to increased sensitivity of *C. difficile* to antibiotics [9].

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METHODS

Patients were assessed using a standardized "Active Surveillance of *Clostridium difficile*" questionnaire. Toxin Enzyme Immunoassays (toxin EIA) was used as test to diagnose *C. difficile* infection (CDI). All hospitalized patients were confirmed by toxin EIA of bacteria by isolating toxins A and toxin B, as well as toxins A and B simultaneously. All patients were treated at five clinics of the Institute for Pulmonary Diseases of Vojvodina. The methodological goals included assessing the distribution of CDI across different age groups and sex, two age categories (66 years of age or older compared to 18–65 years of age), assessing the lethality rates among these age categories suffering from the infection, determining the prevalence of toxic detection (either A, B, or both), determining whether there is a statistically significant difference in the frequency of mortality in relation to the specific clinic (1, 2, 3, 4, and 5). Determining whether there is a statistically significant difference in the frequency of respondents by age category in relation to the year of hospitalization. Clinic 1 is the Clinic for Obstructive Pulmonary Diseases and Acute Pneumopathies; clinic 2 is the Clinic for Granulomatous and Interstitial Lung Diseases; clinic 3 is the Clinic of Urgent Pulmonology; clinic 4 is the Clinic of Pulmonary Oncology; clinic 5 is the Clinic of Thoracic Surgery (Table 1).

Table 1. Distribution of outcomes by clinics

Clinics	1	2	3	4	5
Exitus letalis	3	10	22	1	2
Discharged alive	40	49	47	12	14

This table shows the number of people who were discharged alive and who died at the department's clinics

The study was approved by the Ethics Committee of the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia, IRB No (27-III/3).

Statistical analysis

We used the statistical method for data analysis using the non-parametric χ^2 test and binominal logistic regression. This statistical method was utilized to evaluate several hypotheses concerning CDI and outcomes. The hypotheses tested included: increased prevalence of CDI among the elderly compared to younger demographics, higher mortality rates in the elderly population, and more frequent utilization of diagnostic methods detecting both toxins A and B compared to methods detecting only toxin A or toxin B. For the purpose of sample classification outcomes, based on sex and age categories, we use binomial logistic regression. Results were considered statistically significant at $p < 0.05$.

RESULT

This retrospective examination involved the evaluation of 200 hospitalized patients at the Institute for Pulmonary Diseases of Vojvodina from 2015 to 2018. Analysis of data confirmed the first hypothesis using the χ^2 test, which compared the empirically obtained frequencies against expected frequencies. There are statistically significant differences in the distribution of respondents by age categories, with a higher representation in the age category of 66 years and older, ($p < 0.001$). The second hypothesis was evaluated using the χ^2 test. It revealed no statistically significant differences in mortality rates across age categories ($p = 0.55$).

The third hypothesis indicates that there is a statistically significant difference in the frequency of toxin detection among respondents. Significantly more respondents are in the group where both A and B toxins were isolated, compared to groups where only toxin A or only toxin B was isolated. The hypothesis was confirmed at the level of $p < 0.001$. The fourth hypothesis indicates that there is a statistically significant difference in mortality rates depending on the clinic where treatment was received, with the most notable differences observed in Clinic 3 (31.9% mortality rate, and 68.1% discharge rate) at a significance level of $p < 0.05$. The results of data testing for hypothesis five showed that there is no statistically significant difference at the $p < 0.05$ level in the frequency of patients by age category in relation to the year of hospitalization ($p = 0.33$). Examining the interaction of sex and age category in the context of lethality was performed by binomial logistic regression. The indicator of significance of the logistic regression is the χ^2 test. Sex and age do not make statistically significant contributions to determining whether an individual belongs to the lethality category (*exitus letalis*/discharged).

DISCUSSION

The main characteristic is its multidrug resistance, including resistance to carbapenems. Clinically, CDI often presents with hematochezia, typically associated with significant dysbiosis of the human intestinal microbiota. This dysbiosis exacerbates the clinical manifestations of the infection [10, 11]. Moreover, one of the effective methods of protection and treatment against various pathogens is microbiome refining, offering a safer and more efficacious alternative to fecal microbiota transplantation [12]. In a case report study, we can see the ability of this bacterium to cause emphysematous cystitis [13]. Probiotics are increasingly recognized as an effective intervention for various diseases, with an emphasis placed on the treatment of intestinal infections. Probiotics represent bacteria that are integral to the normal intestinal microflora of an organism [14]. Certain studies have shown that prolonged use of proton pump inhibitors can disrupt this microflora by suppressing hydrochloric acid secretion in the stomach. In such patients, it would be desirable to use probiotics to prevent intestinal infections, including those caused by the bacterium *C. difficile* [15]. Both in vitro and murine studies have highlighted the role of bile acids, which, due to various biochemical processes, slow down and prevent the growth and development of this bacterium [16]. Certain

studies have shown that a mixture of different types of antibiotics have a statistical significance in the prevention and reduction of diarrhea, as well as infections caused by the bacteria *C. difficile* [17]. There is always the possibility of false negative test results for *C. difficile.* In a study conducted over 15 months in an acute care facility, 50 out of 2308 samples tested showed an inverse correlation between negative polymerase chain reaction (PCR) results and positive stool cultures for toxigenic *C. difficile* detection of this bacterium due to discordant samples led to different ribotyping patterns indicating that they originated from different strains. In most cases, false-negative *C. difficile* test results did not appear to affect clinical outcome in these patients. The PCR detection limit can affect the results of molecular methods for the detection of this bacterium [18]. In a single study, a total of 17 isolates of *C. difficile* from garden soil and shoe soles in Perth, Western Australia, failed to grow as black colonies on ChromID agar. MALDI-TOF MS analysis confirmed that these strains are *C. difficile* bacteria. These white colonies of *C. difficile* bacteria from samples and the environment, potentially overlooked when using ChromID bacteria *C. difficile* agar, present no pathogenic threat but highlight risks of false-negative results [19]. There are three leading methods for identifying a toxigenic strain of *C. difficile:* toxigenic culture, a two-step method that combines *C. difficile* culture, cell cytotoxicity assay, and enzyme immunoassay for toxin A/B and glutamate dehydrogenase, and nucleic acid amplification assays targeting toxin-encoding genes, including PCR, quantitative PCR, loop-mediated isothermal amplification, and helicase-dependent isothermal amplification of DNA. The method of toxigenic culture is complex and time-consuming, and is mainly used for epidemiological research and evaluation of new methods. The sensitivity and specificity of immunoassays can vary, and must be combined with a specific high-sensitivity approach to compensate for their shortcomings [20]. The leading detection method of toxin A and toxin B represents a rustic but highly valid method. Toxin A significantly increases the secretion of fluid into the intestinal lumen leading to inflammation and damage to the protein structures of the intestine. Toxin B is responsible for the key cytotoxic effects on the epithelial layer of the digestive tract, but also for the destruction of other cells. At higher concentrations, toxin B can also cause the appearance of blood in the stool. It is believed that toxin A has a greater influence on the gastrointestinal tract. This method of detecting toxins A and B in the stool is one of the fastest and most cost-effective methods for detecting this bacterium [21]. This is also confirmed by our research, which showed that representations are the results that lead to the third hypothesis [22]. In a study conducted in the United States, which examined and followed over 150 million adults, the incidence of CDI was particularly pronounced in hospitalized patients after transplantation [23]. In comparison with our studies, there is a clear correlation between hospitalized patients with CDI and various types of comorbidities, as is the case in our investigations in clinic 3. The mortality rate in our research across the clinics is clearly shown in Table 1. The previous hypothesis is further supported by over 15 studies that were processed through meta-analysis, where individuals with gastrointestinal diseases had comorbidities. However, this study shows the recurrence of CDI in patients with this type of comorbidity [24].

CONCLUSION

In the observed sample of patients, the percentage of deaths was the highest at the Clinic of Urgent Pulmonology, and as a result, CDI poses an increased risk of death for patients in the most critical condition. It is of particular importance in undertaking some preventive measures. Some preventive measures include the therapeutic use of the macrolide antibiotic fidaxomicin. However, *C. difficile* produces strong toxins – toxin A and toxin B, and also leads to the formation of ulcerative colitis posing a severe risk to hospitalized patients with comorbidities. The results also show that the method of isolating toxins A and B is highly reliable for diagnosing this bacterium.

Conflict of interest: None declared.

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Епидемиолошке карактеристике инфекција изазваних токсинима бактерије *Clostridioides difficile*

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САЖЕТАК

Увод/Циљ *Clostridioides difficile* је један од најчешћих инфективних агенаса и важан узрочник инфекција међу хоспитализованим пацијентима, што често резултира тешким и потенцијално фаталним исходима.

Циљ овог истраживања био је да се утврде демографске карактеристике (расподела по полу и старости) и исходи код хоспитализованих пацијената са *Clostridioides difficile*, као и да се анализирају разлике у преваленци токсина А, токсина Б или токсина А/Б међу хоспитализованим пацијентима са инфекцијом бактеријом *Clostridioides difficile*.

Методе Урађена је ретроспективна дескриптивна анализа 200 пацијената хоспитализованих у Институту за плућне болести Војводине, у Србији, у периоду 2015–2018. године. Подаци су добијени применом стандардизованог упитника „Активни надзор над *Clostridioides difficile*". Непараметарски χ^2 тест и биномална логистичка регресија коришћени су за валидацију свих хипотеза: фокусирање на веће стопе инфекције и морталитет код старијих у поређењу са млађом популацијом, и превласт дијагностичких метода које изолују токсине А и Б.

Резултати Постоје статистички значајне разлике у заступљености испитаника у односу на старосне категорије, при чему се већи број испитаника налази у категорији од 66 година и старијих, на нивоу значајности $p < 0{,}001$. Постоји статистички значајна разлика у фреквенци испитаника у односу на изолованост токсина. Проценат заступљености токсина је 61,5%.

Закључак Наши резултати показују да је чешћа заступљеност дијагностичке методе изолованости токсина А и Б него само токсина А или само токсина Б. Али резултати показују да одређене дијагностичке методе треба да буду поткрепљене осталим новијим методама.

Кључне речи: инфекције бактеријом *Closttridium difficile*; хоспиталне инфекције; превентивне мере

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Hand replantation surgery in regional anesthesia – report of two cases

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SUMMARY

Introduction Hand replantation is a microsurgical operation on completely or incompletely amputated hand during which the soft tissue and bone structures are reanastomosed and reconstructed. Blockade of peripheral nerves provides anesthesia and analgesia, but also a sympatholytic effect, improving blood flow and offering better perfusion of the replanted tissue. The aim of this paper is to show the importance of regional anesthesia for hand replantation surgery.

Case report Two male patients sustained a traumatic amputation of the hands by working on industrial machines. The patients underwent a microsurgical hand replantation. An ultrasound-guided brachial plexus block was performed through an axillary approach. A 22G, 10 cm needle was used. Bupivacaine 0.25% 30 ml and lidocaine 1.3% 30 ml without adrenaline were injected perineurally. The medial side of the upper arm was infiltrated with lidocaine since it is the area of intercostobrachial nerve innervation that remains unaffected by the brachial plexus block, preventing the pain caused by the pressure from the tourniquet. During the operation, the patients were sedated with midazolam. Postoperatively, the patients were under observation at the Intensive Care Unit. Analgesia was maintained with intravenous nonsteroidal anti-inflammatory drugs and tramadol, and a single-shot blockade of brachial plexus, intramuscular groove approach. Laboratory tests were conducted, and every three hours, the skin color and turgor, capillary refill, and tactile temperature were monitored.

Conclusion Reducing peripheral vascular resistance, preventing vasospasm, and increasing blood flow through the anastomoses increase the chance of successful replantation and reduce postoperative pain and anxiety, which overall affect patients function and comfort.

Keywords: brachial plexus blockade; hand injury; microsurgery

INTRODUCTION

Hand replantation is a microsurgical operation on a completely or incompletely amputated hand during which the soft tissue and bone structures are reanastomosed and reconstructed [1]. If the amputation is limited to one limb, it is convenient to operate under regional anesthesia, which creates good perioperative conditions and adequate pain control after the operation [2].

Peripheral nerve block provides anesthesia, analgesia, and a sympatholytic effect, improving blood flow and offering better perfusion of the replanted tissue [2]. In this way, sympathetic blockade leads to an increase in venous diameter and causes an increase in blood flow through arterial blood vessels during the operative and postoperative periods [3]. The goal of replantation surgery has changed over time, from establishing the circulation of the replanted part to establishing the anatomical and aesthetic and finally the functional role of the amputated part of the body, in this case, the hand.

In this article, we present the cases of two patients with traumatic hand amputations and indicate the importance of regional anesthesia in replantation microsurgery of the upper extremity.

CASE REPORT

Two male patients, 62 and 74 years old, sustained a traumatic amputation of the hands by working on industrial machines on the day of admission (Figure 1). Initial wound management and amputated segment preservation were made adequately in the regional medical center. On admission, patients were conscious, hemodynamically, and respiratory stable. Upon admission, anesthesiologic and surgical planning was done after immediate radiological and laboratory evaluation. The patients underwent a microsurgical hand replantation in the first three hours after injury.

The patients were premedicated with midazolam intramuscularly (0.10 mg/kg). Two intravenous cannulas were placed. Standard non-invasive monitoring was conducted, non-invasive blood pressure measurement in the contralateral arm, pulse oximetry, and continuous electrocardiogram were attached to the patient. Crystalloid infusions, proton pump inhibitors (pantoprazole 40 mg by intravenous injection), and antibiotic (first-generation cephalosporin – cefazolin, 50 mg/kg/day intravenously) and anti-tetanus serum (1500 U intramuscularly) were started. An ultrasound-guided (eZono®4000, eZono AG, Jena, Germany) brachial plexus block was performed through an

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axillary approach (Figure 2). The patients were placed in the supine position, head turned to the opposite side, injured arm abducted up to 90°, elbow flexed, and forearm in external rotation. The linear probe was transferal over the upper arm's anteromedial part (Figure 3). The axillary artery was identified as a pulsating hypoechoic structure with a vein placed medially. The nerves were identified as hyperechoic structures surrounding the artery. A 22G, 10 cm needle (Stimuplex® Ultra 360® 22 Ga, B. Braun, Melsungen, Germany) was used. Bupivacaine 0.25% 30 ml and lidocaine 1.3% 30 ml without adrenaline were injected perineurally. The medial side of the upper arm was infiltrated with lidocaine since it is the area of the intercostobrachial nerve innervation that remains unaffected by the brachial plexus block, preventing the pain caused by the pressure from the tourniquet. During the operation, the patients were sedated with intravenous boluses of midazolam (0.02 mg/kg) and fentanyl (1 μg/kg) while maintaining spontaneous breathing, oxygen 6 L/min face mask was administered, and intravascular volume was maintained with crystalloids (lactated Ringer's solutions and sodium chloride 0.9%) and colloid (human albumin 5%) infusions. Bones were reduced and fixed with K-wires, blood vessels were anastomosed, and direct suture of tendons and nerves was performed (Figure 4). After identifying the arteries, the tourniquet deflated, Heparin 5000 U was given intravenously, and continuous infusion of Heparin 25,000 U was continued (Initially 3 ml/h, then corrected based on the activated partial thromboplastin time value, which was measured every four hours, aiming to achieve activated partial thromboplastin time 50–70 s). Postoperatively, the patients were observed at the Intensive Care Unit where they were kept normotensive, with an operated arm in an elevated position, above the level of the heart. Analgesia was maintained with intravenous nonsteroidal anti-inflammatory drugs, most often diclofenac (75 mg given intravenously every 12 hours) or ketorolac (30 mg intravenously every 12 hours), tramadol (100 mg given intravenously every 12 hours), and a single-shot blockade of brachial plexus, intramuscular groove approach, with 15 ml bupivacaine 0.125%. The patients

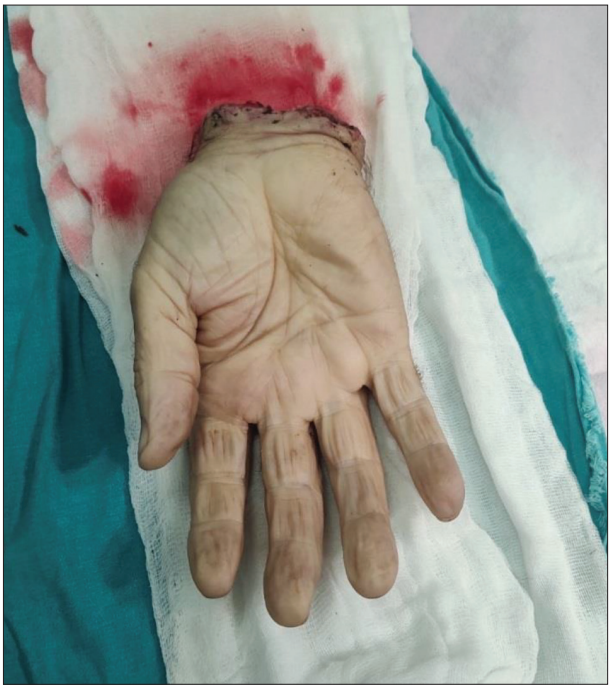

Figure 1. Preoperative view of amputated hand

Figure 2. Performing an ultrasound-guided (eZono®4000) brachial plexus block

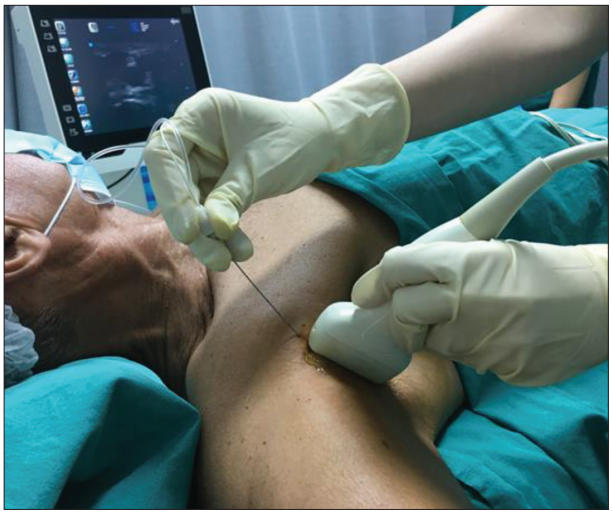

Figure 3. The axillary approach performing brachialis plexus block

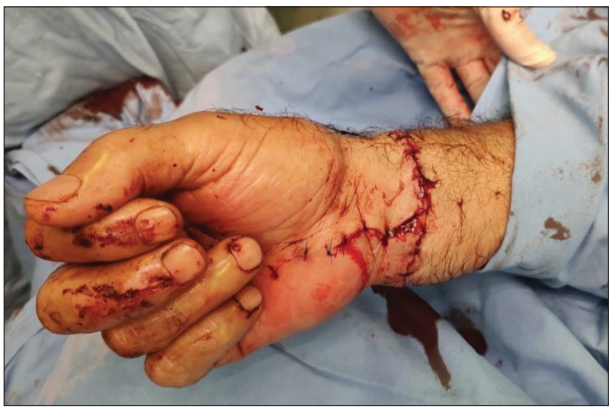

Figure 4. Postoperative aspect after reconstruction

were under observation, laboratory tests were conducted, and every tree hours skin color, turgor, capillary filling, and tactile temperature were monitored. Dressings were changed at least once daily. After 72 hours, the patients were transferred to the plastic surgery ward, with the continuation of anticoagulant therapy, which was gradually reduced, and aspirin (100 mg orally) prophylaxis started on the 10th postoperative day to prevent arterial occlusion. After 21 days, at discharge, both patients had vital hands with preserved motor function. The wounds healed without signs of infection.

Written consent to publish all shown material was obtained from the patients. Ethical approval was obtained by the institutional Ethics Committee (I-87/20). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration.

DISSCUSION

Upper extremity amputations account for more than 65% of traumatic amputations. It occurs more often in men (80%). Based on research, traumatic limb amputations are most often caused by chainsaws and circular saws in 41%, followed by axes in 14.6%. Amputation represents a significant loss for the patient, both physically and mentally, so the treatment of such injuries requires a multidisciplinary approach [4].

Regional anesthesia provides adequate conditions for hand surgery. The block interrupts the sympathetic innervation of the upper limb, which improves blood flow through the arterial blood vessels and causes an increase in venous capacity. This is essential in microvascular surgery because it can improve the possibility of survival of borderline viable tissues and increase the flow of microvascular arterial anastomoses [5]. Sympathetic vasoconstrictor nerve fibers are located in the distal arterial blood vessels of the hand, which is the reason for the frequent appearance of vasospasm in microsurgery of the hand [6]. Thrombosis of vascular anastomoses is the most common cause of failure in microsurgery [7]. Maintenance of adequate blood flow can prevent thrombosis and early failure in microsurgery [3, 8]. Pain after surgery, emotional problems, fear, agitation, and worry are the most important causes of vasospasm. Compared to general anesthesia, blocking the upper extremity with sympathicolysis prevents vasospasm, leading to vasodilatation, consequently preventing blood flow reduction and establishing adequate tissue perfusion [9].

Furthermore, it is a very good method for postoperative pain control, improving sleep quality and overall patient satisfaction [6]. Regional anesthesia may lead to reduction in systemic analgesic requirements, opioid-related side effects and the development of chronic postoperative pain [10]. A reduction of opioids, caused by brachial plexus block, may also decrease the incidence for opioid-induced nausea and vomiting, sedation, hypotension, bradycardia, respiratory depression, biliary colic, urinary retention. Wenger et al. [11] performed a study in which they noninvasively measured the change in blood flow and oxygen saturation in the hand after axillary block and came to the conclusion that axillary block improves oxygen saturation of peripheral tissues six hours after the start of anesthesia, which is of crucial importance for critically perfused tissues. Increased blood flow with reduced prothrombotic coagulation factors are the most important advantages of regional anesthesia techniques that make microsurgery successful [12, 13]. Regional anesthesia has negligible impact on the vital organs, which makes it safer for patients with existing comorbidities. After surgery, patients are awake and have a clear mind, protective reflexes of the upper respiratory tract are present, and, compared to general anesthesia, there are fewer complications such as somnolence, nausea, vomiting, atelectasis, and agitation. Blockade of the brachial plexus through the axillary approach avoids the possibility of anesthetic spreading into the epidural or subarachnoid space, paralysis of the diaphragm, hoarseness, Horner's syndrome, and pneumothorax. Disadvantages of regional anesthesia are the possibility of puncturing blood vessels and consequently the accidental application of local anesthetic intravascularly, the possibility of a toxic reaction, fear of stings and pain, and discomfort due to the presence of noise in the operating room [1, 14]. Regional anesthesia avoids the complications and risks of general anesthesia. Ultrasound-guided regional anesthesia increases the chance of success of the block [14].

Brachial plexus block anesthesia is the most common method for patients who undergo a replantation of a severed hand. This technique is widely used for upper limb surgery, due to fewer complications. The requirements for anesthesia are simple operation, minor impact on the patient's physiological functions, complete immobilizations, painless and postoperative analgesia, easy monitoring, and achieving vasodilatation of distal small vessels. General anesthesia is the method of choice in case of patient refusal of peripheral nerve block, skin infection at the injection site, uncooperative patients, patients with multiple serious injuries, an allergy to local anesthetics, long-term surgery, pediatric, bleeding disorders, dementia and other mental illness [1, 15].

Regarding the choice of local anesthetics, our decision was a combination of diluted bupivacaine 0.25% and lidocaine 1.3%, without the addition of adrenaline. Adrenaline, with its vasoconstrictor effect, reduces the absorption rate and prolongs the effect of local anesthetics. The use of solutions containing adrenaline can reduce blood flow through blood vessels [6, 16]. When it is important that the total blood flow through the extremities does not decrease, adrenaline should be avoided. Also, local anesthetics may delay the onset of block [17].

Postoperative care and rehabilitation are very important for achieving a high success rate. Changes in skin color and temperature, turgor, and slowed capillary refill can indicate even the smallest changes in the replant [18].

Hand amputation limits the patient's physical, psychological, social, and professional life. The survival of the replant depends on the success of the vascular anastomoses. Reducing peripheral vascular resistance, preventing vasospasm, and increasing blood flow through the anastomoses increase the chance of successful replantation and reduce postoperative pain and anxiety, which overall affect patients' function and comfort, which is made possible by the application of regional anesthesia. Adequate regional anesthesia and sedation calm the patient, provide suitable conditions for the surgeon's work, and ensure postoperative requirements, providing analgesia and vasodilatation.

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Conflict of interests: None declared.

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Реплантација шаке у регионалној анестезији – приказ два случаја

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САЖЕТАК

Увод Реплантација шаке је микрохируршка операција потпуно или непотпуно ампутиране шаке, током које се реанастомозују и реконструишу коштане и мекоткивне структуре. Блокада периферних нерава обезбеђује анестезију и аналгезију, али и симпатолитичко дејство, побољшава проток крви и пружа бољу перфузију реплантираног ткива.

Циљ овог рада је приказати значај регионалне анестезије за реплантациону хирургију шаке.

Приказ болесникâ Два мушка пацијента доживела су трауматску ампутацију руку радећи на индустријским машинама. Пацијенти су подвргнути микрохируршкој реплантацији шаке у прва три сата после повреде. Ултразвучно вођен блок брахијалног плексуса урађен је аксиларним приступом. Коришћена је игла од 22*G*, 10 *cm*. Перинеурално су апликовани бупивакаин 0,25% 30 *ml* и лидокаин 1,3% 30 *ml* без адреналина. Медијална страна надлактице је инфилтрирана лидокаином, јер је то подручје инервације интеркостобрахијалног нерва које остаје незахваћено блоком брахијалног плексуса, спречавајући бол изазван притиском турникеа. Током операције пацијенти су седирани мидазоламом. Постоперативно, пацијенти су опсервирани у Јединици интензивног лечења. Аналгезија је одржавана интравенским нестероидним антиинфламаторним лековима и трамадолом, као и блокадом брахијалног плексуса једнократно, интерскаленским приступом. Рађене су лабораторијске анализе, а свака три сата контролисани су боја и тургор коже, капиларно пуњење и тактилна температура.

Закључак Смањење периферног васкуларног отпора, спречавање вазоспазма и повећање протока крви кроз анастомозе повећавају шансу за успешну реплантацију и смањују постоперативни бол и анксиозност, што свеукупно утиче на функцију и задовољство пацијената.

Кључне речи: блокада брахијалног плексуса; микрохирургија; повреда шаке

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Spontaneous upper urinary tract rupture due to urolithiasis

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SUMMARY

Introduction The spontaneous rupture of the upper urinary tract's cavity system, which includes the pelvicalyceal system and ureter, is sporadic. This phenomenon, where urine unexpectedly leaks out of the cavity system without any apparent cause of trauma or medical intervention, is a fascinating and puzzling aspect of urology. This condition is typically attributed to obstructive uropathy, which leads to increased pressure within the urinary tract.

This article illustrates the sporadic occurrence of spontaneous ruptures within the pelvicalyceal system. It underscores the importance of prompt diagnosis and timely treatment to restore wall integrity without significant stenosis.

Outlines of cases We have recorded four cases of spontaneous rupture in urolithiasis, with a median patient age of 47.5 years. The clinical symptoms mimic those of renal colic. Ultrasound, computed tomography scans, and retrograde pyelography were used to diagnose the condition. Treatment consisted of inserting a JJ stent for an average duration of 2.5 months. In all cases, prompt diagnosis and treatment have led to a remarkable restoration of the pelvicalyceal system and the ureter's wall, with spontaneous absorption of the extravasation and without significant ureteral strictures.

Conclusion The positive outcome underscores the importance of early diagnosis and treatment and offers hope for future cases.

Keywords: urolithiasis; spontaneous rupture; extravasation

INTRODUCTION

The spontaneous rupture of the cavity system of the upper urinary tract is infrequent, with only a handful of documented cases [1]. This condition, characterized by the outflow of contrast outside the urinary tract's cavity system, typically occurs without any trauma or surgical intervention. It is most often associated with obstructive uropathy and increased intracavitary pressure during urolithiasis. Less common causes are malignant neoplasms, idiopathic retroperitoneal fibrosis posterior urethral valves, bladder obstruction, connective tissue diseases leading to fibrosis, renal biopsy, extracorporeal shock wave lithotripsy (ESWL), increased diuresis, pregnancy [2–8]. The clinical presentation mirrors renal colic. The most common symptoms are sudden, severe, persistent lower abdominal pain with severe peritoneal irritation. Diagnosis is typically made using ultrasound, CT-urography, or retrograde pyelography. Given the scarcity of cases reported in the literature, much remains to be understood about pathogenesis and the therapeutic-diagnostic algorithm.

REPORT OF CASES

This article comprehensively analyzes four cases involving the spontaneous outflow of contrast from the urinary cavity system. In our analysis, we defined 'spontaneous' as any rupture occurring in the upper urinary tract (pelvicalyceal system and ureter) that was not directly related to trauma or surgical intervention in the area, which directly damaged the wall of the urinary system.

Case 1

A 41-year-old man came to our urology department complaining of pain in the right lumbar region and right abdominal half for the previous five days. He also experienced nausea and vomiting and had a slight fever of 37.4°C. The patient has a history of kidney stone disease. Upon examination, he appeared to be in satisfactory general condition and was not feverish. Tenderness in the right abdominal half with peritoneal irritation and positive succussion was noted on the right side (please see Table 1 for the clinical data of the presented patients).

The patient was referred for a computed tomography scan with the introduction of intravenous contrast. The results revealed an obstructive calculus measuring 9 × 7 × 8 mm in the right kidney's ureteropelvic junction (UPJ). There was also third-degree hydronephrosis and leakage of contrast agent distal to the calculus in the periureteral fat along the entire abdominal segment of the ureter (Figures 1 and 2).

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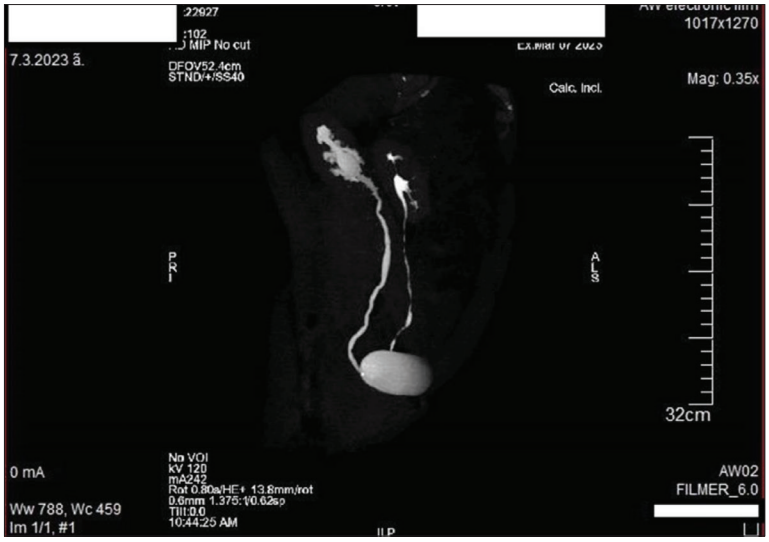

Figure 1. Preoperative CT scan: a spontaneous rupture of the ureteropelvic junction and a leakage of intravenous contrast around the lower pole of the right kidney

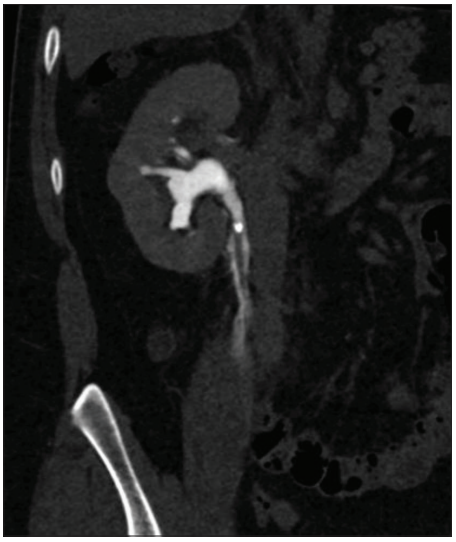

Figure 2. Preoperative CT scan: spontaneous rupture and leakage of intravenous contrast around the right ureter; calculus below the ureteral–pelvic junction

The patient underwent retrograde pyelography on the right side. During the procedure, a 1-cm calculus was found in the UPJ and repositioned in the kidney. Following the procedure, a 6F JJ stent was placed using a hydrophilic guidewire for eight weeks, and a urethral catheter was inserted for one week. The patient was discharged on the second postoperative day.

After two months, the patient was admitted to the urology department for planned stent removal and laser treatment of the kidney stone in the right kidney.

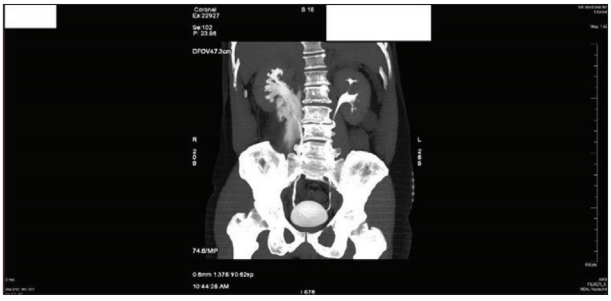

Figure 3. Preoperative CT scan: spontaneous rupture of the pelvis and leakage of intravenous contrast throughout the abdominal segment of the right ureter

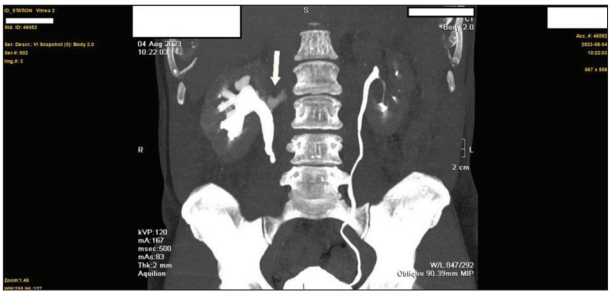

Figure 4. Preoperative CT scan: spontaneous rupture of the fornix of the upper calyx of the right kidney and a small leakage of contrast (arrow)

Case 2

A 46-year-old patient came to the Emergency Center complaining of pain in the right lumbar region, spreading to the right abdominal area, along with urinary difficulties for about a day, as well as nausea and vomiting. No fever was reported, and the patient had no history of kidney stone disease.

Computed tomography with CT urography-revealed a rupture of the pelvis of the right kidney with leakage of contrast agent into the perirenal and periureteral areas and a 4-mm obstructing calculus in the intramural part of the right ureter (Figure 3).

A ureteroscopy was performed on the right side, during which a 4-mm calculus was promptly reached after accessing the right ureteral ostium. The stone was extracted using a nitinol stone extractor. Subsequently, a retrograde pyelography on the right side revealed a contrast agent leakage from the collecting system of the right kidney. A 6F/26cm JJ stent was placed for a period of six weeks, and a urethral catheter was placed for ten days. The patient was discharged on the seventh day.

Case 3

A 58-year-old man complained of pain in the right lumbar region, which radiated along the right ureter for two days. He did not have a fever and had no history of kidney stone disease. An intravenous contrast CT scan revealed a rupture of the fornix of the upper calyx of the right kidney and a small leakage of contrast (Figure 4).

The patient underwent retrograde pyelography on the right. During the procedure, a 1-cm calculus was found below the UPJ. Following the procedure, a 6F JJ stent was placed using a hydrophilic guidewire for three months, and a urethral catheter was inserted for 4 days. The patient was discharged on the fifth postoperative day.

After three months, the patient was admitted to the urology department for planned stent removal and laser

treatment of the kidney stone in the right kidney. One week after the laser lithotripsy procedure, the patient was readmitted to the hospital due to a urinary tract infection caused by *Klebsiella pneumoniae* and received a 10-day course of antibiotics.

Case 4

A 45-year-old female patient arrived at the Emergency Center with complaints of pain and heaviness in the right lumbar region, which had persisted for two days. The pain radiated from the right ureter to the right inguinal region and down to the right thigh. The patient also experienced one episode of nausea and vomiting.

Objectively, the patient was in satisfactory general condition and afebrile. Palpation was moderately painful in the right mesogastrium. Succussion over the right kidney was positive, and ultrasound showed mild drainage disorders in the right kidney. An X-ray revealed a 9/5-mm calcium-dense shadow in the right kidney, suspected to be a stone.

The next day, the patient underwent a retrograde pyelography on the right side, which did not reveal the presence of calculus or ureteral stenosis. A 6F/26cm JJ stent was placed. During the control CT scan with contrast, the following findings were noted for the right kidney: it was positioned abnormally low (ptosis), with the hilus at the L4 level; there was a double drainage system on the right side; a JJ stent was found in the upper part of the collecting system; and the lower part of the collecting system showed second-degree hydronephrosis. Additionally, an 8/6/4-mm oval-shaped calculus was observed in the proximal part of the inferior ureter, 20 mm from the UPJ. At the excretory phase, there is no visualization of contrast agent separation distal from the calculus due to complete obstruction. Contrast extravasation is observed from a caudally located calyx of the upper drainage system (Figure 5).

A follow-up CT scan with contrast enhancement was conducted four weeks after the surgical procedure. The scan showed no perirenal urinomas. Contrast material separated at the excretory phase beyond the previously mentioned stone. The two ureters were observed to have a parallel course and possibly share a common opening – a condition known as ureter duplex. The patient was readmitted to the hospital six weeks after the surgery to remove the inserted JJ stent and perform laser lithotripsy as planned.

All four patients experienced leakage of contrast from the cavity of the upper urinary tract without any direct trauma or iatrogenic damage. The outflow of contrast

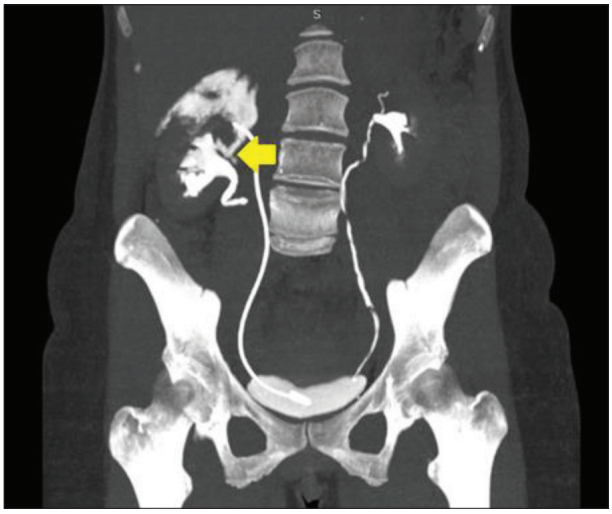

Figure 5. Preoperative CT scan: spontaneous rupture of the pelvis (arrow) and an outflow of intravenous contrast around the upper pole of the right kidney

was a result of renal colic causing acute obstruction of the urinary tract. The patients were diagnosed using a combination of ultrasound, X-ray, and CT with intravenous contrast (Figures 1–4). At the same time, retrograde pyelography was used for the fourth case, following which CT-urography was repeated (Figure 5). All four patients developed acute renal colic, characterized by pain in the lumbar region that radiated along the ureter, nausea, and vomiting, with or without fever (Table 1).

The patients underwent endoscopic upper urinary tract desobstruction by a JJ stent placement on the corresponding side, followed by antibiotic therapy. Three patients underwent surgical intervention at the 24th hour of diagnosis, while one (Patient 2) underwent surgery at the fourth hour. In the case of Patient 2, a JJ placement and an extraction of a 5-mm stone from the distal ureter were performed at one stage. The urethral catheter was retained for three, 10, four, and 14 days for patients 1, 2, 3, and 4, respectively. Notably, symptom management and condition improvement can be achieved immediately after desobstruction. The criteria for discharge include the absence of symptomatology, the normalization of laboratory results, and an ultrasound examination rejecting hydronephrosis or retroperitoneal collection.

Following discharge, three patients underwent a control CT scan: Patient 1 after 30 days, Patient 2 after 15 days, and Patient 4 after 28 days. All three patients showed normal CT scans, and later, laser lithotripsy was performed in Patients 1 and 4. Due to the lack of clinical and ultrasound

Table 1. Clinical data

Patient	Sex	Age	Laboratory results				Comorbidity	Surgery	T°	Onset of the symptoms [days]
			Hgb	WBC	Cr	CRP				
1	Male	41	154	10.3	141	18.7	Nephrolithiasis	No	Up to 37.4°C	5
2	Male	46	156	15.5	133	3.3	Crohn's disease	No	No	2
3	Male	58	127	9	153	110	No	Laparotomy for a puncture wound	No	2
4	Female	45	131	11.8	70	15.3	No	No	Up to 38°C	7

Hgb – hemoglobin; WBC – white blood cells; Cr – creatinine; CRP – C-reactive protein

data for pathology, a control CT scan was deemed unnecessary for Patient 3, who proceeded directly to laser lithotripsy. The stents were removed after 90, 45, 90, and 55 days for patients 1, 2, 3, and 4, respectively. Timely endoscopic treatment proved effective in controlling the condition and preventing complications in all patients.

One complication, indirectly related to the rupture of the cavity system, was observed – a nosocomial urinary tract infection with *Klebsiella pneumonia* In Patient 3, one week after laser lithotripsy, which required re-hospitalization and a 10-day course of antibiotics.

All procedures strictly adhered to the ethical standards set forth by the institutional and national research committee, in line with the 1964 Helsinki Declaration and its subsequent revisions or equivalent ethical standards.

DISCUSSION

Spontaneous rupture of the cavity system in the urinary tract is a rare condition, with only a few reported cases worldwide [9]. This occurs when there is a leakage of contrast into the retroperitoneal area without any trauma or medical intervention, often due to obstructive uropathy and increased pressure in the cavity system [10]. It is typically seen in the proximal third of the ureter, the pelvis, and the fonix of the calyx [11]. Cases of urinoma formation have been documented in the literature, with a median age of 42 and an equal frequency among both sexes [2, 12].

Urolithiasis is the leading cause of spontaneous ureter rupture, with the pathogenetic mechanism involving an obstruction that increases intraluminal pressure and leads to rupture. Other causes include passing stones causing mechanical trauma to the wall and erosions, ulcerations, or necrosis due to stone compression. Less common causes include malignant neoplasms, idiopathic retroperitoneal fibrosis, posterior urethral valves, bladder obstruction, vesicoureteral reflux, connective tissue diseases, renal biopsy, ESWL, urinary tract infection, increased diuresis, pregnancy, and chemotherapy [2–8].

Spontaneous ruptures of the upper urinary tract include the spontaneous rupture of the kidney (also known as Wunderlich syndrome) as well. It is a rare but life-threatening condition [13]. The clinical signs include the Lenk triad, which consists of a sudden onset of pain in the lumbar region, palpable mass, hemorrhagic shock, abdominal pain, and hematuria without any underlying trauma. Factors such as renal cell carcinoma, angiomyolipoma, systemic vasculitis, aneurysms and pseudoaneurysms of renal vessels, arteriovenous fistulas, venous thrombosis, systemic lupus, coagulopathies, infections, and the use of anticoagulants and antiplatelet agents are often implicated in the development of this condition [14, 15].

The clinical presentation of spontaneous rupture of the pelvicalyceal system and ureter includes pain in the lumbar region, abdominal pain with peritoneal irritation, acute abdomen symptoms, nausea with or without vomiting, and fever. It frequently occurs without urinary system symptoms and with normal urine analysis results.

The optimal method for diagnosing a spontaneous rupture of the upper urinary tract involves an ultrasound examination, CT with intravenous contrast, and retrograde pyelography [16–20].

Treatment for a spontaneous rupture of the pelvicalyceal system and the ureter typically includes the placement of a JJ stent for six to eight weeks. Follow-up monitoring may consist of retrograde pyelography and/or CT-urography. If necessary, percutaneous nephrostomy with anterograde insertion of a JJ stent may be an option for a further intervention [21, 22, 23]. Conservative measures such as antibiotics and pain relief may suffice in milder cases [24–27]. Open surgery may also be considered in specific situations.

We are encouraged by the positive progress observed, with the extravasation being spontaneously absorbed within one month of the stenting. In rare cases, a nephrostomy tube may be needed to drain the urinoma. However, our follow-up at four and six months has revealed complete restoration of the pelvicalyceal system and ureter wall, with no signs of stenosis.

The spontaneous rupture of the upper urinary tract is a rare condition, often caused by obstructive uropathy from obstructive nephrolithiasis. In the four cases we examined, rupture occurred spontaneously due to renal colic. Endoscopic treatment, which included desobstruction and placement of a ureteral stent, effectively managed the symptoms. Patient follow-ups involved clinical observations, laboratory tests, ultrasound monitoring, and CT-urography. The stent remained in place for an average of 2.5 months, sufficient for complete symptom control. Timely diagnosis and treatment resulted in the complete restoration of wall integrity, spontaneous resorption of extravasation, and the absence of complications [28].

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Спонтана руптура горњег уринарног тракта као резултат уролитијазе

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САЖЕТАК

Увод Спонтана руптура кавитарног система горњег уринарног тракта (пијелокаликсног система и уретера) ретка је патологија. Представља спонтано цурење мокраће ван кавитарног система, без основне трауме или јатрогене интервенције, најчешће као резултат опструктивне уропатије и повећаног интралуминалног притиска.

Овај рад наглашава важност брзе дијагностике и правовременог лечења како би се обновио интегритет зида без значајне стенозе.

Приказ болесника Приказујемо четири случаја спонтане руптуре код уролитијазе. Просечна старост болесника била је 47,5 година. Клиничка слика подсећа на бубрежне колике. За постављање дијагнозе користили смо ехографију, *CT*-урографију, ретроградну пијелографију. Лечење подразумева фиксацију JJ стента у просеку два и по месеца. Код свих болесника благовремена дијагноза и лечење обезбеђују потпуни опоравак зида пијелокаликсног система и уретера уз спонтану ресорпцију екстравазације и без значајних стриктура уретера.

Закључак Добри резултати наглашавају важност правовремене дијагнозе и лечења спонтаних руптура уретера и дају наду у повољан развој у будућим случајевима.

Кључне речи: уролитијаза; спонтана руптура; екстравазација

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Breakage and dislocation of the Hickman catheter in pediatric patient

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SUMMARY

Introduction The Hickman catheter is a tunneled, open-type catheter often implanted in children for long-term intravenous treatment. Their application can cause numerous complications. Catheter breakage and dislocation of fragments to the intravascular system is a rare but life-threatening condition. When a complication occurs, depending on the patient's clinical condition, the first step is transcutaneous endovascular removal of the catheter's fragment. If this is not possible, surgical thoracotomy is necessary. The objective of this article was to present a case of breakage and dislocation of Hickman catheter in a pediatric patient, as well as the diagnostic and therapeutic approach to complications.

Case outline We report a 14-month-old child who had a Hickman catheter because he was undergoing treatment for acute juvenile myelomonocytic leukemia. Due to a malfunction of the catheter, the existing catheter had to be removed. During the surgical procedure, a breakage and dislocation of the catheter fragment occurred. A chest X-ray and an echocardiography confirmed the position of the catheter fragment in the right atrium. A transcutaneous endovascular procedure was successfully performed to remove the fragment of the catheter.

Conclusion Numerous complications can occur during the insertion, management, and removal of long-term catheters. It is necessary to periodically control the catheter's position by chest X-ray and ultrasound of the heart and neck. If a particular complication is detected, an individual approach to treatment with the lowest risk to the patient should be chosen. Dislocated fragments of the Hickman catheter can be safely removed by endovascular transcatheter procedures.

Keywords: Hickman catheter; complication; children**;** transcutaneous endovascular procedure

INTRODUCTION

The Hickman catheter is a long-term, tunneled central venous catheter (CVC). It is used to administer medications and blood components infusion or to sample blood in pediatric patients. It is implanted with a surgical approach in children with malignant diseases, short bowel syndrome, chronic diarrhea, hemophagocytic syndrome, and hemolytic-uremic syndrome [1, 2]. The catheter is removed when treatment is completed or if complications occur during catheter insertion, use and removal [3]. The most common complication is infection [4]. Less common complications are thrombosis, malfunction, obstruction of the catheter, hemato-pneumothorax, air embolism, injury of the brachial plexus, erosion of the venous wall, dislocation, catheter disconnection or catheter breakage with drug extravasation or secondary embolization [5]. Breakage of the CVC is a severe and life-threatening complication with an incidence in adults in the range of 0.2–4.2% [6, 7]. The first case report of heart embolization in humans by polyurethane peripheral venous catheter fragments was published in 1954 [8]. Depending on the place of insertion, the part of the catheter could be in the superior vena cava or the heart, causing arrhythmias, myocardial perforation, damage to the valvular apparatus or leading to embolization of the pulmonary artery. We report the surgical removal of a Hickman catheter in a 14-month-old child. During the removal, a catheter fracture with embolization of the heart occurred. We want to emphasize the severity of the complication and point out the possibilities of diagnosis and treatment in such situations.

CASE REPORT

A 14-month-old child has been treated for juvenile myelomonocytic leukemia. Due to the challenging course of the disease, a splenectomy was performed in the 11th month of life. A 5 Fr Hickman catheter was installed through the right internal jugular vein in the same operation. Three months later, the catheter malfunctioned, requiring its surgical removal in analgosedation. A preoperative X-ray of the chest indicated the proper position of the tip of the Hickman catheter, its integrity, and a normal finding on the heart and lungs. Preoperative echocardiography demonstrated a normal finding. Blood count and coagulation screening tests were acceptable for general anesthesia. Surgical removal of the Hickman catheter was performed in the operating theatre, in analgosedation, with local anesthesia. We followed the pediatric protocols of

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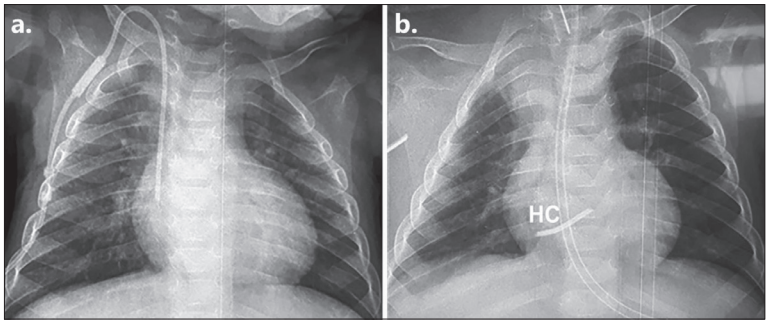

Figure 1. The preoperative chest X-ray (a); the postoperative chest X-ray (b); HC – the part of the Hickman catheter

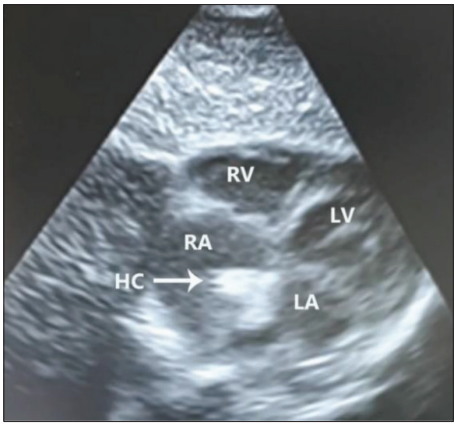

Figure 2. The postoperative heart ultrasound; HC – part of Hickman catheter; LV – left ventricle; RV – right ventricle; LA – left atria; RA – right atria

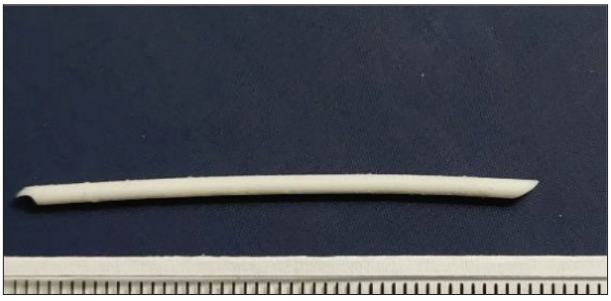

Figure 3. Part of Hickman catheter 4.5 cm long

preoperative fasting, premedication and patient monitoring during the procedure. Analgosedation was performed by intravenous use of propofol and ketamine with inhalation of oxygen and air on spontaneous breathing. Very soon after the surgery, massive bleeding developed with a growing hematoma in the right pectoral region. The child was urgently returned to the operating theatre, intubated, and was put under general anesthesia. Signs of hemorrhagic shock quickly developed. During the exploration of the bleeding site, it was necessary to give transfusion of packed erythrocytes and platelet concentrates platelets, tranexamic acid, crystalloids, 5% albumin and dopamine infusion to maintain the hemodynamic stability. Chest X-ray in the operating theatre showed normal findings without Hickman catheter fragments. During the exploration of the wound, no specific lesion of the blood vessel was found. A hematoma was evacuated from the pectoral area, and drainage was performed.

The child was transferred into the pediatric intensive care unit (PICU). The treatment in the PICU involved mechanical ventilation of the patient, sedation, and relaxation. Hemodynamic stability was established. Laboratory results indicated impaired coagulation, with activated clotting time of 140 seconds, and platelet dysfunction on rotational thromboelastometry. Control blood count showed leukocytosis (white blood cells 27.6×10^9/L), anemia (red blood cells 1.91×10^{12}/L, hemoglobin 61 g/L, hematocrit 0.17), and thrombocytopenia (platelets 46×10^9/L). In order to correct these disorders, the patient received concentrate of clotting factors II, VII, IX, and X, tranexamic acid, packed red cells, platelet transfusion, and fresh frozen plasma. A control chest X-ray performed immediately after admission to the PICU revealed a part of the CVC in the right atrium (Figure 1) confirmed by echocardiography examination (Figure 2).

The child had no clinical symptoms caused by the intracardiac position of the catheter.

Options for foreign-body extraction were catheterization of the heart with a percutaneous endovascular retrieval of the catheter fragment or open thoracotomy. In general anesthesia, interventional cardiologist introduced the transcutaneous endovascular device in the catheterization theatre through the right femoral vein. Hickman CVC fragment, 4.5 cm long (Figure 3), was attached by the snare catheter and successfully retrieved through 7 Fr long sheath introducer. The treatment continued in the PICU for the next five days. The child was afebrile and hemodynamically stable. On the third postoperative day, he was extubated, and oral intake was started. Postoperative laboratory results on discharge were normal, and the child was transferred to the hematologic ward for further treatment.

The authors declare that the article has been written in accordance with the ethical standards of the Serbian Archives of Medicine and the ethical standards of medical facilities for each author involved. No personal data of the patient has been presented in the manuscript. Written consent was obtained from the parents.

DISCUSSION

Using permanent CVCs has changed the perspective of long-term treatment of pediatric patients. Complications are always possible. The most common complication is sepsis, and the less frequent complications are thrombosis, malfunction, dislocation, or catheter breakage. There are several causes of catheter breakage: the length of use, the chemical reaction of the drugs with catheter walls, the pressure at which fluids are injected, chronic pressure to which surrounding tissues expose the catheter and external influences. Many studies have shown that silicone catheters are more durable than polyurethane [9]. "Pinch-off syndrome," which describes catheter compression between the clavicle and the first rib and can be verified by chest X-ray, indicates an imminent breakage of the catheter [10]. Catheter breakages occur in the external parts of the Hickman catheter rather than in

the tunneled part of the catheter [11]. However, in pediatric patients, this complication can be asymptomatic; symptoms can be arrhythmias, paresthesia, palpitations, or catheter malfunction. This complication can be the cause of death due to pericardial tamponade, myocardial perforation, sepsis, endocarditis, thrombosis, pulmonary embolism, myocardial infarction, fatal arrhythmias, the formation of aneurysms or pulmonary abscesses [12]. In the study of pediatric patients, Zhang et al. [13] concluded that Hickman catheters are more prone to mechanical damage than totally implanted port catheters. Also, catheter breakages are more common in occluded catheters when extensive fluid pressure is used to flesh the catheter. CVC occlusion accounted for 14–36% of catheter-related complications within one to two years of insertion.

This complication occurs more frequently in younger children and in children with lower body weight [14]. Breakages during catheter removal or exchange and disconnection are more common in children than in adults [15]. The pulmonary artery is the most common location of fragment dislocation in pediatric patients.

Annual checks of the catheter position by chest X-ray or ultrasound of the heart and neck are necessary [16]. If a catheter compression is observed in the costoclavicular area on the X-ray examination, it is necessary to remove it as soon as possible [10]. Part of the protocol for implantation and explantation of the Hickman catheter in our hospital includes performing a chest X-ray to reveal the appropriate position of the catheter in the operating theatre. In our case, the chest X-ray was performed, but a catheter fragment was not seen either in the heart or in the chest because it remained in the neck (right jugular vein). Afterwards, during the stay at the PICU, the foreign body dislocated and was seen in the right atrium by a chest X-ray and echocardiography. This situation implies the need for periprocedural X-ray imaging of the neck as well as of the chest. When a diagnosis of an intravascular foreign body is made, treatment options include percutaneous retrieval, open thoracotomy, anticoagulant therapy, or expectative management.

Clinical indications for retrieval should be made on a case-by-case basis. Indeed, catheterization extraction through the femoral vein is less radical for the patient. Snares are preferred retrieval devices in pediatric patients because of their safety, availability, and flexibility, with high success and low complication rates [15, 17]. In our case, the intervention was successful. A systematic review of adult patients with percutaneous retrieval of vascular foreign bodies showed an achievement rate of 93.5%, while a pediatric series reported a success rate of 89.5%. The leading causes of failure were the absence of a free-floating end to snare, the small size of fragments, adherence to the vein wall, and fragment lodgment in a thrombosed vessel [15]. An attempt to retrieve the foreign body percutaneously should be made whenever possible [18–21]. If it is impossible to remove a catheter fragment in this way, open thoracotomy is the next step.

In conclusion, long-term CVCs have changed the perspective of treating pediatric patients. Handling this device requires special attention. During implantation and explantation of the Hickman catheter, radiographic and ultrasound examination of the neck and chest can reveal unwanted breakage and dislocation. If complications occur, a multidisciplinary approach is necessary, and percutaneous endovascular retrieval is the treatment of choice.

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Оштећење и дислокација Хикмановог катетера код педијатријског пацијента

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САЖЕТАК

Увод Хикманов катетер је стални тунелизовани катетер отвореног типа, који се често имплантира у дечјем узрасту за потребе дуготрајног лечења. Његова примена може изазвати компликације. Оштећење катетера и дислокација фрагмената у интраваскуларни систем је ретка, али животно угрожавајућа компликација. Када се компликација догоди, у зависности од клиничког стања пацијента, треба прво покушати са транскутаним ендоваскуларним уклањањем фрагмента катетера. Уколико то није могуће, приступа се торакотомији.

Циљ овог рада је да се прикаже начин настанка оштећења и дислокације Хикмановог катетера код педијатријског болесника, као и дијагностички и терапијски приступ компликацијама.

Приказ болесника Приказујемо 14-месечно дете коме је у току лечења јувенилне мијеломоноцитне леукемије уграђен Хикманов катетер. Због малфункције катетера, постојећи катетер је морао бити извађен. Током хируршке процедуре дошло је до оштећења и дислокације фрагмента катетера. Рендгенски снимак плућа и ултразвук срца потврдили су позицију фрагмента катетера у десној комори. Транскутани ендоваскуларни приступ уклањања дела катетера је успешно изведен.

Закључак Током инсерције, примене и уклањања дуготрајних катетера могу се десити бројне компликације. Неопходна је повремена контрола позиције катетера рендгенским снимком грудног коша и ултразвучним прегледом срца и врата. Уколико се открије одређена компликација, треба приступити индивидуалном лечењу са најмањим ризиком по пацијента. Одломљени делови катетера могу бити успешно уклоњени ендоваскуларном транскатетерском процедуром.

Кључне речи: Хикманов катетер; компликације; дете; перкутана ендоваскуларна процедура

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CURRENT TOPIC • АКТУЕЛНА ТЕМА

Stereotactic radiotherapy in the treatment of lung cancer – current prospective

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SUMMARY
Stereotactic body radiotherapy (SBRT) is the standard treatment for early-stage inoperable non-small cell lung cancer. SBRT achieves a high local control rate (74–100%), preserves the quality of life, and the treatment is of low-toxicity. Different fractionation regimens are used, depending on the localization and size of the tumor, the proximity of the organs at risk, and the general condition of the patient.
The radiobiology behind SBRT is largely unknown, precisely defined radiation doses and the number of fractions are still a matter of debate. Numerous studies are ongoing regarding the standardization of SBRT in lung cancer treatment.
Keywords: stereotactic body radiotherapy; lung cancer; early stage

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a technique of external beam radiotherapy that accurately delivers a high dose of radiation to an extracranial target in a single or few fractions. Developed in the early 1990s, SBRT has been further adapted and improved and is currently an important component of modern radiotherapy. Nowadays, SBRT represents the standard treatment for patients with early-stage (TNM classification: T1–T2, N0, M0) inoperable, non-small cell lung cancer (NSCLC), with a high local control rate (74–100%), preserved quality of life, and low treatment toxicity [1, 2].

INDICATIONS AND PATIENT SELECTION

Early-stage NSCLC is traditionally managed by lobectomy and systematic hilar and mediastinal lymph node dissection. Overall survival is 60–92% five years after lobectomy, which makes early-stage NSCLC a curable disease. However, a significant number of patients present as medically inoperable and thus approached with atypical lung resections, radical radiotherapy (60–66Gy), or best supportive care [2].

Randomized trials that compared the results of operative treatment to SBRT found no difference in the three-year survival rate (91% in both arms), while three-year local control was 80% after SBRT and 88% after lobectomy [3]. The ongoing "Patients with operable stage i non-small cell lung cancer" study aims to determine whether the SBRT with a precisely defined dose and delivery technique can be more effective than the surgery. The results of this study are expected in 2026 [4].

According to the ESTRO/ACROP consensus in 2017, candidates for SBRT should have histopathologically confirmed NSCLC, stage I (T1–T2, N0, M0), primary tumor of maximum size up to 5 cm, at least 2 cm away from the main bronchus Eastern Cooperative Oncology Group performance status < 3 and minimal life expectancy of one year. There are no absolute contraindications in terms of age, Charlson Comorbidity Index, chronic obstructive pulmonary disease, and pre-treatment pulmonary function [5].

Localization of the tumor within the lung parenchyma is crucial in making treatment decisions. Centrally localized lung tumors, defined by the Radiotherapy and Oncology Group (RTOG) as lesions located ≤ 2 cm from the proximal tracheobronchial tree (PBT) represent a challenge both for SBRT and the surgical treatment [6]. The implementation of SBRT in this localization is still a matter of debate since it is associated with an increased risk of developing severe radiotherapy-related toxicity (namely esophagitis and bleeding) [7]. Wu [8] indicates that the application of SBRT in tumors localized 2 cm from the proximal bronchial tree is a "no-fly zone" due to high toxicity, and that conventionally fractionated radiotherapy should be the treatment of choice.

Tumors of ultra-central location are defined as tumors located ≤ 1 cm from the PBT. These patients are at a particularly high risk of developing severe toxicity (≥ grade 3 according to the National Cancer Institute-Common Terminology Criteria for Adverse Events). A prospective phase II Nordic study in 2021

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established a cut-off at a distance of 1 cm from the PBT. The SBRT for (ultra) central tumors ≥ 1 cm from the PTB is associated with an acceptable risk of toxicity (grade 1–2), while in tumors ≤ 1 cm away from the PBT it is unacceptable (≥ grade 3) [9, 10].

Therefore, in everyday practice, the patients are assessed multidisciplinary on a "case to case" basis.

SBRT treatment planning

Most of the modern radiotherapy centers are equipped with the necessary devices for the application of SBRT, making it widely adopted. Only four-dimensional computed tomography (4DCT), standard linear accelerator with image guidance and high-resolution multi-lamellar collimator < 10 mm are mandatory. All other equipment is optional [5].

To adequately plan and perform SBRT of lung tumors, the positioning, and immobilization of the patient is extremely important. A "wing board" immobilization device with arms overhead is used as standard, while other SBRT-specific immobilization devices are optional and institution-based.

Treatment planning computed tomography (CT) of the thorax is performed thereafter, with the previous assessment of the patient's respiratory function and the possibility of applying respiration control procedures (such as deep inspiration breath hold). Accordingly, the treatment planning CT is made during free breathing or in a certain phase of respiration (respiratory gating).

For treatment planning, 4DCT is recommended, from the lung apex to the second lumbar vertebra, with 2–3 mm thickness.

Delineation of target volumes is based on International Commission on Radiation Units and Measurements (ICRU) 62 and ICRU 83 recommendations [11].

The tumor volume – gross tumor volume (GTV) is delineated on each CT slice, in the CT lung window, usually without a margin for the potential microscopic spread of the disease (clinical target volume). In GTV delineation, treatment planning PET/CT fusion is recommended.

After GTV delineation, planning target volume (PTV) is added for set-up errors. Defining PTV depends on the treatment planning CT. If 4DCT is used, it is necessary to delineate the internal target volume that corresponds to the position of the target (tumor) during respiration. The PTV is created usually by adding a margin of 5 mm to the internal target volume in all directions [12]. If the patient is scanned while breathing freely and/or with standard three-dimensional computed tomography, the PTV is formed by adding a margin to the GTV of 10 mm in all directions (Figure 1).

Organs at risk (OAR) include the trachea, main bronchi, the esophagus, aorta, heart, spinal cord, both lungs and chest wall.

Intensity Modulated Radiotherapy is the most commonly used technique for lung SBRT, using multiple coplanar fields, with 6–10 MV photons. Since 2011, Volumetric, Modulated Arc Radiotherapy became the preferred technique (Figure 2).

Before carrying out each radiation fraction, it is mandatory to check the patient and tumor position with cone beam CT, and, if necessary, correct the positioning (Figure 3).

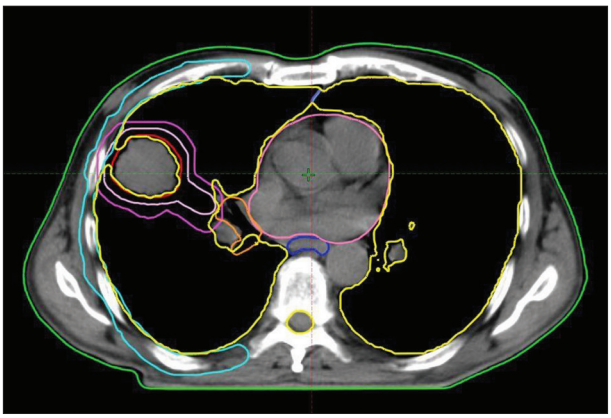

Figure 1. Target volume delineation and organs at risk (Institute for Oncology and Radiology of Serbia)

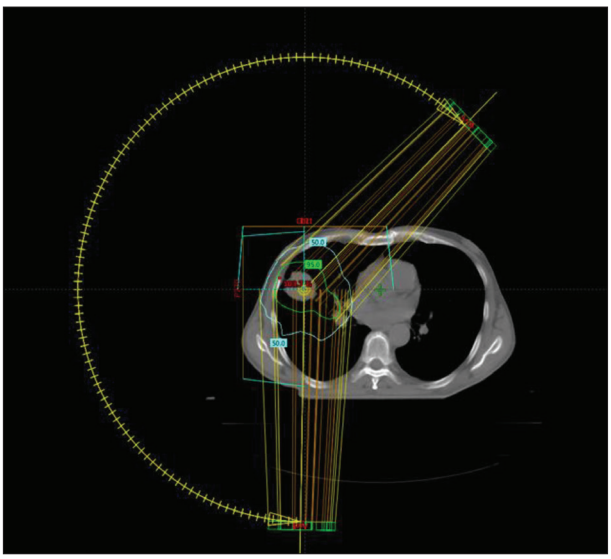

Figure 2. Volumetric modulated arc radiotherapy for lung cancer stereotactic body radiotherapy (Institute for Oncology and Radiology of Serbia)

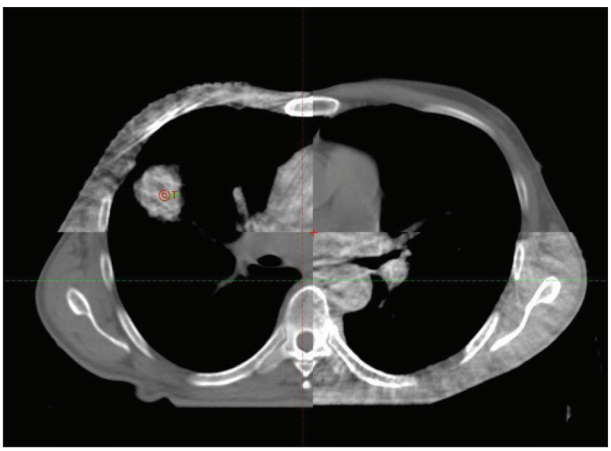

Figure 3. Cone beam computed tomography (Institute for Oncology and Radiology of Serbia)

SBRT TREATMENT DOSE

The application of a high radiation dose with each SBRT fraction leads to a high biologically effective dose (BED), and establishes SBRT as a biologically more potent method than the conventional fractionation regimen.

The radiobiology behind SBRT is largely unknown, so the tumor dose and the number of fractions are still a matter of discussion. The administered dose is risk-adapted and depends on the localization of the tumor within the lung, the proximity of the OAR, tumor volume, and patient's characteristics. Different fractionation regimens are used in practice, but it is recommended BED to be ≥ 100 Gy [13]. In 2019, the Anderson Cancer Center published the results of a retrospective study that high BED (> 130 Gy) was associated with longer survival compared to lower BED (100–129 Gy) suggesting the importance of a total dose rather than a fractionation regimen [14].

In the RTOG 0915 trial, two fractionation regimens (34 Gy in one fraction *vs.* 48 Gy in four fractions, prescription isodose ≥ 60% to < 90%) were compared in patients with peripherally localized tumors. There was no significant difference in the local control, occurrence of late toxicity, and survival between the two regimens [15]. For peripherally localized tumors that are in direct contact with the thoracic wall, Nagata et al. [16] proposed two fractionation regimens: 45 Gy in three fractions and 48 Gy in four fractions.

The RTOG 0813 trial was designed to determine the maximum tolerated dose for centrally localized tumors. The maximum tolerated dose was 12 Gy in five fractions, with a local control of 89.4% [17]. According to the GOECP/SEOR radiotherapy guideline and evidence published so far, a safe dose for centrally located tumors is 50–60 Gy in five fractions, but an 8 × 7.5 Gy regimen can be considered [18].

Ultra-centrally localized tumors represent a special challenge for performing SBRT. HILUS trial in 2022 showed that the fractionation regimen of 8 × 7 Gy for tumors localized < 1 cm from PBT is unacceptable due to the resulting toxicity [9, 10]. However, the delineation, treatment planning, and dose delivery vary throughout studies. The novel results of the phase I SUNSET trial in 2024 suggest that a dose of 60 Gy in eight fractions (precisely planned and delivered) can be considered safe [19].

TREATMENT TOXICITY

The development of acute and late toxicity after lung tumor SBRT is individual, and depends on multiple factors such as patient age, comorbidities, tumor localization in the lungs, the proximity of OAR, and the very method of radiation technique.

The high doses of radiation used during SBRT can cause side effects ranging from mild fatigue to fatal pneumonitis, and bleeding.

One of the most frequent side effects following SBRT is radiation pneumonitis. After SBRT, reported rates of symptomatic radiation pneumonitis vary 9–28% [20].

The most common late complications of SBRT for peripherally localized lung cancer are chest wall pain, rib fracture, and pulmonary fibrosis. In about 16% of cases, chest wall pain is symptomatic and usually occurs 6–9 months after treatment. A rib fracture is recorded in 17% of cases, 13–22 months after SBRT [21].

Complications are significantly more frequent and pronounced when performing SBRT of centrally located tumors, namely esophagitis, damage to the mediastinal vascular structures with bleeding, ulceration, and perforation of the esophagus and trachea.

Nguyen et al. [22] reported that the toxicity of grade > 2 for ultra-central, central, and peripheral localizations was 57.6%, 14.2%, and 7.1% respectively for the same dose. After the radiation treatment of an ultra-centrally localized tumor, Wang et al. [23] reported 22% of patients with pneumonitis and esophagitis grade ≥ 3, while tracheobronchial fistula was documented in two patients.

Prophylactic administration of corticosteroids during SBRT did not show any benefit. The frequency of acute complications is approximately the same in patients receiving prophylactic dexamethasone as in those who did not receive corticosteroid therapy [24].

CONCLUSION

Current research indicates that stereotaxic radiotherapy in patients with early-stage, inoperable peripheral lung cancer represents an optimal treatment modality, associated with an acceptable rate of toxicity. The implementation of SBRT in central and ultra-central lung tumors is still a subject of research due to the risk of developing high-grade toxicity. Numerous studies are ongoing regarding the implementation of SBRT in central localization, the results of which are expected soon.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

Conflict of interest: None declared.

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Стереотаксична радиотерапија у лечењу карцинома плућа – савремене могућности

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САЖЕТАК

Стереотаксична радиотерапија представља стандардни третман у лечењу раног стадијума, иноперабилног, неситноћелијског карцинома плућа. Постиже високу стопу локалне контроле болести (74–100%), уз очуван квалитет живота и прихватљиву токсичност. У клиничкој пракси користе се различити режими фракционисања у зависности од локализације и величине тумора, близине ризичних органа и општег стања болесника.

Радиобиологија стереотаксичне радиотерапије је још увек недовољно позната, тако да су прецизно дефинисане дозе зрачења и број фракција и даље предмет расправе. У току су бројне студије стандардизације стереотаксичне радиотерапије у лечењу карцинома плућа.

Кључне речи: стереотаксична радиотерапија; карцином плућа; рани стадијум

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CURRENT TOPIC • АКТУЕЛНА ТЕМА

Pancreatic carcinoma – diagnosis and modern multimodal treatment

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SUMMARY
Pancreatic cancer is one of the most aggressive tumors and is among the top ten most common malignancies in the world. This is a disease of older adults, and men get it more often. Pancreatic carcinomas risk factors are obesity and type II diabetes, smoking, and alcohol consumption. Symptoms of the disease include obstructive jaundice, loss of appetite, weight loss, fatigue, and back pain. The diagnosis of pancreatic cancer involves computed tomography of the thorax, abdomen and pelvis or magnetic resonance imaging of the abdomen and pelvis, and endoscopic ultrasound with biopsy. The most common histological type of pancreatic cancer is ductal adenocarcinoma. The TNM classification is used to determine the stage of the disease. Pancreatic cancer treatment is complex, multidisciplinary, and multimodal, and involves the use of surgery, chemotherapy, and radiotherapy, alone or in different combinations. Surgery is the main treatment modality for these tumors, especially in localized stages. Chemotherapy is applied in all forms in the treatment of pancreatic cancer as neoadjuvant, adjuvant, and systemic. Immunotherapy, as the newest type of treatment, is used in a limited way in the metastatic phase of pancreatic cancer. The role of radiotherapy in the treatment of pancreatic cancer is still debated, and it is most often applied in a neoadjuvant and palliative approach. Palliative therapy and care are an indispensable part of the treatment of patients with pancreatic cancer.
Keywords: pancreatic cancer; treatment; surgery; chemotherapy; radiotherapy

INTRODUCTION

Pancreatic carcinomas are considered one of the deadliest malignancies because they are usually in advanced stage at the time of diagnosis.

EPIDEMIOLOGY AND ETIOLOGY

Pancreatic cancer is among the top ten cancers in the world in terms of incidence and the seventh most common cause of death from cancer [1]. In the Republic of Serbia, pancreatic cancer is the sixth most common cancer.

Pancreatic cancer is a multifactorial disease. Genetic factors include a positive family history. Demographic risk factors, age and sex, indicate that the disease is more common over the age of 50 and with a male predominance. Acquired risk factors include obesity, type II diabetes, smoking and alcohol consumption [2].

SYMPTOMS AND DIAGNOSIS

Early-stage pancreatic cancer rarely causes symptoms, and when symptoms develop, it is usually at an advanced stage. Symptoms includes obstructive jaundice, loss of appetite, fatigue, weight loss, and abdominal or back pain.

At the time of diagnosis, about 50% of patients have metastatic disease, about 35% have locally advanced disease, and 15% have local disease [3].

Diagnostics of pancreatic cancer includes computerized tomography (CT) of the thorax, magnetic resonance (MR) or CT of the abdomen and pelvis, MR cholangiopancreatography, endoscopic ultrasound (EUS) with biopsy and pathohistological analyses.

CT is widely accepted in the diagnosis of pancreatic cancer. With modern multiphase and multidetector high-resolution CT with multiplanar reconstructions and contrast, the sensitivity of pancreatic cancer detection is 89%, and the specificity is 90% [4].

MR of the abdomen and pelvis provides a much better image of the soft tissues, especially in cases where the CT findings are inconclusive. MR with using diffusion sequences, the sensitivity increases to 92–96%, and the specificity to 97–99% [4].

EUS is not used as a routine method in the detection of pancreatic cancer, but for the detection of small tumors that are not visible on CT and are suspected on MR. EUS is primarily used to biopsy suspicious changes in the head of the pancreas to obtain pathohistological findings. The sensitivity of this method is 89–91% and the specificity is 81–86% [5].

Pancreatic carcinomas form a very heterogeneous group of tumors and ductal adenocarcinomas make about 90% of all pancreatic carcinomas [6]. Although histopathology remains the most reliable method for establishing

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a definitive diagnosis, it may be difficult to distinguish pancreatic carcinomas from metastases without immunohistochemistry [7]. Progress in molecular biology and pathology have led to more precise diagnosis, subtyping, tumor classification and prediction of therapeutic response. Pancreatic cancer genome is very heterogeneous and includes gene mutations and abnormalities (*BRCA1*, *BRCA2*, *TP53*, *KRAS*, etc.), microsatellite instability as well as impaired expression of growth factors (*HER2*) [8].

STAGING

The TNM classification is used to present the stage of pancreatic cancer [9]. The lymphovascular and perineural invasion of pancreatic carcinoma is prominent. The most common sites of pancreatic cancer metastasis are the liver (90%), lymph nodes and lungs (25%), peritoneum (20%) and bones (10–15%) [10].

TREATMENT

Five-year survival of a patient with pancreatic cancer is very modest, about 30% in the local stage, about 10% in the locally advanced stage, and 5% in the metastatic stage of the disease [8]. Pancreatic cancer treatment is multidisciplinary and multimodal. The basic type of treatment for early pancreatic cancer involves surgery, for locally advanced cancers a combination of chemotherapy (HT) with/or without radiotherapy (RT) and surgery, and for metastatic cancers, HT and RT are used. The most widely used recommendations in the treatment of pancreatic cancer are the National Comprehensive Cancer Network [11] and the European Society of Medical Oncology [12].

SURGERY

The primary approach in the treatment of pancreatic cancer is radical surgery and involves complete removal of the visible tumor and obtaining histologically free margins, i.e., microscopically negative margin means a distance of less than 1 mm from cancer cells.

In terms of resectability, pancreatic cancers can be estimated as resectable, borderline resectable, or unresectable [11].

The treatment is surgical for resectable tumors. Borderline resectable and locally advanced tumors are operated upon after neoadjuvant therapy and conversion to a resectable stage. Radical surgical procedures are pancreaticoduodenectomy (Kausch–Whipple procedure), distal pancreatectomy and total pancreatectomy.

Pancreaticoduodenectomy (Kausch–Whipple procedure) is a cancer operation of the head of the pancreas that includes the removal of the distal part of the stomach, duodenum, the end of the common bile duct, the gallbladder and the head of the pancreas with at least a 1 cm margin from the tumor. Reconstruction can be achieved in the form of pancreaticojejunostomy or pancreaticogastrostomy [13]. Lymphadenectomy involves dissection of the associated lymph nodes and standard dissection includes the infra- and suprapyloric lymph nodes, along the common hepatic artery, lymph nodes in the hepatoduodenal ligament, around the pancreatic head, and around the proximal part of the superior mesenteric artery and superior mesenteric vein. Distal pancreatectomy is an operation for carcinoma of the pancreas body and tail with "en-block" splenectomy, and involves mobilization of the body and tail of the pancreas, ligation of the splenic artery and splenic vein, lymphadenectomy, transection of the pancreas and ligation of the pancreatic duct. Total pancreatectomy is a combination of pancreaticoduodenectomy and distal pancreatectomy in patients with multilocular, large, and centrally located pancreatic tumors. It includes "en bloc" resection of the pancreas, gallbladder, duodenum and spleen with accompanying lymphadenectomy and reconstruction with hepaticojejunostomy and duodenojejunostomy.

The operation can be classic (open) and minimally invasive (laparoscopic and robotic). The minimally invasive techniques in the treatment of pancreatic cancer are not inferior comparing to open surgery in terms of surgical and oncological outcome. Laparoscopic technique may lead to a reduced hospital stay and postoperative complications and increased percentage of marginal clearance resections and harvested lymph nodes [14]. Robotic surgery is a promising technique that may lead to shorter hospitalization and lower postoperative complications but longer operative time [14]. Minimally invasive technique should be performed by experienced surgeons in high-volume centers and randomized trials with a large number of patients are necessary to examine the benefits of new technique, especially robotic surgery.

CHEMOTHERAPY

In the treatment of pancreatic cancer, HT is applied in almost all stages of the disease (except in early stages), as preoperative (neoadjuvant), postoperative (adjuvant) and systemic (palliative).

The role of neoadjuvant HT is manifested in marginally resectable pancreatic cancers because it significantly improves overall survival (OS) compared to "up-front" surgery (median OS 19 months *vs.* 29 months with neoadjuvant HT) [15], usually in combination with RT. In locally advanced unresectable pancreatic cancer with median OS of about 11–14 months [16], neoadjuvant HT is essentially induction, with the aim of reducing the size of the tumor and regional lymph nodes, to facilitate resection rate (up to 28%) and increase the chance of achieving R0 resection (up to nearly 70%), thus prolonging OS [17]. It can be combined with RT. Neoadjuvant HT can be applied as polytherapy with 5-fluorouracil plus leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) or as doublet therapy with gemcitabine-cisplatin / gemciatbin-nabpaclitaxel (GP/GN). FOLFIRINOX provides a slightly greater benefit to OS survival (median OS 33.4 months with FOLFIRINOX and

surgery *vs*. 27.9 months with GN and surgery) [17], but also slightly more pronounced toxic effects, so it is used in patients with preserved performance [Eastern Cooperative Oncology Group performance status (ECOG PS)] 0–1, and for more fragile patients gemcitabine-based HT is a good alternative.

Adjuvant HT is indicated in operated patients with pancreatic cancer regardless of resection margin status, in poor prognostic factors such as younger patients, poor tumor differentiation (grade 3–4), T3 and T4 disease stage and positive ln (N+). In patients with preserved ECOG PS, modified (m) FOLFIRINOX is used as standard. PRODIGE 24/CCTG PA6 trial [18] is the most relevant study on the role of adjuvant HT and demonstrated significantly longer survival with (m) FOLFIRINOX (median OS 53.5 months *vs*. 35.5 months in group with gemcitabin), which is much longer OS than those patient with only observation after resection (median OS is 22.3 months) [19]. A good alternative to standard HT is GP doublet, while mono-gemcitabine and fluorouracil and leucovorin (5FU-LV) is reserved for ECOG PS 2–3 patients [12].

Systemic HT is applied in the metastatic phase of the disease and has a palliative purpose. The same types of cytostasis are used. In the first line, in good ECOG PS 0–1, FOLFIRINOX is preferred over GN (median OS 9.6 months with FOLFIRINOX *vs*. 6.1 months with GN) [20], which is not a significant increase of OS (median OS in metastatic pancreatic cancer is 4.6–8.1 months) [21]. In fragile patients, mono-gemcitabine or mono-capecitabine is given [11, 12]. In the second line, in patients with ECOG PS 0–1, who were previously treated with FOLFIRINOX, GN can be used, while in patients who received gemcitabine-based HT in the first line, nanoliposomal irinotecan-5FU-LV is used. Other cytostatic combinations in the metastatic phase of the disease are GP, capecitabine-oxaliplatin and oxaliplatin-5FU-LV [11, 12].

New developments in cytotoxic HT imply that a combination of liposomal irinotecan, fluoracil, leucovorin and oxaliplatin) and it is possible option for frontline therapy in previously untreated patients with metastatic pancreatic cancer [22]. Some of ongoing trials include an efficiency assessment of combination of small molecule and cytotoxic drug in therapy of metastatic pancreatic cancer, like AVENGER 500 trial (mFOLFIRINOX and CPI-613) and NCT03126435 trial (endoTAG-1 and gemcitabine) [23].

IMMUNOTHERAPY

Immunotherapy in the treatment of pancreatic cancer is limited and for the time being is only used in metastatic disease. Poly adenosine diphosphate ribose polymerase enzyme inhibitors (PARP inhibitors) such as olaparib are used, followed by "checkpoint" inhibitors such as pembrolizumab (they act on receptors for programmed cell death-1 (PD-1) and PD-L1 protein in the tumor cell). Olaparib is administered as maintenance therapy in patients with metastatic pancreatic cancer harboring a *BRCA* gene mutation (about 4% of patients) after first-line platinum-based HT [24]. Pembrolizumab in unresectable pancreatic cancers can lead to a good partial remission of the disease [25].

CAR T-cell therapy is a promising development in immunotherapy of pancreatic cancer and is driving future clinical trials. Ongoing immunotherapy trials include combination of PARP inhibitors and PD-1 inhibitor (SWOG2001 trial) and PD-1 inhibitor and small molecule (SX-682) (NCT04477343 trial) [22].

RADIOTHERAPY

The role of radiation in the treatment of pancreatic cancer is still insufficiently defined. State-of-the-art RT techniques such as intensity modulated RT, volumetric modulated arc therapy, and stereotactic "body" RT are used [26]. Four-dimensional CT planning and image-guided RT are recommended. However, there is still no consensus regarding the fractionation of RT in the treatment of pancreatic cancer. RT in the treatment of pancreatic cancer can be preoperative (neoadjuvant), postoperative (adjuvant), and palliative, usually at the same time as HT to enhance the effect of the therapy.

The real role of neoadjuvant HT (HRT) is in marginally resectable pancreatic cancers because they are at increased risk of R1 resection, and RT can lead to downsizing and/or downstaging of the tumor, which increases the chance of achieving R0 resection. Landmark study on the role of neoadjuvant HRT is the PREOPANC study with 250 patients that compared the five-year OS of two groups of patients, treated with surgery alone plus adjuvant HT or a combination of preoperative HRT plus surgery and adjuvant HT (HT with gemcitabine and RT with tolerance dose 36 Gy in 15 fractions). The percentage of R0 resection was 72% *vs*. 43%, five-year OS rate was 20.5% *vs*. 6.5% (HRT and surgery group *vs*. surgery group) [27]. Today, standard therapy includes induction HT for 2–3 months, FOLFIRINOX or GN, and then concomitant HRT with 5-FU or capecitabine or gemcitabine [12]. RT doses of neoadjuvant HRT for borderline resectable pancreatic cancer are varied starting from standard fractionation (45–54 Gy in 25–30 fractions), through hypofractionation (36 Gy in 15 fractions, 30 Gy in 10 fractions) to stereotaxy (28–30 Gy in five fractions, 33–40 Gy in five fractions) [28]. In locally advanced unresectable pancreatic cancer, neoadjuvant therapy can lead to conversion to potentially resectable cancer. It was demonstrated in the CONKO-007 trial with over 300 patients that compared the OS of two groups of patients, treated with induction HT and sequential HT or preoperative HRT plus surgery (induction HT with gemcitabine/FOLFIRINOX and RT with tolerance dose 50.4 Gy in 28 fractions) [29]. The percentage of R0 resection was 25% *vs*. 18%, pathological complete response was 10% *vs*. 0% and two-year OS rate was similar (HT and surgery group *vs*. HRT and surgery group) [29]. The optimal therapeutic approach in the treatment of locally advanced unresectable pancreatic cancer remains controversial, with conversion induction HT followed by neoadjuvant HRT being more commonly used in the US, while induction

HT is favored in most European countries. RT doses of neoadjuvant HRT of locally advanced unresectable pancreatic cancer are also different starting from standard fractionation (50.4–54 Gy in 28–30 fractions) which is less frequently used, through hypofractionation (36 Gy in 15 fractions, 30 Gy in 10 fractions) and ablative RT (67.5 Gy in 15 fractions and 75 Gy in 25 fractions) to stereotaxy (30 Gy in five fractions, 33–35 Gy in five fractions and 45 Gy in six fractions) [28].

Adjuvant HRT is not a therapeutic standard in operated patients with pancreatic cancer because the role of adjuvant RT in the modern era of new and more effective systemic therapies remains unclear [30]. Adjuvant HRT can be considered in pT3 stage and pN+ cases, and RT doses would be 50–55 Gy in 25–30 fractions [28].

Palliative RT is carried out in order to control local symptoms and improve the quality of life of patients in an advanced stage of malignant disease. Indications are pain, bleeding, bone and brain metastases, and RT doses are 8 Gy in one fraction, 16 Gy in four fractions, 20 Gy in five fractions or 30 Gy in 10 fractions.

PALLIATIVE THERAPY AND CARE

Palliative therapy and care are very important parts of pancreatic cancer treatment. It encompasses drug therapy (non-opioid, opioid, and co-analgesics), palliative surgical interventions or endoscopic placement of stents in case of obstruction (gastrojejunostomy or biliary-digestive anastomosis) and palliative RT for bone and brain metastases.

CONCLUSION

Pancreatic cancer is an aggressive invasive tumor with a modest five-year survival. The treatment of these cancers is complex and challenging, and involves the use of surgery, HT and immunotherapy as well as RT, alone or in different combinations. Surgery is the main way of treating pancreatic cancer, especially in the early stages of the disease. Various HT regimens are indispensable in the treatment of pancreatic cancer in the neoadjuvant, adjuvant and systemic approach. Immunotherapy as the newest type of therapy is emerging in the treatment of selected cases of these cancers, especially in systemic disease. RT has an unclear role in the treatment of these tumors, and it is used in marginally resectable and locally advanced cancers in a neoadjuvant approach, usually in combination with HT, but also in a systemic approach. Palliative therapy is complementary and important part of pancreatic cancer therapy.

Ethics: This article was written in accordance with the ethical standards of the journal and the institutions.

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Карцином панкреаса – дијагноза и савремено мултимодално лечење

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САЖЕТАК

Карцином панкреаса је један од најагресивнијих тумора и налази се међу првих десет најчешћих малигнитета у свету. Ово је болест старијих особа, а мушкарци обољевају чешће. Карциноми панкреаса су тумори са утицајем генетских наследних синдрома и стечених фактора као што су гојазност и дијабетес тип II, пушење и алкохол. Симптоми болести укључују опструктивни иктерус, губитак апетита, умор, губитак тежине, инсуфицијенцију панкреаса, бол у трбуху, бол у леђима и умор. Дијагноза карцинома панкреаса подразумева компјутеризовану томографију торакса, компјутеризовану томографију / магнетну резонанцу абдомена и мале карлице, ендоскопски ултразвук са биопсијом. Најчешћи хистолошки тип карцинома панкреаса је дуктални аденокарцином. За одређивање стадијума болести користи се ТНМ класификација. Лечење карцинома панкреаса је мултидисциплинарно и мултимодално, а подразумева примену хирургије, хемотерапије и радиотерапије, самостално или у различитим комбинацијама. Хирургија је основна метода лечења ових тумора, нарочито у раном стадијуму. Хемотерапија се у лечењу карцинома панкреаса примењује као неоадјувантна, адјувантна и системска. Имунотерапија се као најновији вид лечења ограничено примењује у метастатској фази карцинома панкреаса. Улога радиотерапије у лечењу карцинома панкреаса је врло контроверзна, о њој се још увек дискутује, а најчешће се примењује у неоадјувантном и палијативном приступу. Палијативна терапија и нега су незаобилазни део лечења болесника са карциномом панкреаса.

Кључне речи: карцином панкреаса; лечење; хирургија; хемиотерапија; радиотерапија

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 разматран за објављивање 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.

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СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

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