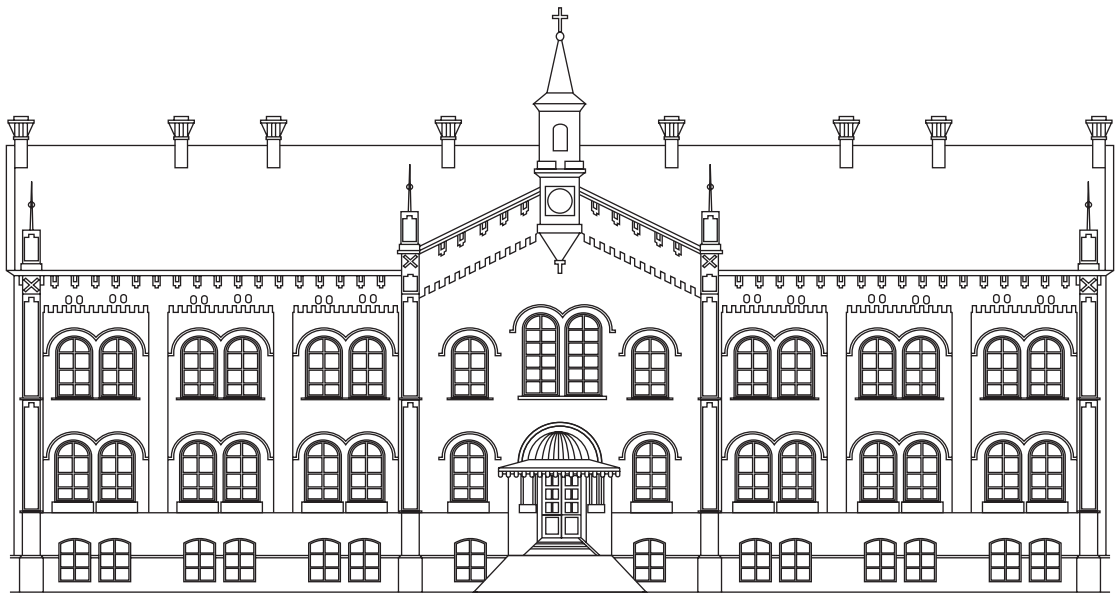
SRP ARH CELOK LEK

ISSN 0370-8179 (PRINT)
ISSN 2406-0895 (ONLINE)

COBISS.SR-ID 3378434
UDC 61(497.11)

СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА



SERBIAN ARCHIVES
OF MEDICINE

JOURNAL OF THE SERBIAN MEDICAL SOCIETY

VOLUME 151 · SEPTEMBER–OCTOBER 2023 · ISSUE 9–10

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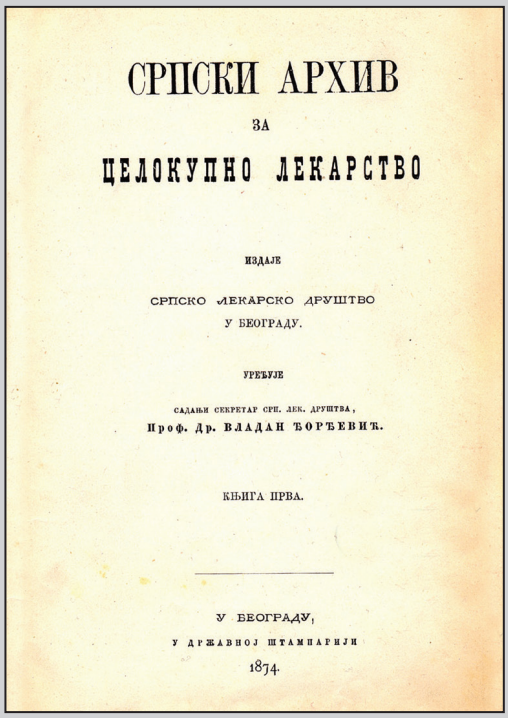

СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

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СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

УРЕЂУЈЕ

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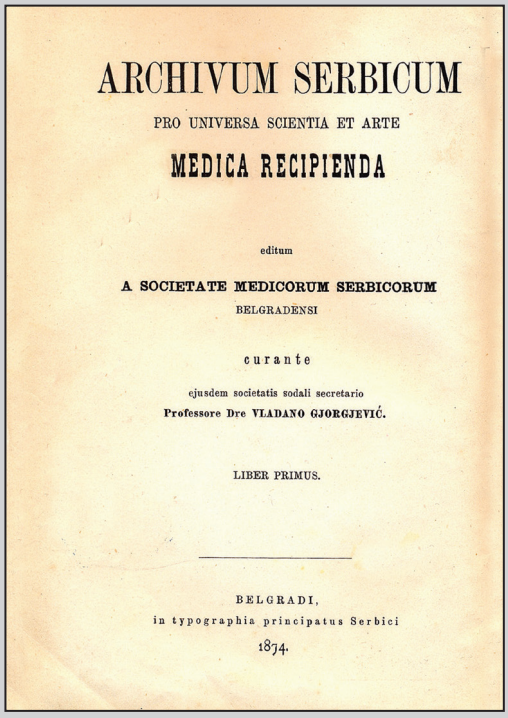
У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



ARCHIVUM SERBICUM

PRO UNIVERSA SCIENTIA ET ARTE

MEDICA RECIPIENDA

editum

A SOCIETATE MEDICORUM SERBICORUM

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1874.

The title page of the first journal volume in Latin

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Srp Arh Celok Lek
ISSN 0370-8179
UDC 61(497.11)
COBISS.SR-ID 3378434
Српски архив за целокупно лекарство
Званичан часопис Српског лекарског друштва
Излази шест пута годишње

Српски архив за целокупно лекарство

ГОДИШТЕ 151 СЕПТЕМБАР–ОКТОБАР 2023. СВЕСКА 9–10

Часопис „Српски архив за целокупно лекарство" је индексиран у базама: Science Citation Index Expanded, Journal Citation Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journals, DOI Serbia.

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Академик Радоје Чоловић
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ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Отворен приступ

Штампано у Србији

Редакција
Технички уредник: Јасмина Живковић
Лектор за српски језик: Дивна Продановић
Лектори за енглески језик: Мирко Рајић, Ана Миловановић
Корице: *MaxNova Creative*

Штампа: ЈП „Службени гласник", Београд

Тираж: 850 примерака

Srp Arh Celok Lek
ISSN 0370-8179
UDC 61(497.11)
COBISS.SR-ID 3378434
Serbian Archives of Medicine
Official Journal of the Serbian Medical Society
Published six times per year

SERBIAN ARCHIVES OF MEDICINE

VOLUME 151 SEPTEMBER–OCTOBER 2023 ISSUE 9–10

The journal "Srpski arhiv za celokupno lekarstvo" (Serbian Archives of Medicine) is indexed in: Science Citation Index Expanded, Journal Citation Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journals, DOI Serbia.

EDITORIAL OFFICE
Technical editor: Jasmina Živković
Serbian language editor: Divna Prodanović
English language editors: Mirko Rajić, Ana Milovanović
Cover & Logo: MaxNova Creative

Printed by: JP "Službeni glasnik", Belgrade

Circulation: 850 copies

FOUNDER, OWNER & PUBLISHER
Serbian Medical Society
President
Academician Radoje Čolović

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+381 (0)11 409 44 79
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SUBSCRIPTION AND DISTRIBUTION
Serbian Medical Society
Džordža Vašingtona 19, 11000 Belgrade
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Phone: +381(0)11 3245-149
Bank accounts: 205-8041-21 and
355-1009094-22

Full-text articles are available at website: www.srpskiarhiv.rs

Calendar year subscription prices are as follows: 3,000 dinars for individuals, 6,000 dinars for institutions, and 100 euros for readers outside Serbia. The price of a current year issue is 600 dinars, and of issues from previous years 300 dinars.

The publishing of the Serbian Archives of Medicine during 2023 is supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Open Access

Printed in Serbia

САДРЖАЈ • CONTENTS

ORIGINAL ARTICLES • ОРИГИНАЛНИ РАДОВИ

DOI: https://doi.org/10.2298/SARH221217082D
UDC: 616.98:578.834]:615.371(497.11)"2021"

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effectiveness of a third dose of COVID-19 vaccines against delta variant of SARS-CoV-2 – a Serbian cohort study

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SUMMARY
Introduction/Objective The duration of vaccine-induced protection against SARS-CoV-2 is shown to be limited.
The aim of this study was to assess vaccine effectiveness (VE) of a third dose of four different COVID-19 vaccines during Delta variant predominance in Serbia.
Methods The data for the period from August 18, to October 1, 2021 were used to estimate the incidence rates (IR) of the SARS-CoV-2 infection, COVID-19-related hospitalization, and intensive care unit (ICU) admission. The study included 41,186 fully vaccinated subjects, of which 13,589 had received the third dose. VE was estimated based on the IR ratio following vaccination with three *vs*. two doses.
Results We found that a third dose of all investigated vaccines reduces the incidence of both SARS-CoV-2 infection and severe illness that requires hospitalization or ICU admission. The highest VE against infection demonstrated BNT162b2, followed by Gam-COVID-Vac and BBIBP-CorV. Third dose vaccination reduced the risk of hospitalization (IR = 0 for Gam-COVID-Vac and BBIBP-CorV), and ICU admission (IR = 0 for all vaccines). The hazard distributions for SARS-CoV-2 infection and hospitalization following vaccination with three versus two doses were significantly different.
Conclusion These findings indicate that an additional, third dose of studied vaccine boosters protection against all investigated outcomes.
Keywords: COVID-19; vaccine effectiveness; BBIBP-CorV; Gam-COVID-Vac; BNT162b2; ChA-dOx1-nCoV-19

INTRODUCTION

In March 2020, the World Health Organization declared the pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During the last two years, the multiple waves of COVID-19 pushed healthcare systems to the breaking point; lockdowns and mobility restrictions left severe consequences on the economy; and social distancing and isolation heavily disrupted human physical and mental wellbeing. The world has been witnessing the magnitude, the extent and the continuance of the perturbations COVID-19 brought on to all spheres of human life, yet, only less than 10% of humanity has been infected with the SARS-CoV-2 so far (https://covid19.who.int/), and the virus continues to spread globally.

The virus spreading can be stopped only by achieving herd immunity – either by infection or by vaccination. SARS-CoV-2 infection, unlike vaccination, enables virus transmission to non-immune people, and in those who are infected could take severe form, lead to hospitalization or intensive care unit (ICU) admission, and end fatally. Hence, the safest and the most effective way to achieve protection against COVID-19 is vaccination. Up to now, about 11.3 billion doses of a COVID-19 vaccine have been administered globally, and 64.6% of the world population has received at least one dose [1]. Although vaccination

Received • Примљено: December 17, 2022
Revised • Ревизија: July 16, 2023
Accepted • Прихваћено: September 6, 2023
Online first: September 8, 2023

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reduces the possibility of infection and lessens the risk of developing severe form of the disease, it has been reported that the SARS-CoV-2 specific response, even after receiving the second dose of vaccine, diminishes over time [2, 3].

Since the waning immunity, especially in the presence of new viral strains, warrants booster immunization, data on a third dose vaccine effectiveness (VE) are of great importance. The main aim of this study was to assess VE of the third dose of four different COVID-19 vaccines, namely BNT162b2 (Comirnaty®, Pfizer-BioNTech, Tokyo, Japan), BBIBP-CorV (Vero Cell®, Sinopharm Group Co. Ltd., Shanghai, China), Gam-COVID-Vac (Sputnik V®, Gamaleya Institute, Moscow, Russia) and ChAdOx1-nCoV-19 (Vaxzevria®, University of Oxford/AstraZeneca, Cambridge, United Kingdom), during Delta variant predominance in Serbia.

METHODS

Study design

This retrospective comparative cohort study was conducted among the resident population of the city of Kragujevac, Serbia, between August 18, 2021 (start of the third dose of COVID-19 vaccines rollout in Serbia) and October 1, 2021. To be included in the study, subjects needed to be older than 16 years of age and completely vaccinated against SARS-CoV-2 (i.e., to have received at least two doses of either BBIBP-CorV, Gam-COVID-Vac, BNT162b2, or ChAdOx1-nCoV-19 vaccine) by the end of the study follow up. However, as the neutralizing antibody levels, which are highly predictive of vaccine efficacy against SARS-CoV-2 infection [4], decrease substantially until three months after vaccination [5], recipients of only two doses were included only if the second dose was received at least three months before the beginning of the study. Subjects were excluded from the analyses if the data on sex, age, vaccination status, and COVID-19 test results were not available, but also if infection with SARS-CoV-2 took place prior to vaccination, or within the first seven days after receiving the vaccine (Figure 1).

The data on vaccination coverage was extracted from the Serbian National Immunization Registry. The Reports of the Primary Health Centre and the University Clinical Centre in Kragujevac provided information on the study outcomes, namely RT-PCR or antigen test confirmed SARS-CoV-2 infection, hospitalization due to COVID-19 and COVID-19-related ICU admission. Subjects were followed up either from the beginning of the study (if they had been vaccinated earlier), or from the day of receiving the last dose of the vaccine; until the end of the study, or until they had been diagnosed with COVID-19. According to available data [6], the Delta variant was the most predominant (if not the sole) circulating strain of SARS-CoV-2 in Serbia during the study period.

The study was approved by the Ethics committee at the University Clinical Centre and the Primary Health Centre, Kragujevac, Serbia (approvals No 01/20-405, No 01/20-497 and No 01-1148/1, obtained on April 3, 2020, May 5, 2020 and February 24, 2021, respectively), and conducted in accordance with the Declaration of Helsinki and its subsequent revisions.

Statistical analysis

SPSS Statistics, version 20 (IBM Corp., Armonk, NY, USA) and Stata Statistical Software, release 16 (StataCorp LLC,

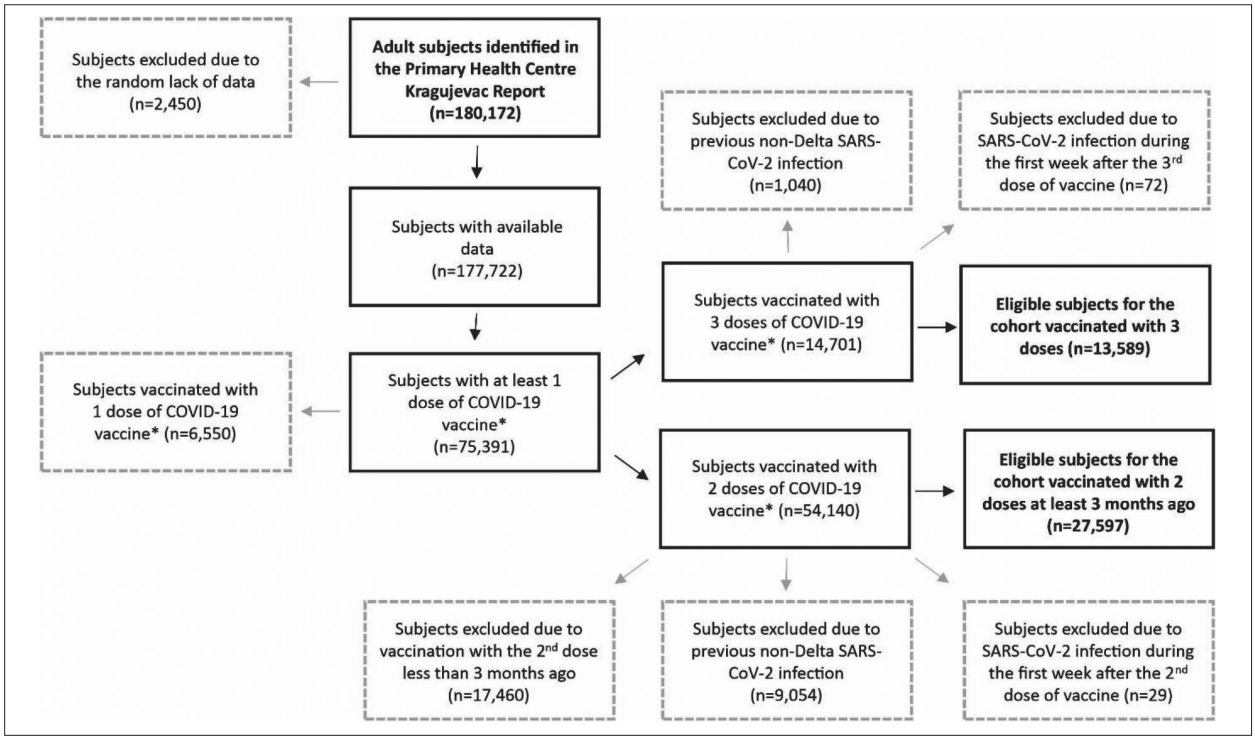

Figure 1. The cohorts' selection process;

*since the launch of the COVID-19 vaccines roll out in Serbia, until October 31, 2021

Table 1. Demographic characteristics, vaccination status, and the total length of the follow-up of subjects involved in the study

Parameters	Vaccinated with three doses		Vaccinated with two doses[a]		Total	
	n	%	n	%	n	%
Total	13,589	33	27,597	67	41,186	100
Age groups (years)						
Up to 24	36	0.26	464	1.68	500	1.21
25–34	180	1.32	1769	6.41	1949	4.73
35–44	807	5.94	4527	16.4	5334	12.95
45–54	1327	9.77	4692	17	6019	14.61
55–64	2502	18.41	5807	21.04	8309	20.17
65–74	5888	43.33	6882	24.94	12,770	31.01
75 and over	2849	20.97	3456	12.52	6305	15.31
Sex						
Male	6538	48.11	12,639	45.8	19,177	46.56
Female	7051	51.89	14,958	54.2	22,009	53.44
Type of vaccine						
BBIBP-CorV	8477	62.38	17,270	62.58	25,747	62.51
Gam-COVID-Vac	1139	8.38	5022	18.2	6161	14.96
BNT162b2	944	6.95	4536	16.44	5480	13.31
ChAdOx1-nCoV-19	0	0	768	2.78	768	1.86
Mix-and-match	3,029	22.29	1	0	3030	7.36
Total person time						
In days	315,033		1,179,279		1,494,312	
In years	863.1		3,230.9		4094	

[a]Second vaccine dose received at least three months before the beginning of the study follow-up

College Station, Texas, USA) were used for statistical analyses. The frequencies of the COVID-19-related events were expressed as incidence rates (IR). VE against all study outcomes was determined based on the sex- and age-adjusted IR ratio (IRR) among those vaccinated with either two or three COVID-19 vaccine doses. Vaccine-preventable disease incidence, the parameter that more directly presents an impact of the vaccines on reducing infection, hospitalization, and ICU admission, is a measure of the difference in the incidence of any particular outcome between vaccinated and unvaccinated populations, and was calculated according to Gessner and Feikin [7]. The number needed to vaccinate, i.e., the number of people or vaccine doses needed to prevent the investigated outcomes, was calculated according to Tripepi et al. [8]. To compare hazard distributions for the study outcomes following vaccination with three versus only two doses, the Kaplan–Meier method and a Logrank (Mantel–Cox) test were used. P values of less than 0.05 were considered significant.

RESULTS

Demographic characteristics, type of vaccine received, and the total length of follow up of all subjects involved in the study, stratified according to the vaccination status, are presented in Table 1. As subjects participating in the study were followed for different lengths of time, a cumulative amount of time (Total person time) was calculated as the sum of the total time contributed by all subjects.

Table 2. The effectiveness of the third dose of COVID-19 vaccinea as compared to two vaccine dosesb in terms of SARS-CoV-2 infection, hospitalization due to COVID-19, and COVID-19-related ICU admission

Infection, hospitalization, ICU admission	Number of events (IR) three doses[a] / two doses[b]	IRR (95% CI)	VE (95% CI), %	NNV	VPDI (95% CI)
SARS-CoV-2 infection					
Any type of vaccine	164 (190) / 1684 (521.2)	0.394 (0.334;0.464)	60.6 (53.6; 66.6)	3	289.9 (248.7; 329)
BBIBP-CorV	139 (256) / 1164 (577.7)	0.494 (0.413; 0.591)	50.6 (40.9; 58.7)	4	265.7 (210.1; 321.4)
Gam-COVID-Vac	7 (154.5) / 299 (507.4)	0.335 (0.159; 0.707)	66.5 (29.3; 84.1)	3	310.2 (182.7; 437.7)
BNT162b2	1 (22.7) / 180 (335.7)	0.074 (0.011; 0.510)	92.6 (49.0; 98.9)	3	295.2 (227.9; 362.7)
ChAdOx1-nCoV-19	0 (ND) / 41 (454.3)	ND			
Mix and match	17 (73.6) / 0 (0)	ND			
Hospitalization due to COVID-19					
Any type of vaccine	8 (9.3) / 126 (39)	0.154 (0.073; 0.235)	84.6 (67.5; 92.7)	21	42.2 (34.8; 59.7)
BBIBP-CorV	8 (14.7) / 113 (56.1)	0.190 (0.090; 0.398)	81.0 (60.2; 91.0)	21	47.6 (35.6; 59.5)
Gam-COVID-Vac	0 (0) / 8 (13.6)	ND		74	13.6 (4.2; 23)
BNT162b2	0 (0) / 5 (9.3)	ND		108	9.3 (1.2; 17.5)
ChAdOx1-nCoV-19	0 (ND) / 0 (0)	ND			
Mix and match	0 (0) / 0 (0)	ND			
COVID-19-related ICU admission					
Any type of vaccine	0 (0) / 7 (2.2)	ND		455	2.2 (0.6; 3.8)
BBIBP-CorV	0 (0) / 6 (3)	ND		333	3.0 (0.6; 5.4)
Gam-COVID-Vac	0 (0) / 0 (0)	ND			
BNT162b2	0 (0) / 1 (1.9)	ND		526	1.9 (1.8; 5.5)
ChAdOx1-nCoV-19	0 (ND) / 0 (0)	ND			
Mix and match	0 (0) / 0 (0)	ND			

IR – crude incidence rate (per 1000 person-years); IRR – incidence rate ratio adjusted for age and sex; VE – vaccine effectiveness; NNV – number needed to vaccinate; VPDI – vaccine-preventable disease incidence (per 1000 person-years);
[a]3rd vaccine dose received at any time during the study follow-up;
[b]2nd vaccine dose received at least three months before the beginning of the study follow-up;
[c] heterologous prime-boost strategy applied;
NA – not applicable; ND – not determined (due to zero vaccinated or zero event count)

The third dose of any vaccine, as compared to only two doses, decreased the overall IRs of SARS-CoV-2 infection, hospitalization due to COVID-19, and COVID-19-related ICU admission. The frequencies of COVID-19-related study outcomes in both cohorts (overall and per vaccine type), and the measures of VE against SARS-CoV-2 infection and hospitalization in subjects vaccinated with three doses, are presented in Table 2.

The complete absence of ICU admission among subjects vaccinated with three doses of any vaccine, as well as hospitalization among those who have received three doses of Gam-COVID-Vac or BNT162b2, precluded VE estimation against these outcomes. The VE of ChAdOx1-nCoV-19 could not be assessed due to the lack of subjects receiving this type of vaccine in three doses. Similarly, only one recipient of only two doses received two different vaccine types, preventing assessment of heterologous prime-boost strategy effectiveness.

Cumulative hazard functions comparing the incidence of the study outcomes following vaccination with three versus only two doses of any of the four available COVID-19 vaccines are presented in Figure 2. The hazard distributions for SARS-CoV-2 infection and hospitalization due to COVID-19 were significantly different ($\chi^2(1) = 150.468$, $p < 0.0001$ and $\chi^2(1) = 21.404$, $p < 0.0001$, respectively). The comparison could not be made for ICU admission, due to the lack of this event among subjects vaccinated with the third dose.

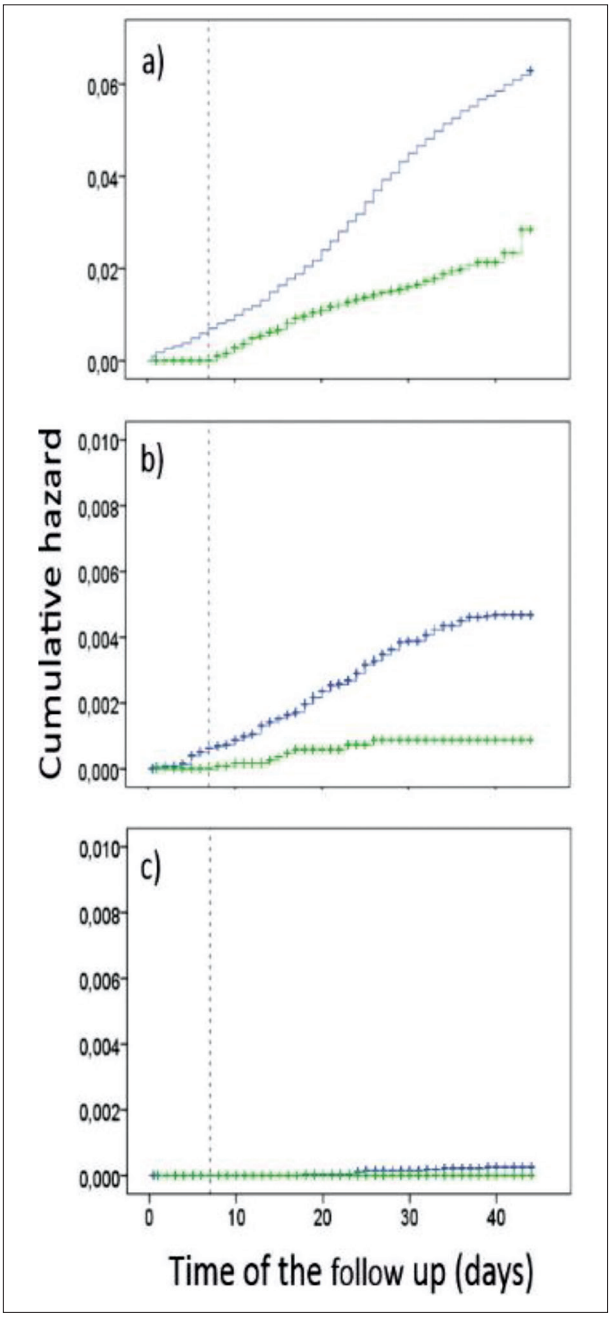

Figure 2. Cumulative hazard function comparing the incidence of a) SARS-CoV-2 infection, b) hospitalization due to COVID-19, and c) COVID-19-related Intensive Care Unit admission, following vaccination with three (green) versus only two (blue) doses of any of the four available COVID-19 vaccines; the dashed vertical line indicates day seven, when the analyses began

DISCUSSION

Our main finding is that the third dose of any of the four investigated COVID-19 vaccines, as compared to the second dose received at least three months prior, significantly reduces the incidence of Delta variant SARS-CoV-2 infection, but also the incidence of hospitalization due to COVID-19, and COVID-19-related ICU admission. Our results support the recommendation of administration of a booster dose in general adult population to restore protection against COVID-19 and its complications.

In terms of infection, the highest VE of a third versus two doses in our study reached almost 93% in those vaccinated with BNT162b2, with as little as three subjects that needed to be vaccinated with a booster dose of BNT162b2 or Gam-COVID-Vac to prevent one case of COVID-19. To prevent one hospitalization, a third dose of any of the COVID-19 vaccines investigated in our study had to be given to 21 subjects fully vaccinated at least three months prior, and VE of the booster reached almost 85%. On the other hand, rare admissions to ICU after receiving two doses, and none in a third dose group, precluded assessment of third dose VE and NNT. In line with our findings, a retrospective cohort study from Israel, comparing infection rates among nearly a million subjects vaccinated with either two or three doses of BNT162b2 vaccine, reported third dose VE of 89.1% [9]. Another Israeli study on almost 1 and a half million participants estimated VE of three versus two BNT162b2 doses to be 93% for hospital admission [10]. Similarly, a large study from United States, conducted on almost half a million veterans, reported 84% and 77% VE of three as compared to two doses of BNT162b2 vaccine against symptomatic SARS-CoV-2 Delta strain infection and COVID-19-related hospitalization, respectively [11]. Among more than a million subjects from California, who were vaccinated with either two or three doses of BNT162b2, VE of a third dose reached 75% against infection and 70% against hospital admission [12]. Again, study from United States, conducted during Delta predominance across 10 states and more than 250 hospitals, estimated BNT162b2 vaccine third-dose effectiveness against hospitalization and ICU admission due to COVID-19, when compared to unvaccinated

population, to reach 94% [13]. In the limited number of studies concerning the effectiveness of three versus two doses of SARS-CoV-2 vaccines, the BNT162b2 vaccine, as the first one approved by WHO, was clearly by far the most investigated [9, 10, 13, 14, 15]. Yet, there are several other vaccines against COVID-19 deployed worldwide [16], calling for the future research to widen the scope, and include not only other internationally available vaccines, but also both available concepts of vaccination – homologous and heterologous [17].

As for the BBIBP-CorV vaccine, while the large-scale effectiveness studies are lacking, strong SARS-CoV-2 specific immunity after the third dose has been reported [18, 19, 20]. Similarly, it has been observed that a third dose of ChAdOx1-nCov-19 boosts T-cell response and increases antibody titers [21]. On the other hand, there were no available reports on Gam-COVID-Vac vaccine boosting. In our study, considerable effectiveness of a booster dose of the same vaccine type against of SARS-COV-2 infection was confirmed for three out of four investigated vaccines. Namely, due to the specific dosing regimen and the relatively short follow-up, our study did not include subjects who had received three doses of ChAdOx1-nCov-19. Also, we were unable to calculate third dose VE of a mix-and-match prime-boost strategy, as the only subject in the two-dose group who was vaccinated with different vaccine types did not get infected with SARS-CoV-2. Nevertheless, it is worth noting that among over 3000 subjects, whose third dose of the vaccine differed from the previous two (mix and match approach), only about 0.5% got COVID-19 during the follow-up, and none were hospitalized or admitted to the ICU. Our results correspond well to the previous reports showing that the immunogenicity of a heterologous third dose boost was as good as, or better than homologous [22–25], especially in fighting against newer SARS-CoV-2 variants of concern [26]. However, after the third vaccine dose, the same level of protection was achieved in both the homologous and heterologous COVID-19 vaccination regimens [27, 28].

The Omicron variant, first identified in South Africa in November 2021 as highly transmissible, has become a globally dominant strain. The Omicron has raised significant global concern due to its large number of mutations, which may impact the effectiveness of vaccines and therapeutics. According to emerging real-world data, the VE of COVID-19 vaccines against symptomatic infection due to Omicron is lower than for the Delta variant, although all vaccines provide high levels of protection against hospitalization and death [29]. However, several studies have shown that the decline in two-dose vaccine VE against Omicron could be increased or restored by a third vaccine dose, emphasizing the importance of booster vaccination [30].

The limitations of the present study include the short follow-up time after the third dose, single-strain- and a single-center study design, as well as the lack of data on many potential confounders, such as the level of exposure to SARS-CoV-2; potential behavioral changes after vaccination; possible under-reporting of COVID-19-like symptoms; asymptomatic (thus undiagnosed) COVID-19 cases; coexisting illnesses and immunocompromising conditions; as well as other medical and demographic risk factors that might affect the susceptibility to COVID-19, and the severity and the outcome of the disease.

CONCLUSION

Despite the limitations of the present study, our results speak in favor of booster vaccination as a necessity in controlling the COVID-19 pandemic. In a view of a waning immunity against SARS-CoV-2 and the emergence of new virus variants, periodic vaccine boosting will most probably become indispensable in future years.

ACKNOWLEDGMENT

This report is independent research supported by the Primary Health Centre Kragujevac (PHCK), Kragujevac, Serbia and Kragujevac University Clinical Centre (UCCK), Kragujevac, Serbia. We thank Dejan Stevanovic from PHCK and Vladan Todorovic from UCCK for technical support. We also thank PHCK COVID-19 Vaccine Coverage team, all staff supporting study delivery at participating sites and all participants for their ongoing commitment and contributions to this study.

Funding: The study was financially supported by the Science Fund of the Republic of Serbia, the program IDEAS, grant No. 7749739.

Conflict of interest: None declared.

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Ефективност треће дозе вакцине против делта варијанте вируса *SARS-CoV*-2 – кохортна студија заснована на подацима из Србије

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САЖЕТАК

Увод/Циљ Показало се да је заштита коју пружа вакцина против *SARS-CoV*-2 временски ограничена.

Циљ ове студије био је да се процени ефективност четири различите вакцине против ковида 19 после примања треће дозе. Истраживање је спроведено у Србији током доминације делта варијанте *SARS-CoV*-2.

Методе Подаци за период од 18. августа до 1. октобра 2021. коришћени су за процену стопе инциденције инфекције *SARS-CoV*-2, хоспитализације због ковида 19 и пријема у јединицу интензивне неге. Студија је обухватила 41.186 субјеката вакцинисаних са најмање две дозе, од којих је 13.589 примило и трећу дозу. Ефективност вакцине је процењена на основу односа стопе инциденције после вакцинације са три у односу на две дозе.

Резултати Трећа доза свих испитиваних вакцина смањила је учесталост и инфекције *SARS-CoV*-2 и тешког облика болести који захтева хоспитализацију или пријем у интензивну негу. Највећу ефективност против инфекције показала је вакцина *BNT*1*62b*2, а затим *Gam-COVID-Vac* и *BBIBP-CorV*. Трећа доза вакцине смањила је ризик од хоспитализације (стопа инциденције *IR* = 0 за *Gam-COVID-Vac* и *BBIBP-CorV*) и пријема у интензивну негу (*IR* = 0 за све вакцине). Расподела ризика за инфекцију *SARS-CoV*-2 и хоспитализацију после вакцинације са три у односу на две дозе значајно су се разликовале.

Закључак Добијени резултати указују на то да додатна, трећа доза испитиваних вакцина појачава заштиту од свих испитиваних исхода.

Кључне речи: ковид 19; ефективност вакцине; *BBIBP-CorV*; *Gam-COVID-Vac*; *BNT*162*b*2; *ChAdOx*1-*nCoV*-19

DOI: https://doi.org/10.2298/SARH230201074S
UDC: 616.98:578.834

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparison of the diagnostic efficacy of the Abbott RealTime SARS-CoV-2 Assay and the BGI Real-Time Fluorescent RT-PCR Kit for the RT-PCR-based detection of Severe Acute Respiratory Syndrome Coronavirus-2

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SUMMARY

Introduction/Objective Based on the WHO Organization guidelines, the current gold standard to diagnose Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is reverse transcription-quantitative real-time polymerase chain reaction (RT-qPCR).

The objective of this study was to compare and analyze the detection performance of two different authorized SARS-CoV-2 nucleic acid detection assays: the Abbott RealTime SARS-CoV-2 (ACOV) assay and the BGI Real-Time Fluorescent RT-PCR (BGI) kit.

Methods Our study included 384 randomly selected nasopharyngeal and oropharyngeal swabs previously tested by the ACOV and subsequently tested by the BGI kit for detecting SARS-CoV-2. All patients were adult individuals with symptoms of or suspected Coronavirus disease 2019 (COVID-19).

Results We found that the ACOV assay detected more cases of COVID-19 infection than the BGI assay. The positive percent agreement was 98.3% (95% confidence intervals (95% CI): 95.7–99.3%), while Cohen's Kappa coefficient was 0.86 (95% CI: 0.80–0.91), indicating a strong level of agreement between these two tests. The negative percent agreement was 85.1% (95% CI: 78.3–90%), while 5.47% of cases were false negative using the BGI test to detect SARS-CoV-2. The sensitivity of the BGI test compared to ACOV was 91.73% (95% CI: 87.64–94.81%), and the specificity of the BGI test was 96.77% (95% CI: 91.95–99.11%).

Conclusion The ACOV showed a bit better diagnostic performance, and due to possible false negative results using the BGI test, we recommend complete testing with the ACOV test.

Keywords: COVID-19; diagnostic efficacy; PCR kits; real-time PCR; RNA isolation; SARS-CoV-2

INTRODUCTION

The first cases of pneumonia with an unknown etiology were recorded in Wuhan, the capital of China's Hubei Province, at the beginning of December 2019. The cause of severe acute respiratory syndrome (SARS), a newly discovered ribonucleic acid (RNA) beta-coronavirus linked to the present severe acute respiratory syndrome Coronavirus (SARS-CoV), was given the name SARS-CoV-2 [1]. As of January 21, 2023, there were 673,035,039 confirmed cases of SARS-CoV-2 infection worldwide, resulting in 6,744,203 deaths [2].

The Republic of Serbia reported its first COVID-19 case on March 6, 2020, and the epidemic is still ongoing. The epidemiological situation is favorable right now, with illness incidence on the decline globally. The Ministry of Health of the Republic of Serbia reports that as of January 21, 2023, 12,065,603 people had been tested in Serbia, of whom 2,464,509 had confirmed cases, resulting in 17,647 deaths and a mortality rate of 0.72% [2].

All data from this rapidly spreading COVID-19 pandemic points to the significance of an accurate molecular diagnosis of coronavirus infection due to the prevalence of coronavirus infection in the Republic of Serbia as well as the worldwide epidemic. Laboratory research is crucial for the epidemiology and illness features of an evolvable infectious disease like SARS-CoV-2, as well as for its transmission monitoring.

The molecular diagnosis of COVID-19 is based on the specific and sensitive detection of viral RNA. RT-qPCR is considered the gold standard in the detection of the SARS-CoV-2 virus, and is based on the fact that genetic material is first extracted from patient samples, and then reverse transcriptase is used to create a complementary deoxyribonucleic acid (DNA) strand from the viral RNA [1, 3]. RT-qPCR can detect several specific genes that encode viral structural proteins, including the spike (S), envelope (E), membrane (M), and nucleocapsid (N), plus eight accessory proteins, as well as open reading frame-1 antibodies (ORF1ab), which encode non-structural proteins (NSPs) – enzymes [4, 5, 6]. Orf1ab polygen is a polyprotein region encoding 16 NSPs, NSP1–NSP16, among which are RNA-dependent RNA polymerase (RdRp, NSP12) and 2'-O-ribose–methyltransferase (2'-O-Mtase, NSP16) [5–8].

Received • Примљено: February 1, 2023
Revised • Ревизија: July 6, 2023
Accepted • Прихваћено: August 1, 2023
Online first: August 28, 2023

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Usually, five to six days after the onset of symptoms, COVID-19 patients had increased viral loads in both their upper and lower respiratory tracts [9, 10]. Researchers are now attempting to build new methods for identifying novel coronaviruses all around the world [11]. Currently, there are roughly 400 commercially accessible genetic tests [12].

Guidelines regarding target genes for SARS-CoV-2 detection vary worldwide. With the emergence of the SARS-CoV-2 virus, the World Health Organization (WHO) recommended protocols targeting the E gene for screening and the RdRp gene for confirmatory testing. As per the Centers for Disease Control and Prevention (CDC) recommendation, among the target genes of the developed SARS-CoV-2 RT-qPCR test, the N gene is the most frequently selected target gene except for ORF1a/b, while the S gene is the least frequently selected target gene [13].

This investigation compared the results of the ACOV and the BGI RT-PCR kit, two approved commercial SARS-CoV-2 RNA virus detection assays, at various viral loads to see if the choice of targeted genes affected the test's specificity. At that time, the reason for comparing two different authorized tests for SARS-CoV-2 nucleic acid detection was that the BGI test was more affordable than the ACOV test.

METHODS

Study design and data analysis

We conducted a prospective study at the tertiary inpatient healthcare facility in Novi Sad [University Clinical Center of Vojvodina (UCCV)]. The Department for Infectious Diseases, and the hospital units of UCCV all enrolled patients as inpatients from October 17, 2022, through October 22, 2022. All physicians and nurses engaged in the trial had ten days of training on appropriate sample handling and sampling techniques before the start of the study [14].

During this time, 384 randomly selected specimens were collected sequentially from adult participants in this study with suspected COVID-19. From each patient, one nasopharyngeal swab and one oropharyngeal swab were collected and put into the same tube with 3 ml of the viral transport medium (SANLI Medical Technology Development Co., Liuyang, Hunan, China) with antifungal and antibiotic supplements. Each patient provided one nasopharyngeal and oropharyngeal swab (NOS) sample. Transport of clinical samples from the sampling site to the UCCV Virology Laboratory was carried out in a manual refrigerator (from +2 to +8°C).

For RT-qPCR SARS-CoV-2 laboratory confirmation, samples were kept refrigerated at 4˚C and tested with ACOV and BGI tests within twelve hours of collection. The 384 NOS samples were heat inactivated in a water bath at 56°C for 30 minutes before testing to lower the possibility of accidental SARS-CoV-2 transmission to lab personnel [14]. Each NOS specimen was utilized for both the ACOV reference assay, which was performed first, and the BGI test, which was performed second, for comparison. The handling of biological samples suspected of containing COVID-19 where the laboratory procedure has the potential to produce aerosols or droplets as a result of vortexing was done according to WHO standards, utilizing a Class II biological cabinet [14].

On September 30, 2022, the UCCV Ethics Committee approved the study (Decision No. 00-166).

Test descriptions

Abbott Molecular RealTime SARS-CoV-2 assay

On the Abbott m2000 System (Abbott Molecular Inc., North Chicago, IL, USA), which consists of amplification and detection equipment called the Abbott m2000rt and a sample preparation unit called the Abbott m2000sp, ACOV testing was performed according to the manufacturer's instructions. On Abbott m2000sp equipment, viral RNA was isolated utilizing the Abbott mSample Preparation Systems DNA kit (Abbott Molecular Inc.). Automated extraction was done using a specimen with an input volume of 500 µl viral transport medium, and then extracts and reagents from the amplification package (40 µl of each) were added automatically for RT-qPCR amplification and detection. The structural N and the non-structural RdRp gene within the Orf1ab domain (RdRp/Orf1ab) (NSP12) gene of the SARS-CoV-2 genome are the targets of the ACOV assay. (Table 1) [15]. To show that the sample preparation method was correctly used with each specimen and control, every sample receives internal control (IC) at the start of the process. Because the two SARS-CoV-2-specific probes are marked with the same fluorophore, fluorescein (FAM), and the IC-specific probe is marked with another fluorophore, 2′-chloro-7′-phenyl-1,4-dichloro-6-carboxyfluorescein, it is possible to detect SARS-CoV-2 as well as IC-amplified products within the same reaction (Table 1). The m2000rt system software analyzed the amplification curve and the result was reported as detected or not detected. The sample was deemed positive if

Table 1. Description of the SARS-CoV-2 identification tests included in this research

Name of the commercial kit	Gene target	Fluorophore	RNA (template) volume per each reaction tube (µl)	Reaction volume (µl)	Cycling time	Analytical sensitivity (LOD)	Positivity cut-off (Ct value)
ACOV	N RdRP/Orf1ab	FAM	40	40	3 hours : 5 minutes	100 copies per ml	≤ 37
BGI	Orf1ab	FAM	10	20	1 hour : 38 minutes	100 copies per ml	≤ 38

ACOV – Abbott real-time of SARS-CoV-2; BGI RT-PCR Kit – BGI Real-TIme Fluorescent RT-PCR Kit; FAM – fluorescein; RNA – ribonucleic acid; LOD – limit of detection; Ct – the cycle threshold

a signal was observed at the cycle threshold (Ct) ≤ 37 for any gene. A sample was deemed negative if the viral genes were not amplified but the IC was. A specimen was considered invalid if the IC was not amplified.

BGI Real-Time Fluorescent RT-PCR Kit

The BGI testing was performed as per the manufacturer's instructions. Viral RNA was isolated utilizing the Viral DNA and RNA Extraction Kit (Xi'an Tianlong Science and Technology Co., Ltd., Xi'an, Shaanxi, China) for the Rotary Nucleic Acid Extraction System (GeneRotex 96L) (Xi'an Tianlong Science and Technology Co.). As per the manufacturer's recommendations, isolated RNA extracts (10 µl) have been aliquoted and put into an aliquoted RT-PCR master mix (20 µl), along with the relevant controls. According to the manufacturer's instructions, amplification was carried out utilizing the Gentier 96E quantitative RT-PCR system (Xi'an Tianlong Science and Technology Co.). To identify SARS-CoV-2 RNA in the FAM channel (Orf1ab gene) as well as a human specimen adequate control in the hexachlorofluorescein channel (IC), the BGI kit uses multiplex RT-qPCR. Each PCR run included an IC (human actin), a positive control, and a negative control. IC was put in place to keep an eye on the laboratory's processes, which included the isolation of nucleic acids, reverse transcription, and amplifying each reaction. The specimen was deemed to be SARS-CoV-2 positive if the FAM channel showed a sigmoidal amplification curve with Ct values ≤ 38. (Table 1). All samples should have positive ICs and Ct values no greater than 35. The specimen was considered negative if the IC was amplified but did not replicate the viral genes. A valid no template (negative) control should have a Ct value of "0" in the FAM channel and no sigmoidal amplification curve. A specimen was found invalid if the IC was not amplified.

Statistical analysis

For statistical analysis, data were collected and analyzed using the IBM® SPSS Version 23.0 software (IBM Corp., Armonk, NY, USA). In total, 254 positive samples were chosen to represent the whole range of observed Ct values on the Abbott assay, spanning 3–29 cycles, to assess assay efficiency at different virus concentrations.

Using ACOV as the reference test, the BGI assay's positive percent agreement and 95% CI 95% were computed. To assess the negative agreement, 124 additional negative specimens were chosen. A 95% CI was also obtained for Cohen's Kappa of qualitative findings (identified or not identified) between the BGI and ACOV tests. A moderate level of agreement was characterized as values of Cohen's Kappa greater than 0.600, while values of 0.80–0.90 were interpreted as a strong agreement between the two assays [16].

RESULTS

In our investigation, 384 NOS samples – 254 (66.15%) positive, 124 (32.29%) negative, and six (1.56%) invalid – were initially tested with the ACOV for SARS-CoV-2 and then again using the BGI RT-PCR kit. All patients, who were aged 17 to 93, were adults with symptoms or suspected COVID-19. For positive samples, the average age was 64.58 years, whereas, for negative samples, it was 55.36 years. In general, male samples produced the majority of positive findings (55.9%), while female samples produced the majority of negative results (61.3%). (Table 2).

Table 2. Patients demographics who were engaged

Abbott C_t category	Average age (years)	Male (%)	Female (%)	Total n of patients
Positive	64.6	142 (55.9%)	112 (44.1%)	254
Negative	55.4	48 (38.7%)	76 (61.3%)	124
Invalid	67.2	2 (33.3%)	4 (66.7%)	6
Total no. of patients		192	192	384

Ct – the cycle threshold

[a]The data is presented as an absolute number (percentage) or mean

Table 3 shows the results of RT-PCR SARS-CoV-2 tests provided by BGI and ACOV. Both tests identified the SARS-CoV-2 gene sequences in 233 (60.68%) specimens; however, neither test found SARS-CoV-2 RNA in 120 (31.25%) of those specimens. Compared to ACOV, the BGI test correctly identified 233/254 specimens that were positive with SARS-CoV-2 target sequences and 120/124 negative samples, yielding a 93.4% (95% CI: 90.4–95.5%) total percent concordance (Table 3). The Cohen's Kappa value was 0.86 (95% CI: 0.80–0.91), and the positive percentage concordance was 98.3% (95% CI: 95.7–99.3%) (Table 3), indicating a strong level of agreement between these two tests. The negative percentage concordance was 85.1% (95% CI: 78.3–90%).

The ACOV assay produced 254 (66.15%) positive results (Table 3). The median Ct value of concordantly positive specimens tested on the ACOV assay was 10.75 (95% CI: 9.65–11.32), ranging from 3.31 to 27.30 with a standard deviation of 5.73. According to the BGI test, the median Ct value of the concordant specimens was 23.56 (95% CI:

Table 3. Proving SARS-CoV-2 ribonucleic acid by the ACOV and the BGI RT-PCR assays

ACOV	BGI			Total no. of samples tested	% of agreement	Value of Kappa (95% CI)
	Detected	Not detected	Invalid			
Detected	233 (60.68%)	21 (5.47%)	0 (0%)	254 (66.15%)	93.4	0.86 (0.80–0.91)
Not detected	4 (1.04%)	120 (31.25%)	0 (0%)	124 (32.29%)		
Invalid	2 (0.52%)	0 (0%)	4 (1.04%)	6 (1.56%)		
Total no. of samples tested	239 (62.24%)	141 (36.72%)	4 (1.04%)	384 (100%)		

ACOV – Abbott real-time of SARS-CoV-2; BGI RT-PCR Kit – BGI Real-TIme Fluorescent RT-PCR Kit; CI – confidence intervals
[a]The data is presented as an absolute number (percentage)
[b]Invalid defined as a sample that gave neither a positive nor a negative result

21.79–24.22), ranging from 11.96 to 37.19, with a standard deviation of 5.81.

Discordant findings were found in 27 (7.03%) of the samples when tested with both tests (Table 3). Twenty-one individuals (5.47%) that tested positive on ACOV but negative on the BGI test had a mean Ct value of 24.47 (95% CI: 24.22–24.74), ranging from 22.48 to 26.60, with a standard deviation of 0.04. Five samples (2.15%) that tested positive on the ACOV test, and had a Ct value ranging from 22.48 to 26.60 were positive on the BGI test with a median Ct value of 35.05 (95% CI: 34.16–35.94), ranging from 33.91 to 36.87, with a standard deviation of 1.27. Our study found six cases (1.56%), including two invalid samples, in which samples examined using ACOV were negative despite being positive obtained using the BGI test, having a mean Ct of 32.65 (95% CI: 29.50–36.83), ranging from 29.50 to 36.83, and a standard deviation of 0.07. Four (1.04%) samples were invalid on both the ACOV and the BGI kits. In total, 27 samples that yielded discordant SARS-CoV-2 results were retested with ACOV and BGI tests within 24 hours of collection. The same results were obtained. ACOV test results were provided to patients as valid.

In comparison to the Abbott test, the BGI test has a sensitivity of 91.73% (95% CI: 87.64–94.81%) and a specificity of 96.77% (95% CI: 91.95–99.11%).

The Ct values obtained from the ACOV assay and those obtained from the BGI kit were compared using a t-test. The ACOV assay Ct values were significantly lower ($p < 0.001$).

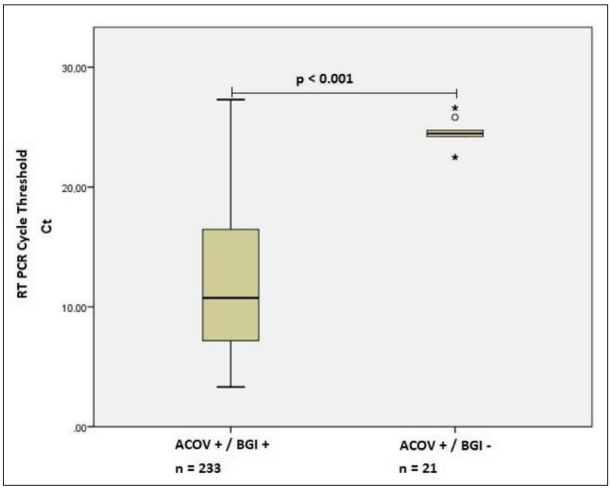

Figure 1. Comparison of (Ct) values between specimens obtained using both assays [Abbott real-time of SARS-CoV-2 (ACOV) and BGI Real-TIme Fluorescent RT-PCR Kit (BGI)] with Ct values between specimens identified with the ACOV assay only.

The values of Ct between samples detected by the ACOV and BGI assays are shown in Figure 1 alongside the Ct values between samples detected exclusively using the ACOV test. To compare median Ct value differences, the Mann–Whitney U-test was used. The Mann–Whitney U-test was utilized to compare differences in median Ct values. The Ct values detected only from the ACOV assay were significantly higher ($p < 0.001$). Overall, the BGI assay compared to the ACOV test demonstrated no significantly different performance characteristics.

DISCUSSION

The global epidemic is still ongoing. To rapidly test, care for, and trace patients' contacts for medical care, reliable, precise, and prompt laboratory-supported pandemic screening and management is essential.

Nucleic acid amplified assays (NAATs) on airway samples are the primary laboratory methods for detecting SARS-CoV-2 infections [9]. A large number of NAATs for SARS-CoV-2 are available because of the global need for COVID-19 testing. The gold standard for SARS-CoV-2 molecular diagnostics is nucleic acid RT-qPCR [12]. The target gene and the Ct threshold used to identify a positive sample are two differences in SARS-CoV-2 detection that are widely recognized and published in the literature. Some techniques reach beyond 39 Ct, which indicates a very low viral burden. In this study, the ACOV assay and the BGI RT-PCR kit were compared for clinical performance [17].

We discovered that the ACOV test identifies more cases of COVID-19 infection compared to the BGI test in our comparative analysis. Additionally, we discovered that there was a strong level of agreement between the ACOV kit and the BGI assay [16]. Our results, which compare the ACOV and BGI tests, are in agreement with the findings reported by Harrington et al. [15], which found that ACOV was more effective in identifying RNA gene sequences for SARS-CoV-2 than the ID Now COVID-19 (IDNCOV) test (Abbott). Between ACOV and IDNCOV, there was a 75% positive agreement (95% CI: 67.74-80.67%) and a 99% negative agreement (95% CI: 97.64-99.89%) [15]. According to a study by Moore et al. [18], ACOV was more effective in detecting RNA gene sequences for SARS-CoV-2 than IDNCOV and a laboratory-developed CDC 2019-nCOV RT-PCR (CDC COV) test [18]. Positive agreement varied from 75.2% to 100%, with the ACOV and IDNCOV tests showing the lowest positive agreement and the ACOV and CDC COV tests showing the highest positive agreement. From 92.4% (ACOV/CDC COV) to 100% (ACOV/IDNCOV), there was negative agreement. Our results, which compare the ACOV and BGI tests, differ from those of Sisay et al. [19], who found that BGI performed less well at identifying SARS-CoV-2 RNA gene sequences than the TIB and DaAn assays. Using 279 COVID-19 suspicious people, there was a significant agreement between the TIB and BGI tests, resulting in a Kappa of 0.61 (95% CI: 0.49–0.72), and a moderate agreement between the DaAn and BGI tests, yielding a Kappa coefficient of 0.55 (95% CI: 0.44–0.67) [19].

In contrast with our findings, Altamimi et al. [20] show a greater agreement of 0.97 (0.93–1) between BGI and the commercial assays used in the research. With a positive percentage agreement of 88.89% (95% CI: 83.4–94.3%), Alcoba et al. and their concordance results with the positive case of BGI of SARS-CoV-2 in Australia have shown significant diagnostic power in identifying SARS-CoV-2. The primary distinction can be the length of the study and the sampling of the presumptive cases [21].

When compared to Abbott, the BGI test's sensitivity and specificity are marginally lower than those of a study employing the BGI kit conducted by Altamimi AM et al.

[20], who reported sensitivity ranges of 100% (94–100%) and specificity of 97% (83–99%). The number of viral analytes varies greatly depending on anatomical location and infection stage. As the illness progresses, the viral load of SARS-CoV-2 fluctuates significantly. Therefore, the biology of the virus ultimately shapes our capacity to identify SARS-CoV-2. The sensitivity of tests for identifying SARS-CoV-2 might depend on the time and location of the sample as well as the assay's technical performance [22]. Furthermore, the performance of our assays was very good. The IC is a powerful element of both of our assays. The hydroxypyruvate reductase gene of the pumpkin plant, *Cucurbita pepo*, provides the IC for the Abbott assay and is given in an Armored RNA® particle dissolved with negative human blood plasma. The identification of IC is important in demonstrating the reliability of the sampling procedure. The IC gene for the BGI assay has been selected to be the human housekeeping gene – β-actin. To assess the effectiveness of the extraction of RNA as well as identify possible inhibitors of PCR that will be added to the samples prior to the extraction of RNA. Furthermore, it has been demonstrated that inadequate nasopharyngeal sample collection is one of the most frequent and likely sources of false negative results and, consequently, of a late diagnosis. This is an important aspect of the preanalytical phase that significantly impacts NAAT findings [12].

Twenty-one samples (5.47%) that tested and retested positive on ACOV but negative on the BGI test showed a mean Ct of 24.47 (95% CI: 24.22–24.74), ranging from 22.48 to 26.60, with a standard deviation of 0.04, and were consistent with lower viral loads. All samples were a follow-up/control NOS of a patient that tested SARS-CoV-2 positive 14 days earlier. A Ct indicates the number of replicating cycles necessary to generate a fluorescent signal. Lower values for Ct indicate larger viral RNA concentrations. A lower Ct value indicates a more favorable result with a quick turnaround time and a PCR cycle that may be more successful than all of the others, whereas a greater Ct value suggests a requirement for more time and resources. Eight discordant samples (of a total of 200 tested for COVID-19) were not identified or yielded unclear findings on the CDC COV test, yet they were found on the ACOV test in a study by Moore et al. [18]. According to the ACOV test, the mean Ct value of these samples was 27.73 (95% CI: 27.37–28.40). Almost all of the discrepant results were found in specimens that had greater Ct values, that is, that had lower virus quantities. [17, 18]. These results indicate that the lower limit of detection (LOD) of the tests varied. The official instructions to utilize ACOV specify a LOD of 100 copies/ml for the ACOV test and 100 copies/ml for the BGI assay.

According to literature data, the N gene being targeted may be the most sensitive to SARS-CoV-2 identification because it produces fewer sub-genomic N gene RNA messengers compared to other targets [21, 22]. The N gene is known to have a broader detection window than other gene targets. In addition to the findings of our investigation, those hypotheses were highly confirmed in a previously published study, which discovered that the N gene targeted could increase the SARS-CoV-2 detection's sensitivity. This might be the reason why samples examined with the BGI assay yielded fewer positive findings more frequently false-negative results on the BGI test are most likely because the ORF1ab gene is the target of the primers and probe sequences used in this test. Our results imply that the need for improvement should concentrate on the quick adjustment of primer sets, the selection of cut-off Ct values, and the emergence of novel variations. But a "positive" PCR test does not always indicate the existence of a living virus; rather, it only indicates the detection of RNA from the virus.

The reduced input volumes utilized for the extraction (200 µl) and amplification (10 µl) in comparison to the extraction volumes of 500 µl and the amplification volumes of 40 µl in the ACOV test might help to explain the negative results acquired utilizing the BGI assay. The ACOV assay's targets of amplification and detection are simpler to attain; however, the ACOV yielded more positive SARS-CoV-2 results, indicating that the same samples were misclassified as false negatives when tested with the BGI kit [15].

CONCLUSION

In conclusion, we discovered that the ACOV test identifies more cases of COVID-19 infection compared to the BGI test. There was strong agreement between both the ACOV and the BGI tests, with just 5.47% of SARS-CoV-2 detection cases producing false-negative results with the BGI assay. We suggest complete testing using the ACOV kit because the Abbott kit showed slightly better diagnostic performance and because employing the BGI assay may produce false-negative results.

ACKNOWLEDGMENT

We are thankful to our patients who contributed to the accomplishment of this study. Partial results of this research were previously presented during the 25th International Congress of Clinical Chemistry and Laboratory Medicine (IFCC-EFLP WorldLab • EuroMedLab Roma 2023) in Rome, May 21–25, 2023, and therefore have been included in the Congress abstract book as: Comparison of two commercial kits for SARS-COV-2 RNA detection, page 725, Abstract ID: P0639.

Conflict of interest: None declared.

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Поређење дијагностичке ефикасности тестова *Abbott RealTime SARS-CoV-2* и *BGI Real-Time Fluorescent RT-PCR* за *RT-PCR* откривање тешког акутног респираторног синдрома коронавирус-2

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САЖЕТАК

Увод/Циљ На основу смерница Светске здравствене организације, тренутни златни стандард за дијагнозу тешког акутног респираторног синдрома коронавирус-2 (*SARS-CoV-2*) квантитативна је реакција ланчане полимеразе реверзне транскрипције у реалном времену (*RT-qPCR*).
Циљ ове студије био је да упореди и анализира учинак откривања два различита овлашћена теста за детекцију нуклеинске киселине *SARS-CoV-2*: *Abbott RealTime SARS-CoV-2* (*ACOV*) и *BGI Real-Time Fluorescent RT-PCR* (*BGI*).

Методе Наша студија је укључивала 384 насумично одабрана назофарингеална и орофарингеална бриса која су претходно тестирана од стране теста *ACOV*, а затим тестирана помоћу теста *BGI* за откривање *SARS-CoV-2*. Сви болесници су одрасле особе са симптомима или сумњама на вирус корона 2019 (ковид 19).

Резултати Открили смо да је тест *ACOV* детектовао више случајева инфекције ковид 19 него тест *BGI*. Позитиван проценат слагања био је 98,3% [95% интервали поузданости (95% *CI*): 95,7–99,3%], док је Коенов капа коефицијент био 0,86 (95% *CI*: 0,80–0,91), што указује на чврст ниво сагласности између ова два теста. Негативан проценат слагања био је 85,1% (95% *CI*: 78,3–90%), док је 5,47% случајева било лажно негативно коришћењем теста *BGI* за откривање *SARS-CoV*-2. Осетљивост теста *BGI* у поређењу са тестом *ACOV* била је 91,73% (95% *CI*: 87,64–94,81%), а специфичност теста *BGI* била је 96,77% (95% *CI*: 91,95–99,11%).

Закључак Аботов тест је показао нешто боље дијагностичке перформансе, а због могућих лажно негативних резултата коришћењем теста *BGI*, препоручујемо комплетно тестирање тестом *ACOV*.

Кључне речи: ковид 19; дијагностичка ефикасност; *PCR* тестови; real-time PCR; РНК изолација; *SARS-CoV-2*

DOI: https://doi.org/10.2298/SARH221221077P
UDC: 616.98:578.834(497.11)"2020"; 616.6-083.98(497.11)"2020"

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The impact of the COVID-19 pandemic on the treatment of emergency urological patients during lockdown – Serbian tertiary center experience

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SUMMARY

Introduction/Objective The COVID-19 pandemic affected the functioning of health care systems, including emergency services worldwide. The aim of this study was to examine the impact of the pandemic and lockdown on the care of urgent urological patients in daily practice.

Methods Data were retrospectively collected from patients urgently hospitalized at Emergency Department of Clinic of Urology, University Clinical Center of Serbia, during the first three months of lockdown between March 15 and June 15, 2020, and compared to the same period in 2019. The collected data included demographic and clinical characteristics, as well as treatment characteristics and treatment outcomes.

Results This study included 80 patients who were hospitalized during the 2020 lockdown and 68 patients who were hospitalized in the same period in 2019. There was no difference in total number of hospitalized patients, age and sex when comparing these two periods. Among patients with urinary tract infection, the number of patients with urosepsis was significantly higher in 2020 ($p = 0.028$). The median time from symptoms' onset to hospitalization was significantly longer in patients who were hospitalized in 2020 ($p = 0.049$). No difference was found in duration of hospitalization and characteristics of treatment between the two periods. The number of deaths was significantly higher in 2020 ($p = 0.034$).

Conclusion During lockdown in Serbia, patients sought emergency urology service significantly later. Furthermore, a higher number of patients with urosepsis and a higher number of deaths among hospitalized patients were found during lockdown compared to the previous year.

Keywords: COVID-19; pandemic; lockdown; urological emergencies; urology

INTRODUCTION

Since the first case of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, in December 2019, the disease has spread around the world in a few months. On March 11, 2020, the World Health Organization declared coronavirus disease 19 (COVID-19) a pandemic [1]. From there on, the COVID-19 pandemic has become a global challenge for health care systems in terms of providing necessary treatment to both COVID-19 and non-COVID-19 patients with adherence to epidemiological measures and strict separation of these pathways. Given the limited capacity of health systems being faced with the growing demands in management of COVID-19 patients, it was necessary to adopt guidelines and prioritize the care of other diseases and conditions [2, 3]. However, reorganization of health systems with limited access to health care, numerous lockdown restrictions and other anti-pandemic measures parallel with fear of getting COVID-19 infection, altogether affected the number of emergency department patient visits [4, 5]. The first case of COVID-19 in Serbia was reported on March 6, 2020 [6]. Soon after, a state of emergency was declared in the country and lockdown was introduced on March 15 [7, 8]. Implemented epidemiological measures included restriction to free movement affecting all persons, but especially those over 65 years old [7, 8]. Also, the functioning of the health system has changed.

During lockdown, initial examination, triage and testing for suspected COVID-19 patients were managed in primary care, while most of secondary and tertiary institutions were transformed into COVID-19 hospitals [9, 10]. Consequently, in Belgrade, among five emergency departments that were available for urgent urological conditions in pre-pandemic period, only the University Clinical Center of Serbia (UCCS), Clinic of Urology, remained open to take care of both urgent and elective urological conditions of non-COVID patients from the beginning of the pandemic until today.

Since the previously published studies related to the impact of COVID-19 on urological practice have mainly focused on the elective treatment, data on hospital care of urgent urological conditions during the COVID-19 pandemic are limited [2, 11, 12]. The findings of previous studies indicated the impact of the

Received • Примљено: December 21, 2022
Revised • Ревизија: July 31, 2023
Accepted • Прихваћено: August 24, 2023
Online first: August 29, 2023

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COVID-19 pandemic on the care of patients with other emergency conditions [13, 14].

Therefore, the aim of this study was to examine the impact of the COVID-19 pandemic on routine work of Emergency Department of the Clinic of Urology, UCCS, Belgrade and treatment outcomes of hospitalized patients during the first three months of lockdown in Serbia compared to the same period in 2019.

METHODS

This was a single-center observational retrospective study focused on evaluating the daily urologic practice during the COVID-19 pandemic at the Emergency Department of the Clinic of Urology, University Clinical Center of Serbia. The data were retrospectively collected from electronic and paper medical records of patients urgently hospitalized at the Emergency Department during the first three months of lockdown, between March 15 and June 15, 2020, as well as from patients urgently hospitalized at the department during the same period of 2019 [7, 8]. The collected data included demographic and clinical characteristics, as well as treatment characteristics and treatment outcomes. The study has been approved by the Ethics Committee of the University Clinical Center of Serbia (number 602/5).

At the time of diagnosis, all patient met criteria for urgent hospital admission. Reasons for hospitalization were urologic emergencies which required urgent care and were categorized as the following: fever, hematuria, hydronephrosis, azotemia, urological malignancy, urinary tract calculosis, urinary tract infections, scrotal phlegmon, testicular torsion, priapism, urogenital trauma and urinary retention. Noteworthy, one patient could have more than one admitting diagnosis. Among patients with urinary tract infection, those who met the criteria for urosepsis represented the subgroup of special interest [15, 16].

Time from symptoms' onset to hospitalization was defined as a number of days between the date of the first appearance of symptoms related to the disease which led to hospitalization and the date of admission to hospital. Treatment interventions performed during hospitalization were categorized as the following: surgery (open or minimally invasive / endoscopic), hemodialysis, blood transfusion, transfer to intensive care unit, mechanical ventilation. Treatment outcome was defined as cured or improvement, or death for any reason. Duration of hospitalization was defined as the time from hospital admission to discharge, or death for any reason. During 2020, patients who were hospitalized and suspected of COVID-19 infection later on were tested by PCR and/or serological tests for the presence of COVID-19 infection. Patients with confirmed COVID-19 infection would be immediately transferred to COVID-19 institution, and were not included in this study.

Statistics

We used the methods of descriptive and analytical statistics for statistical analysis. The significance of the difference for variables with normal distribution among groups of patients was analyzed by the Student's t-test for two independent samples, while the Mann–Whitney U-test was used for variables without normal distribution. Differences in frequency between subgroups of patients were analyzed by the χ^2 test or Fisher's exact test. The value of $p < 0.05$ was considered statistically significant. We used IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) for statistical analysis.

The study has been approved by the Ethics Committee of the University Clinical Center of Serbia (decision number 602/5; date: December 31, 2021).

RESULTS

This observational study included 80 patients hospitalized during the lockdown from March 15 to June 15, 2020, and 68 patients hospitalized in the same period of 2019. All the patients met criteria for urgent hospital admission to the Emergency Department of the Clinic of Urology, UCCS, Belgrade.

Demographic and clinical characteristics at the time of hospital admission are shown in Table 1. Most of the patients in both groups were men. No significant difference in terms of age and sex was found between the two observed periods. Moreover, there was no difference in the total number of hospitalized patients when comparing these two periods. Among patients who were hospitalized with a diagnosis of urinary tract infection in 2020, the number of patients with urosepsis was significantly higher (n = 10) compared to the same period in 2019 (n = 3) (p = 0.028) (Table 1). However, no significant differences were observed in terms of other admitting diagnoses between the two periods. The median time from symptoms' onset to hospitalization was significantly longer in patients who were hospitalized in 2020 (4.5 days) compared to the same period in 2019 (three days) (p = 0.049) (Table 1).

Characteristics of treatment and treatment outcomes are shown in Table 2. The median duration of hospitalization was seven days in 2020, and did not differ significantly compared to 2019. Moreover, there was no significant difference in terms of the number and type of treatment interventions performed during hospitalization in two observed periods. In assessing treatment outcome, the number of deaths was significantly higher in 2020 (n = 10) compared to 2019 (n = 2) (p = 0.034) (Table 2).

None of the hospitalized patients at the Department of Emergency Urology had a confirmed COVID-19 infection in the observed period in 2020.

DISCUSSION

The COVID-19 pandemic has disrupted functioning in all spheres of society, including healthcare systems worldwide. Hence, healthcare systems have suddenly faced the demand of caring for an increasing number of COVID-19 patients, with numerous unknowns in the epidemiology,

Table 1. Demographic and clinical characteristics of patients

Characteristics	2019	2020	p
Number	68	80	0.324[a]
Sex, n (%)			
Male Female	51 (75%) 17 (25%)	50 (62.5%) 30 (37.5%)	0.104[a]
Age (years), mean ± SD	57.93 ± 19.056	60.88 ± 17.469	0.328[b]
Time from symptoms' onset, days (range)	3 (0–30)	4.5 (0–30)	0.049[c]
Admitting diagnoses, n (%)			
Fever	23 (33.8%)	26 (32.5%)	0.865[a]
Hematuria	11 (16.2%)	23 (28.7%)	0.070[a]
Hydronephrosis	28 (41.2%)	40 (50%)	0.283[a]
Azotemia	29 (42.6%)	33 (41.8%)	0.864[a]
Urological malignancy	28 (41.2%)	37 (46.2%)	0.535[a]
Calculosis	16 (23.5%)	19 (23.8%)	0.975[a]
Urinary tract infection Urosepsis	30 (44.1%) 3 (10%)	30 (37.5%) 10 (33.3%)	0.083[a] 0.028[a]
Scrotal phlegmon	0 (0%)	1 (1.2%)	1.000[d]
Testicular torsion	2 (2.9%)	1 (1.2%)	0.467[d]
Priapism	3 (4.4%)	1 (1.2%)	0.237[d]
Trauma	3 (4.4%)	3 (3.8%)	0.839[d]
Urinary retention	1 (1.5%)	5 (6.2%)	0.219[d]

SD – standard deviation;
[a]Pearson's χ^2 test;
[b]Student's t-test;
[c]Mann–Whitney U-test;
[d]Fisher's exact test

Table 2. Characteristics of treatment and outcomes

Characteristics	2019	2020	p
Duration of hospitalization (days), median (range)	7 (1–55)	7 (1–55)	0.622[a]
Surgery, n (%) Open Minimally invasive / endoscopic Both	38 (55.9%) 16 (42.1%) 21 (55.3%) 1 (2.6%)	41 (51.2%) 16 (39%) 24 (58.5%) 1 (2.4%)	0.573[b] 0.909[b]
Hemodialysis, n (%)	3 (4.4%)	8 (10%)	0.196[b]
Blood transfusion, n (%)	20 (29.4%)	31 (39.2%)	0.212[b]
Transfer to intensive care unit, n (%)	6 (8.8%)	7 (8.8%)	0.987[b]
Mechanical ventilation, n (%)	0 (0%)	2 (2.5%)	0.500[c]
Death, n (%)	2 (2.9%)	10 (12.5%)	0.034[b]

[a]Mann–Whitney U test;
[b]Pearson's χ^2 test;
[c]Fisher's exact test

clinical presentation and treatment of the disease itself. Consequently, all of it resulted in the redirection of resources to the management of COVID-19 patients, thus limiting the proper diagnostic workup and treatment of other diseases.

In this study, we aimed to examine the impact of the COVID-19 pandemic on the routine work of the Emergency Department of the Clinic of Urology, UCCS, Belgrade and treatment outcomes of hospitalized patients during the first three months of lockdown in Serbia compared to the same period in 2019.

In this study, we have found that number of emergency hospitalizations increased by 17% in the pandemic period, but the difference was not significant compared to the prepandemic period. Movement restrictions during lockdown, limited availability of health services, and the fear of infection with COVID-19 during visits to healthcare facilities had an impact on the frequency of patient visits to emergency services [4, 17]. By reviewing available literature, a decline in the number of patient visits to emergency urological services was reported in many countries during the beginning of the pandemic. However, conflicting results were obtained considering emergency urological hospitalizations and surgical treatments [18, 19, 20].

In our study, the emergency hospitalized patients did not differ in sex and age when comparing prepandemic and pandemic periods. Partly in line with ours are the results obtained in Portugal, where no difference in age was observed, but fewer women visited emergency urology services during the pandemic period compared to the previous year [19]. Similar findings were obtained in Turkey, with no difference in age between hospitalized patients in the Emergency General Surgery Department and in the Burn Department during the first months of the pandemic [21, 22].

When compared with prepandemic, during the pandemic period our results showed a significantly longer time from symptoms' onset to hospital admission. Similar results were reported in Brazilian study that included patients with obstructive pyelonephritis in the pandemic period [23]. Our findings may be partly explained by the restricted free movement and reduced transportation during lockdown, but also by the patients' fear of getting infected in a healthcare facility [4]. Moreover, the establishment of COVID clinics in primary healthcare centers for initial examination of febrile patients and the conversion of secondary and tertiary healthcare centers into COVID-19 hospitals potentially influenced the time from the symptoms' onset to hospital admission [21].

In this study we have found that established diagnoses for urgent admission did not significantly differ between the two periods. However, among patients with urinary tract infection we noticed a significantly higher number of patients who met the criteria for urosepsis in the pandemic period. A study conducted in Brazil showed a significantly higher percentage of patients with systemic inflammatory response syndrome among patients with obstructive pyelonephritis in the pandemic period, which is comparable with our results [23]. A recent study by Kaczmarek et al. [24] also showed increased values of inflammatory parameters in patients with stones treated at a urology emergency department during the pandemic period, which the authors potentially interpret as the later coming of these patients to the emergency department. Given the fact that prolonged time from symptoms' onset to receiving definitive treatment may lead to more complicated course of urinary tract infection, it can explain the higher number of patients with urosepsis found in our study.

Our findings show that duration of hospitalization was similar when comparing the COVID and the pre-COVID

period. Currently, the data from studies related to the emergency urological service during the COVID-19 pandemic is limited. Studies published so far are mainly focused on data from emergency urological outpatient clinics or on specific urological pathology [18, 19, 23]. In contrast to our results, Silva et al. [23] showed a significantly longer duration of hospitalization of patients treated for obstructive pyelonephritis in the pandemic period.

Moreover, inconsistent findings were reported in studies related to the emergency departments of other surgical branches even in the same country. Namely, one study group from Turkey showed no difference in the duration of hospitalization among patients who were hospitalized for the treatment of burns in the prepandemic and pandemic periods [22]. In contrast, another study group from the same country found longer hospital stays in emergency general surgery departments during pandemic period [21].

In our study, we found no significant difference in the requirement for surgical treatment of hospitalized patients between the two observed periods, both in terms of number and types of surgery. Consistent with our results are the findings of Cicerello et al. [18], who also did not notice a difference in the need for both open and endourological surgeries in the prepandemic and pandemic periods. In contrast, Madanelo et al. [19] reported an increase in the number of patients who required surgical urological treatment at the beginning of the pandemic, even though the number of visits to the emergency urological service were reduced. A study conducted in the United Kingdom indicates constant surgical treatment of urgent urological conditions during the autumn peak of the pandemic, in contrast to the reduction recorded during the first spring lockdown in 2020 [25].

When analyzing treatment outcomes, we found a significantly higher incidence of deaths among hospitalized patients during the first three months of lockdown. Noteworthy is that none of the hospitalized patients at the Department of Emergency Urology of the UCCS had a confirmed COVID-19 infection. To the best of our knowledge, the impact of the pandemic and lockdown on mortality among emergency urology patients has not been assessed so far. However, in one study from a tertiary hospital, Italian investigators reported a negative effect of the COVID-19 pandemic and lockdown on the treatment outcomes of urgent surgical conditions [26]. Based on the findings that delayed access to the emergency department was associated with increased 30-day mortality risk from that study, we could hypothesize a potential association between our results. It is likely that longer time from symptoms' onset to hospital admission additionally with higher population with urosepsis among hospitalized patients have the greatest impact on the increased number of deaths in the pandemic period in our cohort.

Limitations of study

The limiting factor of our study is that it is a single-center observational retrospective study with a small number of patients. Also, the reasons for a delayed patient visit were not examined. However, these limitations reflect everyday clinical practice, which is also the quality of this study.

CONCLUSION

During lockdown in Serbia, patients applied to the emergency urology service significantly later. Furthermore, a higher number of patients with urosepsis and a higher number of deaths among hospitalized patients were found during lockdown compared to the previous year. In the future, prospective studies to evaluate a more complex factors which may influence daily urological practice in emergency departments are needed. These well designed studies will certainly help to detect the field for improvements in taking care of emergency urological conditions.

Conflict of interest: None declared.

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Утицај пандемије ковида 19 на лечење ургентних уролошких болесника током карантина – искуство терцијарног центра у Србији

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САЖЕТАК

Увод/Циљ Пандемија ковида 19 има утицај на функционисање здравствених система широм света, укључујући и ургентне службе.

Циљ овог рада био је испитивање утицаја пандемије и карантина на збрињавање ургентних уролошких болесника у свакодневној пракси.

Методе Подаци су прикупљени ретроспективно од болесника ургентно хоспитализованих на Одељењу ургентне урологије Клинике за урологију Универзитетског клиничког центра Србије, током прва три месеца карантина, између 15. марта и 15. јуна 2020. године, и поређени су са истим периодом током 2019. године. Прикупљени подаци су обухватали демографске и клиничке карактеристике, као и карактеристике лечења и исходе лечења.

Резултати Ова студија је укључила 80 болесника који су били хоспитализовани током карантина 2020. године и 68 болесника који су били хоспитализовани у истом периоду 2019. године. Нисмо уочили разлику у укупном броју хоспитализованих болесника, старости и полу поредећи ова два периода. Међу болесницима са инфекцијом уринарног тракта, број болесника са уросепсом је био значајно већи у 2020. години ($p = 0,028$). Просечно време од почетка симптома до хоспитализације било је значајно дуже код болесника хоспитализованих у 2020. години ($p = 0,049$). Нисмо уочили разлику у дужини хоспитализације и карактеристикама лечења између ова два периода. Број смртних исхода је био значајно већи у 2020. години ($p = 0,034$).

Закључак Током карантина у Србији, болесници су се јављали у ургентну уролошку службу знатно касније и утврђен је већи број болесника са уросепсом и већи број умрлих међу хоспитализованим болесницима у односу на претходну годину.

Кључне речи: ковид 19; пандемија; карантин; ургентна урологија; урологија

DOI: https://doi.org/10.2298/SARH220920085G
UDC: 616.71-006.3-07

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Can we distinguish conventional osteosarcoma subtypes (osteoblastic and chondroblastic) based on their magnetic resonnace signal intensities

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SUMMARY
Introduction/Objectives Osteosarcoma is the most common primary malignant bone tumor in adolescents and young adults, with a tendency to produce variable amounts of osteoid, cartilage, and fibrous matrices.
The objective of this study is to differentiate between osteosarcoma subtypes: osteoblastic and chondroblastic according to their magnetic resonance imaging (MRI) signal intensities and X-ray findings.
Methods We performed a retrospective analysis for 21 pathologically proven osteosarcoma subtypes: osteoblastic (n = 14) and chondroblastic (n = 7). Conventional images of the bone of origin, periosteal reactions, lytic and sclerotic features, the presence of calcification, and pathological fractures were investigated with X-rays. We measured the mean region of interest values for each lesion with MRI sequences.
Results Among the osteosarcoma lesions, 57% were localized at the knee. X-ray evaluations of the osteoblastic osteosarcomas revealed pure lytic lesions in 35.7%, and pure sclerotic lesions in 42.9% cases. Chondroblastic osteosarcomas revealed pure lytic lesions in 14.3% and pure sclerotic lesions in 42.9% cases. Due to variable osteoblastic, chondroblastic, and fibroblastic areas and proportions of the ossified matrix, osteosarcoma lesions have a heterogeneous MRI signal. However, no statistically significant value was detected.
Conclusion According to our results, MRI signal characteristics and X-ray findings may not be able to distinguish osteosarcoma subtypes, so prospective studies with larger patient cohorts are needed.
Keywords: magnetic resonance imaging; osteosarcoma; subtype; region of interest

INTRODUCTION

Osteosarcoma (OS) is the most common primary malignant bone tumor in adolescents and young adults, comprising 10% of solid cancers in patients between 15 and 19 years of age, with a tendency to produce variable amounts of osteoid, cartilage, and fibrous matrices. Although myeloma is the most common primary bone tumor in adults, OS also shows a second peak in adults in their 70s and 80s [1]. OS is classified according to the World Health Organization, with conventional high-grade central OS (HG-OS) as the most common subtype, accounting for 75–80% of all cases [2, 3]. Differentiating OS subtypes has clinical importance because of the differences in their prognosis and treatment [4].

Conventional OS are divided into three general subtypes: osteoblastic, chondroblastic, and fibroblastic. They all contain varying amounts of all three cell types in their matrices [5].

Radiographic assessment still has an unprecedented value in the initial assessment of HG-OS. The classic radiographic features include aggressive lytic bone destruction, osteoblastic matrix production, extraosseous soft tissue extension, and periosteal reactions [6]. These allow for a confident radiological diagnosis in the majority of cases as Figure 1. Other rare morphologic forms of conventional OS are giant cell-rich variants (numerous osteoclast-like giant cells), epithelioid variants, osteoblastoma-like variants, chondroblastoma-like variants, chondromyxoid fibroma-like OSs, clear cell variants, and small cell variants. Although few in numbers, there are still ongoing studies about the differentiation of OS subtypes and other primary bone tumor types based on the radiological findings [7, 8, 9].

In this study, we aimed to radiologically distinguish the osteoblastic type, which is the most common type of conventional OS, from the chondroblastic type, which is characterized by chondroid-looking immature tissues next to osteoid-forming areas, based upon X-ray findings and localizations and the quantitative values of intensity of the tumoral area detected with MRI imaging.

METHODS

This retrospective study was approved by the "Ethical Committee of the Faculty of Medicine, our institution," and is in compliance with the Helsinki Declaration (ID:2022/0403). Information on patients diagnosed with OS between January 2015 and March 2021 was retrieved from the database. Patients who

Received • Примљено: September 20, 2022
Revised • Ревизија: August 28, 2023
Accepted • Прихваћено: September 20, 2023
Online first: September 29, 2023

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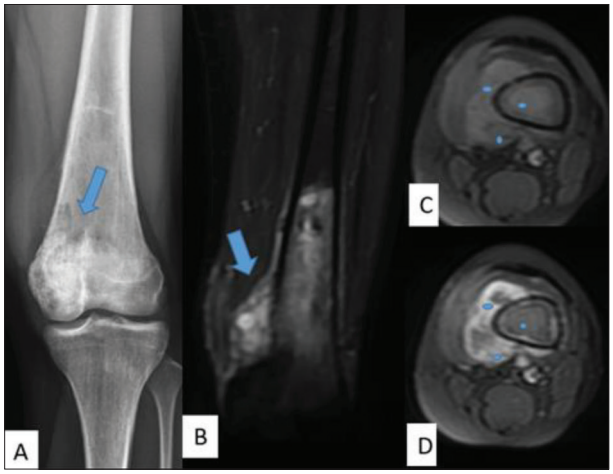

Figure 1. Osteoblastic osteosarcoma: A – anteroposterior radiograph shows a lytic sclerotic lesion of the distal femoral epiphysis-metaphysis (arrow); B – coronal T2 fast spin echo magnetic resonance image, distal femoral intramedullary tumor, and extraosseous extension (arrow); C – axial T1 fast spin echo magnetic resonance image; three dots indicate region of interest measurement sites; D – axial postcontrast T1 magnetic resonance image three region of interest marks placed in the same location

were operated on in our hospital, who had a pathologically confirmed diagnosis of OS, and had MRI scans were included in this study. Patients with secondary OS were not included. MRI scans with inadequate assessment quality as well as those that did not have fat-suppressed sequences and without contrast enhancement were excluded. Patients only diagnosed with osteoblastic or chondroblastic conventional subtypes were included in our study.

Direct radiographs of all patients were viewed from the picture archiving and communication system. Localization of lesions, Codman's and/or sunburst-type periosteal reactions, lytic and sclerotic features, the presence of calcification, and pathological fractures were investigated with X-rays.

Magnetic resonance imaging and measurement protocols

T1-weighted, T2-weighted, and contrast-enhanced T1-weighted images were obtained. For the contrast-enhanced studies, gadopentetate dimeglumine (0.1 mmol/kg body weight) was administered, and T1-weighted sequences with similar imaging parameters to the pre-contrast T1-weighted images were obtained.

T1-weighted spin-echo images were taken from the 1.5 Tesla MR device [field of view (FOV) 16, section thickness 4 mm, repetition time (TR) 426, echo time (TE) min], and T2 fast spin-echo images were taken from the 1.5 tesla MR device (FOV 16, section thickness 4 mm, TR 1500, TE 45).

These variations of TR, slice thickness, and FOV were changed depending on the number of slices and the size of the masses.

Lesions were grouped as femoral, tibial, and other according to their location in the bone. The diaphyseal, metaphyseal, and epiphyseal involvement sites in the bone were also noted (Table 1).

Table 1. Radiological findings of cases

Parameters	Group-1 (Osteoblastic) n = 14	Group-2 (Chondroblastic) n = 7	p value
Age (years)	25.5 ± 19.6	20.8 ± 11.3	0.573
Male	4 (28.6%)	4 (57.1%)	0.346
Female	10 (71.4%)	3 (42.9%)	
T1-ROI	636.3 ± 387.0	873.5 ± 610	0.288
T2-ROI	973.2 ± 525.7	981.5 ± 878.6	0.978
Contrast	1586.2 ± 945.7	1625.8 ± 1744.2	0.948
Localization			
Femur Tibia Other	6 (42.9%) 3 (21.4%) 5 (35.7%)	3 (42.9%) 3 (42.9%) 1 (14.3%)	0.599
Only D Only M D + M E + M E + M + D Other localization	4 (28.5%) 0 4 (28.5%) 1 (7.1%) 0 5 (35.6%)	2 (28.6%) 1 (14.3%) 2 (28.6%) 1 (14.3%) 1 (14.3%) 1 (14.3%)	0.499
Codman triangle	7 (%50)	2 (28.6%)	0.622
X-ray findings			
Sclerosis Pathological fracture Calcification Lytic lesion	5 (35.7%) 2 (14.2%) 1 (7.1%) 5 (35.7%)	3 (42.9%) 2 (28.6%) 0 1 (14.3%)	0.395
According to T1			
Hyperintense Hypointense Isointense Heterogenous	5 (35.7%) 4 (28.6%) 2 (28.6%) 3 (21.4%)	3 (42.9%) 3 (42.9%) - 1 (14.3%)	0.688
According to T2			
Hyperintense Hypointense	11 (78.6%) 3 (21.4%)	4 (57.1%) 3 (42.9%)	0.299

ROI – region of interest; D – diaphysis; M – metaphysis; E – epiphysis

Region of interest (ROI) was placed in three different areas of the tumors in enhanced sequences. While placing ROI, the areas with contrast enhancement were chosen and care was given not to involve-enhancing areas showing necrosis and cystic cavity. Then, the average ROI value was calculated for each sequence (Table 1).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY, USA). Normality testing was performed with the Kolmogorov–Smirnov test. Normal distributions were shown as mean ± standard deviation, non-normal distributions as median (interquartile range), and categorical variables as numbers and percentages. Differences between groups of numerical variables were evaluated with either the Student's t-test, or Mann–Whitney U-test according to normality distribution. Comparisons of categorical variables were performed using χ^2, Yates's correction, and Fisher's exact tests. The correlations between numerical variables were tested by the Spearman correlation analysis. Changes in cardiovascular magnetic resonance parameters were performed with paired sample t-tests, while differences between groups were by repeated measures of ANOVA analysis.

RESULTS

We retrospectively analyzed 21 patients with OS between 2015 and 2021. Osteoblastic OS was detected in 14 patients (66.6%). Chondroblastic OS was detected in seven patients (66.6%). In nine patients (42.8%), lesions were localized at the femur, and in six patients (28.5%) at the tibia. The sacrum was involved in three patients (14.2%), fibula in one patient (4.7%), and extraskeletal in two patients (9.5%).

All but three patients underwent resection of the tumor for diagnostic purposes. Patients were grouped according to their pathological subtypes. We found no correlation between X-ray findings and T1-ROI, T2-ROI, and their contrasts (Table 1).

The studied OS lesions showed heterogeneous signal patterns on different MRIs. Ossified matrices, although in variable proportions, were present in all lesions. X-ray evaluations of the osteoblastic OSs revealed pure lytic lesions in 35.7% and pure sclerotic lesions in 35.7%; other X-ray findings involved pathological fracture and calcifications. X-ray evaluations of the chondroblastic OSs revealed pure lytic lesions in 14.3% (Figure 2), pure sclerotic lesions in 42.9%, and pathological fractures in 28.6%. Of the chondroblastic OS lesions, 85.8%were located in the long bones. No statistically significant difference was detected according to the involvement sites in the bone (Table 1). There was no statistically significant difference in T1 and T2 signal intensities and fat-suppressed contrast-enhanced T1signal intensity between osteoblastic and chondroblastic types ($p = 0.288$, $p = 0.978$, and $p = 0.948$, respectively).

DISCUSSION

In this study we evaluated the correlation of OS subtypes with a pathological diagnosis with MR sequences conducted on 21 patients, no correlation was found between MR findings and OS subtypes.

Combining diagnostic imaging and a histopathological examination for the detection of bone tumors is indispensable [10]. Radiologically, OSs usually seem intense relative to muscle on T1-weighted images while hyperintense on T2-weighted images. Areas of low signal intensity are common in both T1-weighted and T2-weighted MR images and represent a mineralized matrix. In both intraosseous and soft tissue components, central hemorrhage foci appear hypointense on T1–T2 images; necrosis is hypointense on T1-weighted images and hyperintense on T2-weighted images. Variable imaging characteristics of rarer subtypes of OSs create diagnostic difficulties [11]. It may be possible with a combination of histopathological and radiological features to diagnose OS subtypes and manage appropriate treatment strategies, which have an important role in the survival of patients.

Conventional radiography is the first imaging procedure that provides a clue to the initial diagnosis, such as the aggressiveness of the tumor and hence prognosis. It also provides a differential diagnosis. Although the incidence of sclerotic lesions was higher in chondroblastic OS compared to osteoblastic sarcoma, this was not enough to produce a statistically significant value. However, the incidence of lytic lesions was higher in the osteoblastic sarcoma group compared to the chondroblastic OS group, but this did not reach a statistically significant value, probably owing to osteoid and chondroblastic matrix content heterogenicity. Bone lesions detected in radiography (the periosteal reaction, defined as Codman's triangle) were higher in osteoblastic OS, although not enough to reach a statistically significant value.

Although MRI modality may be superior in the staging of suspected or proven osteosarcomatous disease, as with other intraosseous lesions, it is the radiographic features of the tumor that are of primary importance in the generation of a specific diagnosis.

Conventional OSs are usually presented as intramedullary masses. Differentiating chondroblastic OS from other conventional OS types has clinical importance because of the differences in the prognosis [12]. Unfortunately, chondroblastic OSs are associated with a poor response to chemotherapy and display a high incidence of metastases. As chondroblastic OS are chemoresistant, the effect of a resection margin and the role of radical surgery is more important compared to osteoblastic OS for treatment and survival [13].

Due to the relatively low incidence of chondroblastic OS, cases describing its diagnosis and treatment strategies are extremely rare. The diagnosis of chondroblastic OS was made when the chondroid component involved at least 30% of the lesion, which is not always easy to detect. Non-enhanced T1-weighted magnetic resonance imaging (T1WI MRI) is an important preoperative examination used to visualize the intramedullary extent of malignant long bone tumors (Figures 2 and 3). Early reports showed that MRIs, especially T1WI MRIs in patients with primary bone tumors, were reliable for delineating lesion characteristics [14]. T1signal characteristics for the non-mineralized component is isointense, and for the mineralized/ossified component, it is hypointense. However, the T2 signal characteristics of the non-mineralized component are hyperintense, and the mineralized/ossified component is hypointense. No statistically significant difference was found between the T1 and T2 signal characteristics for osteoblastic and chondroblastic OSs. The potential additional value of Diffusion MRI imaging is to provide *in vivo* functional tissue information when it has been added to conventional MR to improve the specificity of lesion characterization. It is well understood that apparent diffusion coefficient (ADC) values reflect the pathological content of the tissues and the diffusion of water molecules in the extracellular space. Hence, it is expected in malignant tumors that high cellularity, pleomorphism, and hyperchromatism contribute to diffusion restriction [15, 16].

Diffusion-weighted (DW) MRI can be used to evaluate chemotherapy response in OS.

An increase in ADC is expected in assessing adequate treatment response [17]. Multiple studies have demonstrated the ability of DWI to differentiate between good and poor treatment responses in HG-OS. Wang et al. [17] assessed chemotherapy responses with DWI between different histological subtypes of HG-OS, identifying that

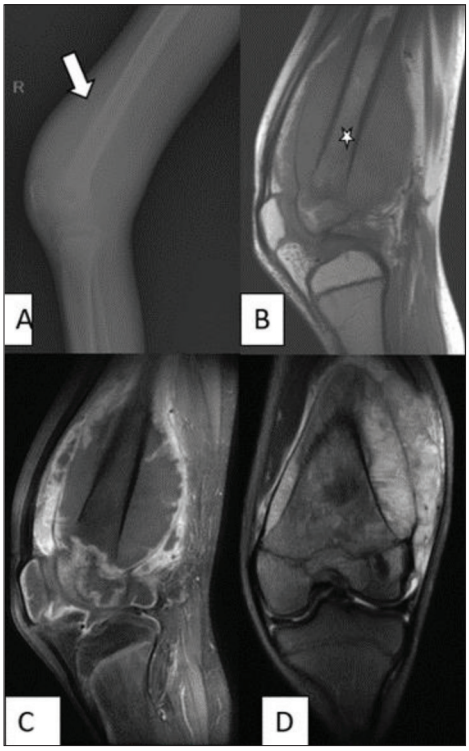

Figure 2. Chondroblastic osteosarcoma: A – lateral radiograph shows Codman triangle (arrow); B – sagittal T1-weighted fast spin echo magnetic resonance image of the femur intramedullary tumor extension diaphysis to epiphysis; C – postcontrast T1-weighted magnetic resonance imaging significant contrast enhancement; D – coronal T2-weighted fast spin echo magnetic resonance imaging extramedullary extension

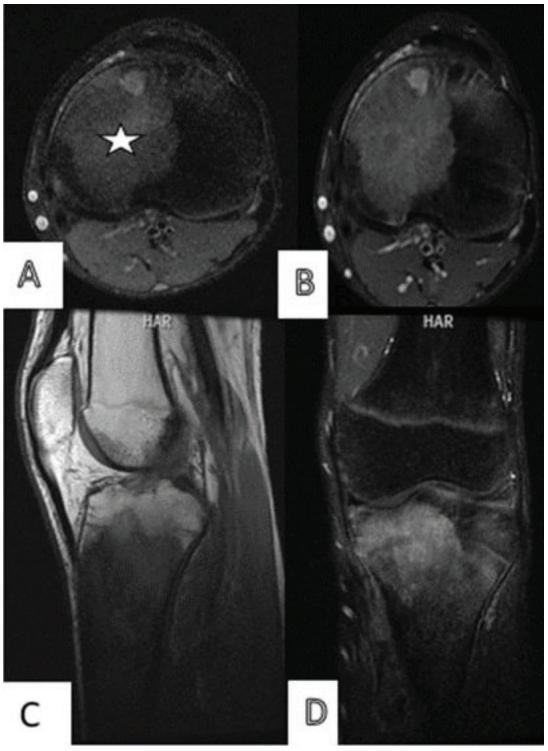

Figure 3. Chondroblastic osteosarcoma: A – axial T1-weighted fast spin echo magnetic resonance image of the tibia showing a lobular isointense morphology to the tumor (Stars); B – axial postcontrast T1-weighed magnetic resonance imaging displaying significant contrast enhancement; C – sagittal T1-weighted magnetic resonance imaging showing a lobular hypointense intramedullary component; D – hyperintense lesion extending to the epiphysis at coronal T2 weighted fast spin echo image

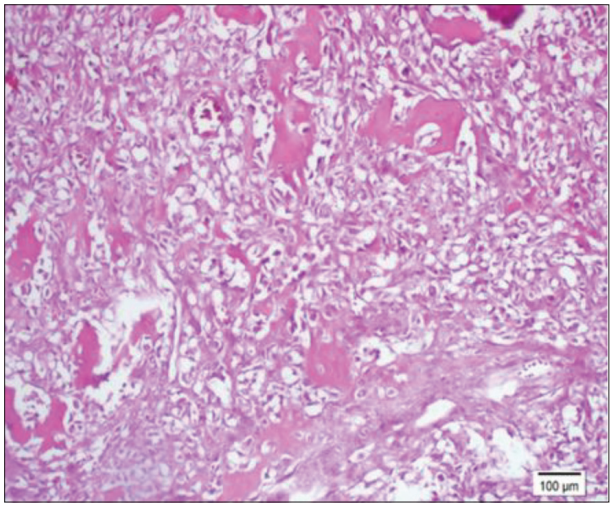

Figure 4. In osteoblastic osteosarcoma, the osteoid matrix is thin, reticulated, and lacy (Hematoxylin eosin × 100)

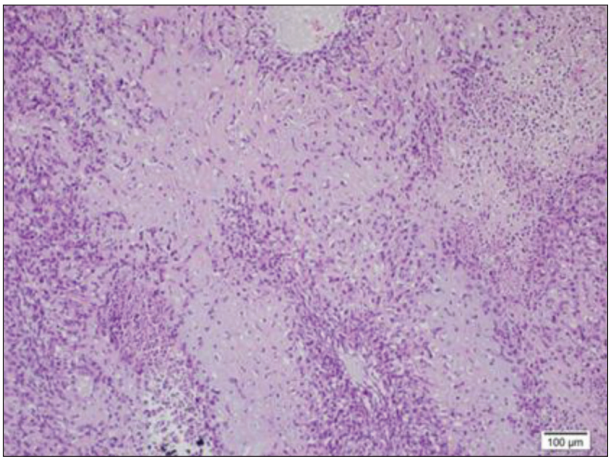

Figure 5. In chondroblastic osteosarcoma, the dominant component (usually 80–90%) is the chondroid, which is usually hyaline, less often myxoid cartilage matrix (Hematoxylin eosin × 100)

tumor necrosis could be differentiated from a viable tumor in fibroblastic and osteoblastic OS, but not in chondroblastic OS due to the inherently high ADC values of viable chondroblastic tissue [18].

In their studies, Pekcevik et al. [19] reported that chondrosarcomas had the highest ADC values among malignant bone tumors. Hayashida et al. [20] reported that there was no significant difference between the ADC values of solitary bone cysts, fibrous dysplasia, and chondrosarcomas with chondrosarcomas values lying in between the other two benign lesions. In another study, it was revealed significantly higher minimum ADC values of chondroblastic OS compared to other OS subtypes [8]. In our study, we could not involve DW MRI and ADC values because DW images (DWI) have only become standard after 2021.

Setiawati et al. [21] tried to analyze the histological subtypes of OS with dynamic contrast-enhanced MRI in addition to ADC characteristics. They found that osteoblastic OS had the highest value according to time intensity curve analysis and chondroblastic type OS had the highest value

according to ADC. They argued that in addition to determining the subtypes, the healing status of the disease and treatment response can be evaluated with this study [21].

Conventional OSs contain varying proportions of osteoblastic, chondroblastic, and fibroblastic areas. OS is classified as subtypes according to the matrix and dominant components. The variable histopathological structure of OS subtypes complicates the diagnosis. In OS, cells display marked pleomorphism and atypia. Neoplastic cells are in close association with the osteoid or chondroblastic matrix. In osteoblastic OS, the osteoid matrix is thin, reticulated, and lacy, and it has a yellowing appearance (Figure 4). In chondroblastic OS, the dominant component is usually the chondroid tissue (Figure 5). Chondroid areas are usually similar in grades 2–3 chondrosarcoma histology, and even a small amount of neoplastic osteoid formation should be present in chondroblastic OS. OS usually have mixed histology. ROI values in our study failed to distinguish between chondroblastic or osteoblastic types possibly due to mixed histological heterogeneity.

To our knowledge, this is the first study to differentiate conventional OSs involving osteoblastic and chondroblastic subtypes with quantitative T1, T2, and post-contrast signal intensity values by MRI. The main limitation of this study was having a small sample and studies with larger population should be planned in the future. Another limitation is that the study was conducted by a single observer.

CONCLUSION

Although no correlation was found between MRI parameters and histopathological findings in OS subtypes in the current study, it is promising to evaluate measurable parameters in MR sequences for prospective studies with larger patient groups to be conducted on this subject.

Conflict of interest: None declared.

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Можемо ли разликовати конвенционалне подтипове остеосаркома (остеобластичне и хондробластичне) на основу интензитета магнетне резонанце

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САЖЕТАК

Увод/Циљ Остеосарком је најчешћи примарни малигни тумор костију код адолесцената и младих одраслих, са тенденцијом да производи различите количине остеоида, хрскавице и фиброзног матрикса.

Циљ овог истраживања је да се направи разлика између остеосаркомских подтипова, остеобластичних и хондробластичних, на основу налаза магнетне резонанце (МР) и рендгенског сигнала.

Методе Ретроспективна анализа је урађена за 21 патолошки доказан подтип остеосаркома: остеобластични ($n = 14$) и хондробластични ($n = 7$). Рендгенским снимком су испитана уобичајена коштана порекла, периосталне реакције, литичке и склеротичне карактеристике, присуство калцификације и патолошких прелома. Измерили смо средње вредности области интересовања за сваку лезију помоћу МРИ секвенце.

Резултати Међу лезијама остеосаркома, 57% је било локализовано на колену. Рендгенски прегледи остеобластичних остеосаркома су открили чисте литичке лезије у 35,7% и чисте склеротичне лезије у 42,9% случајева. Хондробластични остеосаркоми су открили чисте литичке лезије у 14,3% и чисте склеротичне лезије у 42,9% случајева. Због променљивих остеобластичних, хондробластичних и фибробластичних подручја и пропорција окошталог матрикса, лезије остеосаркома имају хетерогени МР сигнал. Међутим, није откривена статистички значајна вредност.

Закључак Према нашим резултатима, карактеристике МРИ сигнала и рендгенски налази можда неће моћи да разликују подтипове остеосаркома, тако да су неопходне проспективне студије са већим групама болесника.

Кључне речи: магнетна резонанца; остеосарком; подтип; област интересовања

DOI: https://doi.org/10.2298/SARH211230080P
UDC: 613-056.24:616.379-008.64

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Quality of life in patients with diabetes – limited activity hinders women more

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SUMMARY

Introduction/Objective Diabetes mellitus and its chronic complications impair quality of life (QoL) when compared to the one of the general population.
The objective of this study was to determine the prevalence of > 14 unhealthy days per month among the patients with diabetes in Serbia and to determine the association of the socio-demographic characteristics and health characteristics with the total of > 14 unhealthy days.

Methods Serbian version of a generic self-administered questionnaire from Centers for Disease Control and Prevention (CDC-HRQOL-4) was used for data collection in all three levels of care.

Results The study involved 4898 patients with diabetes, 2283 (46.6%) men and 2611 (53.4%) women. Overall mean age was 57.3 ± 12.2 years with over one fifth (23.2 %) were younger than 50 years. Multivariate logistic regression analyses indicated that age > 65 (OR:1.575, 95%CI 1.100–2.256), being a woman (OR: 1.287, 95% CI 1.042–1.588), lower education (OR: 1.383, 95%CI 1.091–1.754), felt depressed ≥ 14 days (OR: 3.689, 95% CI 2.221–6.128), felt anxious ≥ 14 days (OR: 1.749, 95% CI 1.113–2.749), poor sleep ≥ 14 days (OR:2.161, 95%CI 1.569–2.988), fair or poor self-rated health ≥ 14 days (OR: 4.322, 95%CI 3.474–5.376) were associated with unhealthy days ≥ 14 days. The strongest negative association was observed between limited physical activity ≥ 14 days and a decrease in the QoL of people with diabetes (OR: 22.176, 95%CI 10.971–44.824).

Conclusion This study highlights association between impaired QoL in patients with diabetes and physical activity limitations. Limited physical activity is the factor with the greatest negative impact on the QoL particularly in older, less educated, and women with diabetes.

Keywords: diabetes mellitus; health-related quality of life; unhealthy days; sex differences

INTRODUCTION

Diabetes mellitus (DM) is a chronic, non-communicable disease associated with micro and macrovascular complications with a notable impact on health-related quality of life (HRQoL). Diabetes affects general health and wellbeing from various aspects including functional disability and mortality. The epidemic of obesity in the world contributes to the increase in the number of patients with diabetes mellitus which becomes an increasing global health burden. According to 2021 International Diabetes Federation atlas [1], the burden of the disease keeps growing with some 537 million people suffering from diabetes worldwide, and the highest increase expected to be seen in Africa (134%), followed by Middle East and North Africa (87%) and South-East Asia (68%), where currently 24 million, 73 million, and 90 million of inhabitants have diabetes, respectively. Europe with its mere 61 million in 2021 and the estimated 13% increase to 69 million in 2045 seems tolerable; however, the long-term complications and the unrecognized burden of women with gestational diabetes and their offspring is still unknown, since comprehensive data are lacking. According to the latest Institute of Public Health of Serbia "Dr Milan Jovanović Batut" report [2], 12.4% of people in Serbia have diabetes with 8.1% being aware of it and receiving treatment, while others who are unaware remain untreated. Diabetes is the fifth leading cause of morbidity and mortality in Serbia, with 90% of the patients having Type 2 diabetes (T2DM) and the majority are aged 40–59 years. Quality of life (QoL) and HRQoL could be used to assess the impact of medical conditions on patients' life and as a useful measure for policy-making and economic setting

Received • Примљено: December 30, 2021
Accepted • Прихваћено: August 29, 2023
Online first: September 1, 2023

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[3, 4, 5]. Diabetes mellitus impairs the patients' QoL. Socio-demographic factors also have physical, and mental health influence on HRQoL in patients with diabetes mellitus. Being a woman has been associated with lower QoL, as women report a higher impact of diabetes on their daily lives and are also influenced by lower educational level, duration of symptoms, adherence with prescribed treatment [4, 6–10]. Although global data might seem conflicting [11], the consensus are needed on which aspects of HRQoL should be measured in people with T2DM [11–14], while depression is gaining traction [5, 9, 15, 16, 17].

The aim of this study was to determine the prevalence of > 14 unhealthy days per month among the patients with diabetes in Serbia treated in outpatient care in the health care institutions in the public health care system. We also aimed to determine the association of the socio-demographic characteristics and health characteristics with a total of > 14 unhealthy days.

METHODS

The cross-sectional survey was conducted between January 2011 and December 2011. The 5500 questionnaires were offered to patients with diabetes who reported in outpatient healthcare settings in Serbia, during the investigated period. Of the total number, 602 respondents did not want or were unable to complete the questionnaire. The study included 4898 patients with diabetes mellitus from the urban and rural areas. Data was collected by Centers for Disease Control and Prevention questionnaire (CDC-HRQoL-4). The questionnaire was modified and translated into Serbian following the standard World Health Organization method translated to Serbian and previously published [18]. Participation in the research was voluntary. Research aims were introduced to participants both verbally and in written form. Anonymity, confidentiality, and privacy of data were also explained in verbal and written form, and all data were guaranteed to be used only for research purposes. We considered that all of the participants who filled out and returned the questionnaires after receiving all needed information gave their consent for the research. The willing participants filled out the questionnaire in the waiting room. All patients who visited their physician in the outpatient healthcare setting in Serbia were asked to participate in the study. The participants who were illiterate, did not speak Serbian fluently, or had mental or physical inability to understand or fill in the questionnaire were excluded from the study. The study was approved by the Ethical Committee of the Clinical Center of Serbia (Nr 1856/21, December 16, 2010). Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

The outcome variable in our study was "having ≥ 14 unhealthy days in the past month". The CDC-HRQoL-4 questionnaire examines the total number of physically unhealthy days, mentally unhealthy days, and days with limitation in physical activity in the past 30 days. These numbers are added together in order to obtain the "unhealthy days index" (UHD). UHD is commonly presented as a binary variable (< 14 unhealthy days and ≥ 14 unhealthy days) [19, 20].

Categorical data were expressed as numbers (%). Numerical variables (mentally, physically, activity limitations, total unhealthy, pain limitation, feelings of depression, anxiety, poor sleep, and healthy days) were tested for normality and were presented as mean, median (25th and 75th percentile). Univariate logistic regression was used, with ≥ 14 total unhealthy days during the previous 30 days as dependent variables as previously suggested [21]. Socio-demographic independent variables in logistic regression were: age (three categories: < 45 years, 45–65 years, and > 65 years), education (lower – elementary, high school, and higher – college), and place of residence (big town, small town, and rural area). Among QoL independent variables: self-rated health (fair and poor), mentally, physically, activity limitations, total unhealthy days, pain limitation, felt depressed, anxious, poor sleep, and healthy days were used. Variables with $p < 0.05$ were included in multivariate logistic regression. The level of significance was set at 0.05. Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among 4898 patients with diabetes mellitus, 2283 (46.6%) were men and 2611 (53.4%) were women. The mean age was 57.3 ± 12.2 years. More than a fifth of participants (23.2 %) were younger than 50 years. Most of them, (71.5%) had lower education level and 28.5% had higher, college or university education.

Among all the patients with diabetes, 2756 (56.8%) self-reported their health as fair or poor. More than 14 unhealthy days, during the previous 30 days, reported 44.9% of patients (Table 1).

Table 1. Self-rated health and unhealthy days

Variables	n (%)
Self-rated health (fair or poor)	2756 (56.8%)
≥ 14 mentally unhealthy days	751 (19)
≥ 14 physically unhealthy days	932 (23.7)
≥ 14 total unhealthy days	1620 (44.9)
≥ 14 activity limitation days	726 (18.4)
≥ 14 days limited by pain	632 (15.8)
≥ 14 days felt depressed	776 (20.1)
≥ 14 days felt anxious	865 (22.6)
≥ 14 days had difficulty with sleep	1003 (26.2)
≥ 14 days felt healthy	1016 (29)

Means and medians of mentally, physically, activity limitations days and ≥14 total unhealthy days were higher for women older than 50 years and patients with lower educations. There were 6.2 activity limitations days in men *vs.* 6.7 in women. Days of activity limitations were doubled in the group of 50 and more years of age (3.9 *vs.* 7.3). The

Table 2. Mentally, physically, activity limitation and total unhealthy days by socio-demographic characteristics

Socio-demographic characteristics mean		Mentally unhealthy days		Physically unhealthy days		Total unhealthy days		Activity limitation days	
		mean	med (25th–75th)	mean	med (25th–75th)	mean	med (25th–75th)	mean	med (25th–75th
Sex	Men	6.5	4 (0–10)	7.7	5 (0–10)	12.2	10 (2–20)	6.2	3 (0–10)
	Women	7.6	5 (0–10)	8.8	7 (2–15)	13.9	12 (3–25)	6.7	4 (0–10)
Age	< 50	5.1	3 (0–8)	5.5	3 (0–10)	9.4	6 (0–15)	3.9	0 (0–5)
	50 or more	7.7	5 (0–10)	9.1	7 (2–15)	14.2	12 (4–25)	7.3	5 (0–10)
Education	≤ 8 years	7.9	5 (0–10)	9.3	7 (2–15)	14.3	14 (4–25)	7.5	5 (0–10)
	> 8 years	5.2	2 (0–10)	5.9	4 (0–10)	10.0	7 (0–17)	4.1	0 (0–5)

Table 3. Pain limitation, felt depressed, anxious, had poor sleep and felt healthy days by sex, age, education

Socio-demographic characteristics mean		Pain limitation (days)		Felt depressed (days)		Felt anxious (days)		Had poor sleep (days)		Felt healthy (days)	
		mean	med (25th–75th)	mean	med (25th–75th)	mean	med (25th–75th)	mean	med (25th–75th)	mean	med (25th–75th)
Sex	Men	5.6	2 (0–10)	6.9	5 (0–10)	8.1	5 (2–10)	8.9	7 (3–12)	9.6	7 (0–18)
	Women	6.3	3 (0–10)	8.2	5 (1–10)	8.9	7 (2–10)	9.8	8 (3–15)	8.2	5 (0–15)
Age	< 50	3.4	0 (0–5)	5.6	3 (0–10)	6.7	5 (0–10)	7.5	5 (2–10)	11.8	10 (2–20)
	Over 50	6.7	4 (0–10)	8.2	5 (1–10)	9.1	7 (2–13)	9.9	8 (3–15)	8	5 (0–15)
Education	lower	6.7	4 (0–10)	8.4	5 (1–10)	9.2	7 (2–14)	10	10 (3–15)	7.9	5 (0–15)
	higher	3.9	0 (0–5)	5.7	3 (0–10)	6.8	5 (1–10)	7.7	6 (2–10)	11.2	10 (2–20)

Table 4. Univariate logistic regression with ≥ 14 total unhealthy days as the dependent variable

Variables	p	OR	95% CI for EXP(B)	
			Lower	Upper
Age	< 0.001			
Age category 45–65 years	< 0.001	1.880	1.540	2.295
Age category > 65 years	< 0.001	3.539	2.830	4.425
Women	< 0.001	1.319	1.156	1.505
Education (lower)	< 0.001	2.138	1.837	2.487
Duration of symptoms (months)	< 0.001	1.003	1.002	1.004
Therapy compliance	0.203	1.433	0.824	2.492
Place of residence	0.110			
Small town	0.083	1.138	0.983	1.317
Rural area	0.743	0.965	0.777	1.197
Activity limitation ≥ 14 days	< 0.001	71.374	44.370	114.813
Pain limitation ≥ 14 days	< 0.001	20.237	14.720	27.821
Felt depressed ≥ 14 days	< 0.001	24.395	17.980	33.098
Felt anxious ≥ 14 days	< 0.001	15.438	12.083	19.724
Poor sleep ≥ 14 days	< 0.001	9.963	8.135	12.201
Fair poor self-rated health ≥ 14 days	< 0.001	9.201	7.857	10.776

persons with lower education level have 7.5 activity limitations days, whereas patients with higher education level were limited active 4.1 days (Table 2).

Means and medians of pain limitation, feelings of depression, anxiety, had poor sleep days were higher for women, older than 50 years and patients with lower educations. As much as 10 poor sleep days were in the group with lower education level. The participants in the same group have the greatest number of days that felt anxious (9.2) or depressed (8.4) as well as days with limited activity (6.7) caused by pain. Mean and median for felt healthy days were higher in men, < 50 years, and with higher education (Table 3).

Age, being a woman, being of lower education, duration of symptoms, activity and pain limitation, feelings of depression, anxiety, poor sleep, and poor self-rated health were associated with ≥ 14 unhealthy days in univariate logistic regression (Table 4). Therapy compliance, place of residence was not statistically significantly associated with ≥ 14 unhealthy days (Table 4).

Multivariate logistic regression analyses indicated that age > 65 OR 1.575 (95 CI 1.100–2.256), being a woman OR 1.287 (95%CI 1.042–1.588), lower education 1.383 (95%CI 1.091–1.754), felt depressed ≥ 14 days OR 3.689 (95%CI 2.221–6.128), felt anxious ≥ 14 days OR 1.749 (95%CI 1.113–2.749), poor sleep ≥ 14 days OR 2.161 (95%CI 1.569–2.988), fair poor self-rated health ≥ 14 days OR 4.322 95% (95% CI 3.474–5.376) were associated with unhealthy days ≥ 14 days. The strongest negative association was observed between limited physical activity ≥ 14 days and unhealthy days ≥ 14 days with OR 22.176 (95% CI 10.971–44.824) (Table 5, Figure 1).

DISCUSSION

There were a large number of studies that evaluated the effect of diabetes on QoL, and most of them have shown that socio-demographic characteristics such as being a woman and being older are associated with lower QoL [4, 6, 7, 8, 11, 17, 22–25]. Our results showed that older age and lower education level were statistically significant with fair and poor self-rated health and mentally, physically, activity limitations, total unhealthy days, pain limitation, felt depressed, anxious, and had poor sleep (≥ 14 days).

In our study women felt more anxious and had poor sleep days. The participants in the group with < eight years of education had 9.2 days in which they felt anxious and 8.4 days felt depressed. Depression, in turn, degrades overall QoL in an interplay of lack of physical exercise, smoking, unhealthy diet, stressful life events and cultural difference in perception of illness [5, 7, 9, 10, 14–17]. Still, at least

Table 5. Multivariate logistic regression with ≥14 total unhealthy days as dependent variable.

Variables	p	OR	95% CI for OR	
			Lower	Upper
Age	0.015			
Age category 45–65 years	0.436	1.134	0.826	1.558
Age category > 65 years	0.013	1.575	1.100	2.256
Sex (women)	0.019	1.287	1.042	1.588
Education (lower)	0.007	1.383	1.091	1.754
Duration of symptoms (months)	0.065	1.002	1.000	1.003
Activity ≥ 14 days	< 0.001	22.176	10.971	44.824
Pain limitation ≥ 14 days	0.094	1.537	0.930	2.539
Felt depressed ≥ 14 days	< 0.001	3.689	2.221	6.128
Felt anxious ≥ 14 days	0.015	1.749	1.113	2.749
Poor sleep ≥ 14 days	< 0.001	2.161	1.563	2.988
Fair poor self-rated health 14 days	< 0.001	4.322	3.474	5.376

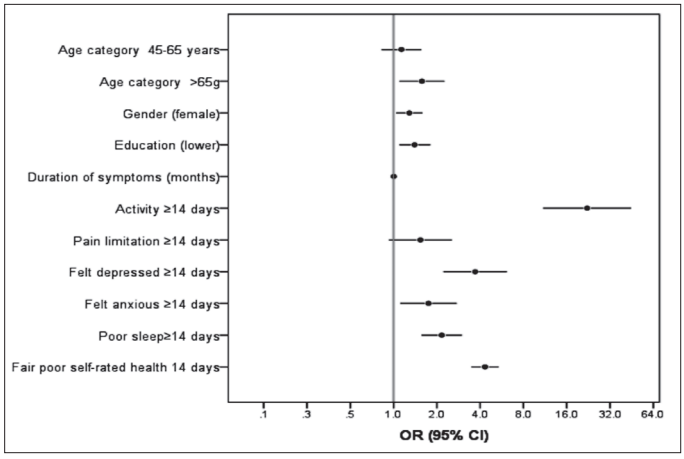

Figure 1. Multivariate logistic regression with ≥ 14 total unhealthy days as depended variable

for women, the solution can be found within the women's heart programs and centers worldwide [26, 27, 28], while the Serbian model [28] is currently the only one offering independent Clinics that actually encompass all four levels of prevention – from primary to quaternary – that can mitigate effects of diabetes in women of all ages and, practically, covering all IDF-defined [1] forms of diabetes.

In our study, 26.2% of participants had more than 14 days with sleep difficulties. The participants in the group with lower education had 10 days of poor sleep, while participants with higher education levels had six days with sleep deprivation. Patients older than 50 years had 10 days with difficulties with sleep, but younger than 50 years had five days with sleep impairment. Sleep deprivation in turn leads to anxiety and consequent depression.

Among all the patients in our study, 23.7% had ≥ 14 physically unhealthy days and 18.4% reported ≥ 14 activity limitation days. Therapy compliance, place of residence, urban or rural, was not statistically significantly associated with total unhealthy days.

Our participants could not have regular activity 6.7 days in the past month due to pain, which is rather in accord with findings of other authors [4, 5, 8, 29] as neuropathy has a significant negative impact on QoL, the key variable with a negative impact on life quality was activity limitations more than 14 days per month, with OR 22.17 (Figure 1).

In support of our research is the fact that only a few studies have addressed the magnitude of the impact of individual factors on the QoL of patients with diabetes. Previous studies in the Serbian population investigated different aspects, confirm HRQoL lowered in presence of angina, heart failure and retinopathy [6, 30], however, global consensus is required on HRQoL [13, 14, 16, 17]. Harnessing power of new technologies in mitigating effects of T2DM and motivating patients is sorely needed to improve long-term outcomes of the most underserved, as women are [16, 28], taking in consideration their well-described low inclusion in clinical trials and registries, requiring more detailed sex-specific research [28] which will elucidate better both the burden of disease and optimal prevention management strategies both nationally in Serbia, as well as internationally with targeted research agenda with alike-patient populations.

The limitations of this study were the use of the general instrument for assessing the QoL of the patients with diabetes, lack of information regarding the type of diabetes, duration of diabetes, and the presence of complications. Another limitation is the cross-sectional design as it does not allow the establishment of the causal relationship between the variables. The strength of the study is the number of participants, and the place of recruitment, as it allowed us to include the diverse population of patients with diabetes, and not only patients treated in hospitals.

CONCLUSION

For many years, the reason for the impaired QoL of patients with diabetes has been insulin therapy and chronic complications of diabetes. Thanks to the improved insulin formulations and almost painless application, lower incidence of macro- and micro-vascular complications due to significantly improved glycemic control, limited physical activity has become the factor with the greatest negative impact on the QoL of patients with diabetes. In addition, older age, lower educational level, particularly in women, with a significant restriction on their daily activities contributes to feelings of dissatisfaction and poor QoL in the diabetic population. Health promotion and therapeutic strategies including physical activity to increase independence, self-esteem, and better QoL for the patient with diabetes are needed.

This work was supported by the Ministry of Education and Science and Technology, Republic of Serbia (Grant No. 41004, Contract No. 175042 (2011–2014).
Conflicts of interest: None declared.

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Квалитет живота болесника са дијабетесом – ограничење покретљивости штети највише женама

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САЖЕТАК

Увод/Циљ Дијабетес мелитус и његове хроничне компликације нарушавају квалитет живота болесницима.

Циљ овог истраживања је било одређивање преваленце > 14 нездравих дана месечно код болесника са дијабетесом у Србији и одређивање социодемографских карактеристика и здравствених карактеристика са укупно > 14 нездравих дана.

Методе За прикупљање података на сва три нивоа здравствене заштите коришћена је српска верзија упитника Центра за контролу и превенцију болести (*CDC-HRQOL*-4).

Резултати Студија је обухватила 4898 болесника са дијабетесом, од чега 2283 (46,6%) мушкараца и 2611 (53,4%) жена. Просечна старост је била 57,3 ± 12,2 године са више од једне петине (23,2%) млађих од 50 година. Мултиваријантном логистичком регресијом показано је да су узраст > 65 (*OR*: 1,575, 95% *CI* 1,100–2,256), женски пол (*OR*: 1,287, 95% *CI* 1,042–1,588), ниже образовање (*OR*: 1,383, 95% *CI* ,1,091–1,754), осећај депресије ≥ 14 дана (*OR*: 3,689, 95% *CI* 2,221–6,128), осећај анксиозности ≥ 14 дана (*OR*: 1,749, 95% *CI* 1,113–2,749), лош сан ≥ 14 дана (*OR*: 2,161, 95% *CI* 1,569–2,988), субјективни осећај осредњег или лошег здравља ≥ 14 дана (*OR*: 4,322, 95% *CI* 3,474–5,376) били фактори који су удружени са нездравим данима у трајању од ≥ 14 дана. Најјача негативна удруженост показана је између ограничене физичке активности ≥ 14 дана и смањења квалитета живота код болесника са дијабетесом (*OR*: 22,176, 95% *CI* 10,971–44,824).

Закључак Наше истраживање указује на везу између сниженог квалитета живота код болесника са дијабетесом и ограничене физичке активности. Ограничена физичка активност је фактор највећег негативног утицаја на квалитет живота, посебно код старијих, оних нижег образовања и жена са дијабетесом.

Кључне речи: дијабетес мелитус; квалитет живота, нездрави дани, полне разлике

DOI: https://doi.org/10.2298/SARH230804087P
UDC: 616.992.282.23-036.88

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Factors' analysis associated with adverse outcome of the treatment of patients with invasive candidiasis

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SUMMARY

Introduction/Objective Invasive candidiasis (IC) is the most common invasive fungal infection in humans. It manifests as candidemia, and can affect internal organs and lead to sepsis and septic shock. A good knowledge of the factors that lead to the morbidity and mortality of these patients is necessary. We aimed to investigate the factors associated with the unfavorable outcome of patients with IC treated at our institution.

Methods The research was conducted at the Military Medical Academy in Belgrade, Serbia. The retrospective cohort study included 145 patients of both sexes, aged over 18, with a proven diagnosis of IC. Demographics, comorbidities, use of therapeutic procedures, antibiotics, antifungal treatment and outcome were compared between deceased and surviving patients with IC. The results were analyzed using Student's t-test, Mann–Whitney U test, multivariate statistical analysis.

Results The results showed that the predictors of death were diabetes mellitus (adjusted OR 6.886; CI: 2.608–18.178; p = 0.000) and chemotherapy (adjusted OR 6.826; 95% CI: 2.037–22.866; p = 0.002), which increase the risk of death seven times compared to the basal risk and mechanical ventilation, which increases the risk of death about three times (adjusted OR: 3.056; 95% CI: 1.132–8.253; p = 0.012).

Conclusion Optimal treatment is necessary in terms of early detection and identification of the causative agent of IC. In susceptible patients, such as immunocompromised patients, appropriate treatment should be initiated as soon as possible.

Keywords: fungal infection; invasive candidiasis; diabetes mellitus; death

INTRODUCTION

Candida species are normal commensals of humans, residing in the gastrointestinal tract, the female genital tract, and the anterior urethra. However, these fungi can cause a severe and life-threatening conditions, if *Candida* enters the bloodstream [1].

Invasive candidiasis (IC) is an infection caused by yeasts of the genus *Candida* that can affect different internal organs, such as the heart, brain, eyes, or bones and can lead to the development of sepsis and/or septic shock. IC is the most common fungal infection in hospitals, accounting for more than 85% of all invasive fungal infections in hospitals; approximately 45% of candidemia cases are treated in intensive care units (ICUs) [2, 3]. In Europe, IC is the fourth leading cause of nosocomial blood infections, with mortality ranging from 42% to 70%, and more than half of patients are diagnosed with septic shock [4, 5].

Risk factors for IC include: more than four days of ICU treatment, mechanical ventilation (MV), APACHE > 20, surgical procedures, total parenteral nutrition (TPN), renal and/or cardiac failure, and aminoglycoside administration [3, 6, 7]. Recent studies have shown that the number of patients with IC is increasing in the group of young intravenous opiate users without other risk factors [8]. During the COVID-19 pandemic, an increased number of patients with IC was recorded as a result of the administration of immunosuppressive and immunomodulatory drugs and prolonged treatment in the ICU [9, 10].

IC is one of the causes of morbidity and mortality in patients with HIV/AIDS immunodeficiency, in individuals with solid organ and stem cell transplants, in patients undergoing chemotherapy (CHT), in persistent neutropenia, in individuals with central venous catheters (CVC), in dialysis patients, and in patients receiving therapy with broad-spectrum antibiotics [7, 11]. Other studies confirmed diabetes mellitus (DM) and immunosuppression as significant risk factors for the occurrence of IC and emphasized the importance of the presence of a CVC, prolonged use of glycopeptide antibiotics, quinolones, and aminoglycosides [12, 13], and gastrointestinal tract surgery and prolonged ICU stay [4, 14].

The aim of this study was to analyze factors associated with death in hospitalized patients who were admitted with IC or developed it during hospitalization.

METHODS

The study was designed as an observational, retrospective cohort study of a random sample

Received • Примљено: August 4, 2023
Revised • Ревизија: September 21, 2023
Accepted • Прихваћено: September 22, 2023
Online first: October 2, 2023

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of 145 patients from the Military Medical Academy in Belgrade (MMA), Serbia, hospitalized between 2008 and 2021. Patients were enrolled based on the following inclusion criteria: hospitalization in one of the clinics of surgery / internal medicine or at the ICU of the MMA, aged over 18 years, both sexes, patients with a confirmed diagnosis of IC – proven isolate of any fungal species of the genus *Candida* in a blood culture or in sterile areas or tissues, or patients with a probable diagnosis of IK – positive results of radiological tests and markers of invasive fungal infection (*Candida* mannan). The BACT/ALERT® system (bioMérieux, Marcy-l'Étoile, France) was used to isolate fungi from blood cultures and peritoneal fluid. Microorganisms were differentiated using the Matrix Assisted Laser Desorption Ionization – Time of Mass Spectrometer and Video Artificial Intelligence Technology. Serum samples for *Candida*-specific antibodies and *Candida*-specific antigen – mannan were analyzed by enzyme-linked immunosorbent assay. All microbiological analyzes were performed in the microbiology laboratory of the MMA. Exclusion criteria were incomplete medical documentation, combined invasive fungal infections with *Candida* and other fungi, and late initiation of antifungal therapy. The study was approved by the Ethics Committee of the MMA (resolution number 56/2019, date 06/24/2019) before initiation.

Data were obtained from the MMA's information system. Primary study outcome was in-hospital mortality, and secondary outcomes were relapse of IC (new diagnosis of IC within 30 days of initiation of treatment for the first episode of disease) and occurrence of subsequent complications in patients previously diagnosed with IC, such as vital organ failure or surgical intervention. Putative predictors of study outcomes were DM, previous surgery, previous peritoneal or hemodialysis, TPN, administration of antibiotics for more than four days, administration of more than three antibiotics, administration of a CVC, invasive and noninvasive MV, corticosteroids, immunosuppressive therapy, biological therapy, CHT, radiotherapy, neutropenia, bacterial sepsis, solid organ transplantation, and bone marrow transplantation, while confounding factors considered were: sex, age, body temperature, hospital department where the patient was treated, comorbidities, concomitant therapy, and the underlying disease that was the reason for hospitalization.

The minimum sample size sufficient to find factors significantly associated with mortality as a study outcome was calculated based on the Schlesselman method. The inputs for this calculation were: Probability of type 1 error of 0.05, power of the study 0.8, incidence of the primary outcome 20%, prevalence of DM as a risk factor of 62%, and a meaningful adjusted odds ratio of two for the risk factor. The minimum sample size sufficient for the inputs was 66 patients per study group, for a total of 132 patients.

Data collected from the MMA information system were first numerically coded, tabulated, and checked for errors. Data were then described by measures of central tendency and variability (for continuous data) or frequencies and relative numbers (percentages) (for categorical data). Normally distributed continuous data were described by mean and standard deviation, and not-normally distributed data were described by median and interquartile range. The effects of putative predictors and confounders on the study results were analyzed using multivariate binary logistic regression. Before using this multivariate technique, we checked that the assumptions were met (binary outcome, independence of observations, no multicollinearity, no extreme outliers, and sufficiently large sample). The quality of the regression model was tested using the Hosmer–Lemeshow test, Cox & Snell's R-squared, and Nagelkerke's R-squared. Results were considered statistically significant if the probability of the null hypothesis was 0.05. Survival curves were constructed for significant categorical predictors, and the equality of survival distributions for different levels of such predictors was tested with the log-rank test. All calculations were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 18.0.

RESULTS

This study included 145 patients (70 men and 75 women) with a mean age of 52.8 ± 17.5 years who were hospitalized at MMA Belgrade between 2008 and 2021. In total, 60 patients (41.1%) died during hospitalization, 85 recovered (58.2%), and only one patient (0.7%) had a relapse of IC. Age, sex, length of hospital stay, and other characteristics of the study sample related to the primary outcome are shown in Table 1.

The association of independent and confounding variables with death during hospitalization was tested using multivariate binary logistic regression. The model was built using the backward conditional deletion method, starting from a complete set of potential predictors and confounders: DM, previous surgery, previous peritoneal or hemodialysis, TPN, administration of antibiotics for more than four days, administration of more than three antibiotics, administration of a CVC, invasive and noninvasive ventilation, corticosteroids, immunosuppressive therapy, biological therapy, CHT, radiotherapy, neutropenia, bacterial sepsis, solid organ transplantation, bone marrow transplantation, sex, age, body temperature, hospital unit in which the patient was treated, comorbidities, concomitant therapy, and the underlying disease that was the reason for hospitalization. The assumptions of a binary outcome (death during hospitalization or not), independence of observations, absence of multicollinearity, absence of extreme outliers, and a sufficiently large sample were all met. The linear relationship between the explanatory variables and the logit of the outcome was tested for all continuous variables with the Box-Tidwell test, but none of these variables was included in the final model. The final binary logistic regression model included the variables listed in Table 2, and fit the data satisfactorily: Hosmer–Lemeshow test was 6.476 (df = 6, p = 0.372), Cox & Snell's square was 0.180, and Nagelkerke's square was 0.244.

Survival curves for patients with and without DM are shown in Figure 1. The logrank test (Mantel–Cox) showed a significant difference in survival distributions: $\chi^2 = 17.456$, df = 1, p = 0.000.

Table 1. Characteristics of the study sample; the data are presented as mean ± SD; the differences among the groups were tested by Mann–Whitney U test for continuous variables and by χ^2 test (or Fisher's exact test where appropriate) for categorical variables; p – probability of null hypothesis

Variable		Died (n = 60)	Survived (n = 85)	p
Age (years)		56.7 ± 17.6, 56 [25]	50.7 ± 16.8, 53 [27]	0.042
Sex (m/f)		30/30	40/45	0.727
Length of stay (days)		55.2 ± 66.2, 37 [59]	48.8 ± 34.1, 40 [28]	0.224
Treatment in intensive care unit (yes/no)		15/45	21/64	0.968
Number of antibiotics administered		3.7 ± 1.8, 4 [1]	3.8 ± 1.7, 4 [2]	0.715
Length of antibiotic therapy (days)		46.5 ± 52.6, 30 [47]	40.1 ± 28.3, 30 [31]	0.564
Length of antifungal therapy (days)		19.1 ± 11.9, 20 [15]	19.3 ± 14, 17.5 [6]	0.662
Time delay from diagnosis to antifungal therapy onset (hours)		22.6 ± 46.9, 17 [24]	18.6 ± 24.8, 24 [24]	0.886
Time delay from symptoms to antifungal therapy onset (hours)		25.5 ± 31.4, 24 [48]	41.1 ± 97.8, 24 [48]	0.473
Day of death since hospitalization		55.1 ± 62.5	-	
Day of death since initiation of antimicrobial therapy		44.0 ± 41.7	-	
Full/reduced dose of antifungals		52/8	80/5	0.168
Wide spectrum antibiotic used (yes/no)		59/1	83/2	0.313
Urinary catheter (yes/no)		60/0	81/4	0.115
Place of isolation of the causative agent (blood / pleural punctate / abdominal fluid)		58/1/1	83/2/0	0.748
Antifungal prophylaxis (yes/no)		39/21	50/35	0.452
Intravenously immunoglobulins (yes/no)		60/0	85/0	cannot be calculated
Blood culture from central venous catheters / peripheral vein		30/27	45/36	0.857
Isolated Candida type	Candida species	14	18	0.025
	Candida albicans	18	40	
	Candida glabrata	7	1	
	Candida parapsylosis	17	22	
	Candida kefiri	1	0	
	Candida lusitanie	0	2	
	Candida sake	0	1	
	Candida guillermondi	0	1	
Candida antibodies measured (yes/no)		0/60	2/83	0.342
Mannan measured (yes/no)		0/60	1/84	0.586
Type of antimycotic prescribed (azole / echinocandin / amphotericin B / unknown)		48/6/1/5	76/8/0/1	0.334
Oral / parenteral / unknown route of administration of antimycotics		3/52/5	6/78/1	0.484
Invasive fungal infection proven/probable		60/0	84/1	1,000
Supportive therapy (yes/no)		5/55	2/83	0.126
Hemodialysis (yes/no)		8/52	5/80	0.122
Peritonitis (yes/no)		5/55	7/78	0.625
Sepsis (yes/no)		12/48	14/71	0.585
Solid organ transplantation (yes/no)		2/58	1/84	0.570
Bone marrow transplantation (yes/no)		4/56	10/75	0.398
Pancreatitis (yes/no)		4/56	8/77	0.761
COVID-19 (yes/no)		0/60	1/84	1,000
Diabetes mellitus (yes/no)		28/32	14/71	0.000
Mechanical ventilation (yes/no)		34/26	37/48	0.119
Therapy with potential to suppress the immune system	No	29	51	0.319
	Biological drugs	0	2	
	Immunosuppressant drug	13	11	
	Radiation therapy	2	1	
	Chemotherapy	16	20	
Central venous catheter (yes/no)		39/21	62/23	0.306
Central venous catheter removed after diagnosis of fungal infection with delay of more than 24 hours (yes/no/unknown)		13/8/18	27/16/19	0.945
Abdominal surgery (yes/no)		27/33	43/42	0.507
Neutropenia (yes/no)		15/45	18/67	0.589

Table 2. Risk factors for death during hospitalization of patients with invasive candidiasis

Risk factors	Raw OR (95% CI)	p	Adjusted OR (95% CI)	p
Diabetes mellitus	4.437 (2.064–9.539)	0.000	6.886 (2.608–18.178)	0.000
Mechanical ventilation	1.696 (0.871–3.305)	0.120	3.056 (1.132–8.253)	0.028
Chemotherapy	1.407 (0.632–3.131)	0.403	6.826 (2.037–22.866)	0.002
Radiotherapy	3.517 (0.306–40,489)	0.313	3.788 (0.271–52.844)	0.322
Immunosuppressants	2.078 (0.826–5.233)	0.120	3.094 (0.980–9.770)	0.054

OR – odds ratio; CI – confidence interval

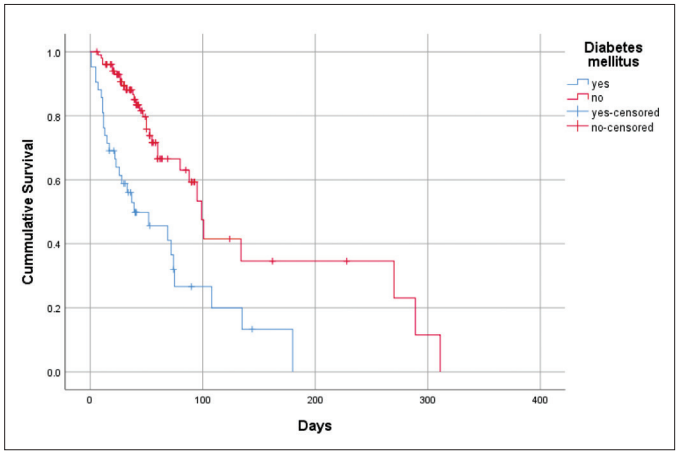

Figure 1. Survival curves for patients with and without diabetes mellitus

DISCUSSION

The prevalence of infection IC is increasing [1]. The use of antineoplastic and immunosuppressive agents, broad-spectrum antibiotics, DM, neutropenia, and more aggressive surgical procedures are potential risks for the increasing number of IC patients worldwide [11, 13, 15].

Our study showed that there are three independent predictors of death in hospitalized patients with IC: DM and CHT, which increase the risk of death almost sevenfold compared to baseline risk, while MV increases the risk of death threefold. Among other factors tested, age and isolation of *Candida glabrata* and *Candida parapsylosis* appeared to have a tendency to negatively affect hospital mortality, but this was lost after adjustment for other factors in multivariate analysis.

Candida albicans remains the most common cause of IC. In recent decades an increase in non-albicans candidemia has been observed. *Candida glabrata* is responsible for 15–25% of invasive fungal infections and is second only to *Candida albicans* in the United States and northwestern Europe, and that predisposing factors include older age and frequent use of medical devices [16]. Some authors emphasized the growing medical importance of *Candida glabrata* in the population of patients with immunodeficiency syndrome, DM, and malignant diseases, as well as in the elderly [16, 17]. IC caused by *Candida glabrata* causes significant morbidity and mortality of 40–60%, mainly due to low sensitivity to the most commonly used azoles [18]. Indeed, it was reported that *Nakaseomyces glabrata* (formerly *Candida glabrata*) was isolated in 14% of patients with IC, with an average age of 55 years, and what is more significant, 6% of isolates were resistant to echinocandins [19]. Also, in a study in Turkey, results obtained from six different medical centers the presence of *Candida glabrata* was found to be the causative agent of IC in ICUs in 10% of patients [20].

In our study, *Candida glabrata* was found to be isolated in 11.6% of patients in the observed group and in 1.17% of patients who recovered, which is in accordance with data from the literature. On the basis of a multifactorial regression analysis adjusting for other factors, *Candida glabrata* isolate had no significance in the outcome of our patients.

In our hospital, DM was registered in 29% of patients with IC, which is a lower frequency compared with data from other studies (62.5% and 50%) [21, 22]. Here, we have shown that there was a statistically significant difference in the outcome of patients with IC in relation to the presence of DM. DM is an independent factor that increased the risk of death sevenfold. The mortality was 41.4%, consistent with the results of other studies in which it ranged from 28% to 45% [23].

DM is a multifactorial, chronic metabolic disease and is a major health problem worldwide. Patients with DM often have other comorbidities that further worsen the outcome of IC. In an analysis of numerous studies on DM and IC, Rodrigues et al. [12] showed the importance of DM as an independent factor in the development of IC and the fatal outcome of these patients. Numerous studies have shown an association between *Candida* sp. infection and DM, related to oral, vulvovaginal candidiasis or IC [18].

In patient with persistent candidemia, isolates responsible for biofilm formation, including *Candida albicans, Candida tropicalis,* and *Candida glabrata* were significantly more common [18, 24]. *Candida glabrata* was more frequent in DM patients (52.9% *vs*. 32%) than in patients without DM and in infections originating from the abdomen, which is explained by the greater pathogenicity of the pathogen [24]. A retrospective study in China showed that candidiasis was the most common fungal infection in the elderly patients with DM (46.8%) [17]. In patients with DM and IC, treatment is even more difficult because of reduced sensitivity to antifungal agents, up to 47% to ketoconazole, while other authors show significant resistance to five antifungal agents in diabetics [18].

Given the increasing resistance of *Candida albicans* [25] to fluconazole and *Candida glabrate*, as well as to echinocandins [19] found in a large percentage of DM patients, the treatment of these patients is difficult both in terms of choice and dose of drugs used. In addition, the

pharmacokinetics and pharmacodynamics of antifungal drugs are impaired in patients with DM. The absorption of the drug is poor, which is due to the structural alteration of albumin and the decreased binding of the drug, which increases the concentration of free drug in the serum. Due to the damage of microcirculation and vascular permeability, the penetration of the drug to the site of infection is weak [18]. Adequate treatment is of great importance for this group of patients.

Long-term MV in the ICU exposes patients to fungal colonization and leads to candidemia. This is due to the presence of medical devices (peripherals, cannulas, CVC, urinary catheters, Hickman catheters, tubes, oxygen masks, etc.), the use of broad-spectrum antibiotics and immunosuppressive therapy. The association of TPN and MV with candidemia increases mortality by up to 77% [26]. Chakraborti et al. [27] showed that there is a significant increase in fungal colonization in endotracheal aspirates between the first and seventh day after intubation. New strategies for the use of protective MV showed a lower incidence of complications compared with the use of conventional MV (8.7% *vs*. 14.7%), which should also lead to lung injury reduction [28]. Also, increased colonization with *Candida glabrata* during the use of MV, which tends to form biofilms with the development of resistance to existing azoles, leads to treatment failure and death [13, 16, 19]. Our results show that in patients with IC MV was applied in 56.7% of cases in the observed group and in 43.5% of cases in the control group of surviving patients. Multivariate regression analysis revealed that the use of MV in patients with IC was associated with three times higher risk of death or significantly increased the probability of death. Our results are consistent with the findings of other studies [22].

In our study, 44% of patients with IC received some type of therapy affecting the immune system. In the observed patient group, 26.67% received CHT, and in the survivor group, 23.53% did. In our CHT-receiving patients, the risk of death was seven times higher compared to patients without CHT. Such a high risk of death can be explained by the nonspecific effect of CHT on cells, the occurrence of immunosuppression and the development of opportunistic infections, among which *Candida* infections take the first place. IC is very common in patients with malignant diseases, has a high incidence of morbidity and mortality, which significantly increases the cost of treatment.

CHT leads to disruption of epithelial barriers and alters the host immune response, allowing the development of IC. Following CHT, *Candida* sp. overgrowth occurs due to decreased production of antimicrobial peptides by epithelial cells or decreased levels of bacterial metabolites that normally inhibit *Candida albicans* growth, as well as direct effects of CHT on *Candida albicans* itself [29].

In our study, neutropenia as an independent factor did not increase the probability of death in patients with IC, there was no difference in the prevalence of neutropenia in the deceased and survivor groups, which may be explained by the lack of damage to the gastrointestinal barrier, insufficient degree of mucosal colonization, or colonization with less virulent *Candida* strains.

Surgical intervention in the upper abdomen was recorded in 48.27% of our patients and did not affect the outcome, while other authors presented this intervention as a risk factor for the occurrence and outcome of IC due to increased antibiotic consumption, secondary infections, and the use of MV [14].

Among the other comorbidities, sepsis, peritonitis, and pancreatitis did not affect the outcome of patients with IC. Solid organs transplantation, bone marrow transplantation, use of hemodialysis, presence of urinary catheter, and placed CVC were not significant for death outcome of patients with IC.

The presence and extraction of CVC 24 hours or more after the diagnosis of IC was not a risk factor for the unfavorable outcome of our patients, while previous studies describe CVC as an independent risk factor [13]. The results of recent studies suggest that CVC is a significant predictor of candidemia in internal medicine departments with prior use of cephalosporins and inadequate body weight. Poissy et al. [7] show that CVC is still a risk factor for candidemia in all patients and an independent risk factor for candidemia in non-ICU patients received glycopeptides and TPN.

A broad-spectrum antibiotic was used equally frequently in both groups and the average number of antibiotics was used in patients with IC in the observation and control groups. Poissy et al. [7] described the use of multiple antibiotics as a risk factor for death, which was not demonstrated in our results. Considering the duration of antifungal use in the studied groups, there was no statistical significance in relation to the outcome.

In our study, the length of hospital stay did not significantly affect the outcome of death, as the studied and control groups did not differ significantly on this parameter, as did ICU treatment. One meta-analysis has shown that ICU stay is a significant risk factor for the occurrence of IC and death [4].

Our study has several limitations. First, the sample size was limited, so the study may not be sufficiently powered to identify other putative factors because of the low prevalence in this population. Second, this was a unicenter study, so some local practices not captured by the study data may have influenced the outcome and amplified or neutralized the effects of some true predictors.

CONCLUSION

In conclusion, patients with DM or patients receiving CHT, especially if mechanically ventilated, are several times at a greater risk of dying in the hospital and therefore require special attention and timely administration of appropriate antifungal and other supportive measures.

ACKNOWLEDGMENT

The authors contributed equally to this work.

Conflict of interest: None declared.

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Анализа фактора удружених са неповољним исходом лечења болесника са инвазивном кандидијазом

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САЖЕТАК

Увод/Циљ Инвазивна кандидијаза (ИК) најчешћа је инвазивна гљивична инфекција код људи. Манифестује се као кандидемија, а може захватити унутрашње органе и довести до сепсе и септичног шока. Неопходно је добро познавање фактора који доводе до морбидитета и морталитета ових болесника.

Циљ рада је био да истражимо факторе повезане са неповољним исходом лечења болесника са ИК у нашој установи.

Методе Истраживање је спроведено на Војномедицинској академији у Београду, у Србији. Ретроспективном кохортном студијом обухваћено је 145 болесника оба пола, старости преко 18 година, са доказаном дијагнозом ИК. Демографија, коморбидитети, примена терапијских процедура, антибиотици, антифунгални третман и исход упоређени су између умрлих и преживелих болесника са ИК. За анализу резултата коришћени су Студентов т-тест, Ман–Витнијев *U* test, мултиваријантна статистичка анализа.

Резултати Показано је да су предиктори смртног исхода дијабетес мелитус (кориговани *OR* 6,886; *CI*: 2,608–18,178; *p* = 0,000) и хемотерапија (кориговани *OR* 6,826; 95% *CI*: 2,037–22,866; *p* = 0,002), који повећавају ризик за смртни исход седам пута у поређењу са базалним ризиком, и механичка вентилација, која повећава ризик за смртни исход око три пута (кориговани *OR*: 3,056; 95% *CI*: 1,132–8,253; *p* = 0,012).

Закључак Неопходан је оптималан третман у смислу раног откривања и идентификације узрочника ИК. Код осетљивих болесника, као што су болесници са ослабљеним имунитетом, одговарајући третман треба започети што је пре могуће.

Кључне речи: гљивична инфекција; инвазивна кандидоза; дијабетес мелитус; смрт

DOI: https://doi.org/10.2298/SARH221221073P
UDC: 616.712-001.5-06; 616.25-076:575.112

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Significance of fibrinogen, interleukin-6, and C-reactive protein as predictors of pleural complications after rib fractures in blunt chest trauma

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SUMMARY

Introduction/Objective Rib fractures are common in blunt chest trauma (BCT), and when they are associated with pleural complications (PC) – pneumothorax, hemothorax and hemopneumothorax – the treatment of these patients is prolonged and difficult. Without the ability to predict PC after rib fractures in BCT, most doctors are forced to initially treat these patients through observation and conservative treatment.

The goal of this research is to determine which of the investigated biomarkers of inflammation – fibrinogen, interleukin-6 (IL-6), and C-reactive protein (CRP) – are significantly associated with the occurrence of PC after rib fracture in BCT, and whether they can be used in stratifying patients for hospitalization and further treatment.

Methods The prospective study included 90 patients with rib fractures caused by BCT. The test group comprised 45 patients with rib fractures and the presence of PC, and the control group consisted of 45 patients with rib fractures without PC. Blood sampling was performed on admission, on the second, third, and fifth day after the injury, and PC were monitored until the seventh day after the injury.

Results Serum values of IL-6 on the second day and fibrinogen and CRP on the second and third day after injury were statistically significantly higher in patients with PC, and IL-6 showed a good discriminative ability in assessing the occurrence of PC on the second day after a rib fracture in BCT.

Conclusion The investigated biomarkers of inflammation – fibrinogen, IL-6, and CRP – can be used as predictors of PC after rib fracture in BCT, and their application can significantly replace clinical observation.

Keywords: blunt chest trauma; rib fractures; pleural complications; fibrinogen; IL-6; CRP

INTRODUCTION

Chest trauma is one of the leading causes of morbidity and mortality in all age groups. Chest injuries are the most frequent injuries followed by head and limb injuries [1]. Mortality in patients with chest injury is 4–60% [1]. Chest injuries are divided into two entities – blunt and penetrating, where blunt chest trauma (BCT) is characterized by injury to structures of the chest without open communication between the pleural space and the external environment [2]. BCT accounts for 10–15% of all trauma cases [3]. BCT is more common than penetrating injury and accounts for more than 90% of chest injuries [1]. Such a high frequency of BCT poses a major social and medical problem [4]. The most common causes of BCT are traffic trauma (in 70% of the injured), injuries at home (very often due to falls from a height or downstairs), and workplace accidents [1, 2, 3].

Rib fractures are common in BCT [1]. Some patients with rib fractures develop pleural complications (PC) – pneumothorax (presence of air in the pleural space), hemothorax (blood in the pleural space), hemopneumothorax (combination of the aforementioned conditions) – which largely affect the outcome of treatment [5]. In patients without rib fractures after BCT, pneumothorax and/or hemothorax occur in 6.7% of cases, while in patients with rib fractures these complications occur in 24.9% (with one or two rib fractures) up to 81.4% (with fracture of more than two ribs) of cases [6].

In cases of BCT with rib fractures special care must be taken since PC can occur within 24–72 hours after the initial injury and examination of the patient, and in elderly patients even within one week of the injury [7]. If PC are not recognized in time, death is also possible [8]. Prompt and accurate diagnosis of

Received • Примљено: December 21, 2022
Revised • Ревизија: July 30, 2023
Accepted • Прихваћено: August 12, 2023
Online first: August 18, 2023

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injuries and PC in BCT is very important since it enhances further medical treatment of these patients.

Without the ability to predict PC after rib fractures in BCT, most doctors are forced to initially treat these patients through observation and conservative treatment, even in the absence of visible injuries, which significantly burdens a country's health care system financially.

Little data can be found on predicting the occurrence of PC after BCT. Also, there is still no clear evidence that inflammatory biomarkers (and particularly which ones) can be used as predictors of PC in rib fractures in BCT.

Immediately after injury, the body's immune system is activated, releasing inflammatory mediators, which are also biomarkers of inflammation [9]. According to the definition of the World Health Organization, biomarkers represent "any substance, structure, or process that is measurable in the body, or its products and effects are measurable, or that predict the incidence of an outcome or disease." Chest trauma does not have "its own" biomarkers, since the role of cytokines and inflammatory biomarkers in BCT has not yet been fully explored [10].

Fibrinogen, interleukin-6 (IL-6), and C-reactive protein (CRP) are among the most significant and frequently used markers of inflammation in clinical practice.

Fibrinogen as an acute phase protein is synthesized in the liver and released into the circulation, and as a damage-associated molecular patterns (DAMP) molecule it is found in the extracellular matrix and is released after trauma-induced tissue damage (especially after blunt trauma) [11]. Fibrinogen participates in blood coagulation, inflammation, mediates interactions between cells and the extracellular matrix, wound healing and neoplastic processes [12]. Rib fractures are accompanied by significant accumulation of fibrin deposits that promote inflammation at the fracture site and in the surrounding tissue [13].

DAMP molecules are endogenous nuclear, mitochondrial, or cytoplasmic molecules that have their physiological role inside the cell, which are released from the damaged or dying cell and/or the extracellular matrix after injury and as mediators indirectly stimulate a "sterile" inflammatory response [14]. As a DAMP molecule, fibrinogen is found in the extracellular matrix and indirectly stimulates a "sterile" inflammatory response after injury [14].

IL-6 is a pro-inflammatory cytokine released by activated monocytes and macrophages and plays a role in amplifying inflammatory signals, thereby activating leukocytes that in turn produce other inflammatory mediators [15]. Also, IL-6 participates in the activation of the complement cascade and coagulation, enhances hematopoiesis and increases vascular permeability [16]. IL-6, after being released from activated macrophages, induces the synthesis and release of acute phase proteins, especially CRP. IL-6 is one of the key pro-inflammatory cytokines in trauma due to its significant association with injury severity and clinical complications [15]. The level of IL-6 in the serum is significantly increasing during the first two hours after the injury and continuing to increase over the next 24 hours, dropping significantly afterwards, reaching its peak four to six hours after the injury, which is significant earlier than the increase in the level of other reactants of the acute phase [17]. Some of the authors state that IL-6 as a reactant of the acute phase is elevated in a patient with BCT and that determining the level of IL-6 can be used to determine the severity of the injury in the first 24 hours after the injury [18].

CRP is an acute-phase protein primarily synthesized in the liver, but also in smooth muscle cells, macrophages, endothelium, lymphocytes, and adipocytes and is released in the plasma [19]. In addition to the fact that CRP is a traditional marker of cardiovascular events, it has been proven that it participates in the process of inflammation and the host's response to infection, in the complement pathway, apoptosis, phagocytosis, the release of nitrogen monoxide and the production of cytokines, especially IL-6 and tumor necrosis factor α [19]. Plasma concentrations of CRP can increase a thousandfold within 24–48 hours, especially in conditions of local and systemic infection and/or after tissue damage [20]. A persistently high level or a secondary increase in CRP indicates the presence of complications and is widely used to diagnose postoperative wound infections and other complications [21]. A sudden increase in CRP levels in traumatized patients with a peak concentration in the period over 48–72 hours is followed by a rapid decrease in CRP concentration and a return to the initial levels before trauma and surgery within two to three weeks [21]. A similar increase in peak CRP concentration on the third and the fifth day after the injury also exists in abdominal surgery [22]. Certain authors determined the initial level of CRP in traumatized persons upon admission to treatment in order to verify the possible later occurrence of infection, whereby they noted that an increase in CRP level was not always associated with infection [19]. CRP is a simple, inexpensive, and sensitive test widely used in medical institutions. The main disadvantage of CRP as a diagnostic tool is its low specificity in determining the cause of inflammation. In addition to its sensitivity, due to its low specificity, CRP does not have a high predictive value in the detection of postoperative complications [22]. Despite the fact that the positive predictive value of CRP is limited, a low CRP level can be used to exclude the existence of complications.

The main hypothesis of this research is that there is a statistically significant relationship between the change in the level of inflammation biomarkers – fibrinogen, IL-6, and CRP – in the plasma and the occurrence of PC in patients with rib fractures caused by BCT, which can be used to stratify patients for hospitalization and further treatment.

The aim of this study is to determine which of the investigated biomarkers of inflammation – fibrinogen, IL-6, and CRP – are statistically significantly associated with the occurrence of PC – pneumothorax, hemothorax and hemopneumothorax – in rib fractures after BCT.

METHODS

This research was conducted in the Clinic for Thoracic Surgery, Emergency Center and Anesthesia Clinic of the University Clinical Center in Niš, Serbia, in the period

from November 2020 to January 2022, and was approved by the Ethics Committee of the Faculty of Medicine in Niš (N⁰. 12-3094/4). Examinations of the patients' biological material were performed at the Center for Medical Biochemistry and at the Immunology Laboratory of the University Clinical Center in Niš. Radiological examinations were performed at the Radiology Center of the University Clinical Center in Niš.

The prospective study included 90 patients with rib fractures caused by BCT. The patients were divided into two groups: the test group and the control group; 1) the test group included 45 patients with rib fractures and PC, and 2) the control group consisted of 45 patients with rib fracture, without PC. Blood sampling was performed on admission, on the second, third, and fifth day after the injury, and complications were monitored until the seventh day after the injury.

Inclusion criteria were as follows: persons of both sexes over 18 years of age, with isolated blunt chest injury and rib fracture who were observed and treated in the aforementioned institutions. Exclusion criteria were the following: persons under 18 years of age, patients with penetrating chest trauma, patients with BCT as part of polytrauma, and pregnant women.

Biomarkers of inflammation examined in the research were: fibrinogen, IL-6, and CRP. The level of fibrinogen in the serum was determined on the coagulometer BE Trombostat, (Behnk Elektronik, Norderstedt, Germany). Reference values for fibrinogen were 2–4 g/l. The level of IL-6 in the serum was determined by the immunochemical electrochemiluminescence immunoassay method on the immunochemical analyzer Cobas e411 (Roche, Basel, Switzerland). IL-6 reference values were 0.0–40.0 pg/ml. Serum CRP values were determined by standard International Federation of Clinical Chemistry methods on a Beckman Coulter/Olympus AU680 biochemical analyzer. Reference values for CRP were 0.0–5.0 mg/l.

PC are marked as: pneumothorax, hemothorax and hemopneumothorax. The diagnosis of PC was made through anamnestic, clinical examination and radiological examinations – standard radiography and multislice spiral computed tomography of the chest. All patients with PC underwent therapeutic chest drainage.

Statistical analysis was performed in the R software package (R Core Team, Vienna, Austria) [23]. Data are presented as mean ± standard deviation, or frequency and percentage. Comparison of continuous variables was performed by t-test and Mann–Whitney test. Comparison of categorical characteristics was performed using the χ^2 test. The discriminative ability of the tested biomarkers was assessed by receiver operating characteristic curve analysis. The null hypothesis was tested with a significance level of $p < 0.05$.

RESULTS

The study included 90 subjects (74 male and 16 female subjects). The demographic, clinical and biochemical characteristics are provided in Table 1. The mean age of the enrolled patients was 61.97 ± 13.87 (min 25 years, max 92 years). At the first measurement, there was no statistically significant difference in the investigated clinical parameters (Table 1).

Table 1. Demographic and clinical characteristics in groups

Group	Complications		Other		p
Age†	62.91 ± 14.32		61.05 ± 13.51		0.535[1]
Sex‡					
Male	37	(82.2%)	37	(82.2%)	1.000[2]
Female	8	(17.8%)	8	(17.8%)	
Number of ribs‡					
1	4	(8.9%)	9	(20%)	
2	8	(17.8%)	3	(6.7%)	
3	8	(17.8%)	5	(11.1%)	
4	6	(13.3%)	4	(8.9%)	
5	4	(8.9%)	6	(13.3%)	
6	3	(6.7%)	7	(15.6%)	
7	7	(15.6%)	1	(2.2%)	
8	1	(2.2%)	0	(0%)	
10	2	(4.4%)	0	(0%)	
11	1	(2.2%)	0	(0%)	
Multiple	1	(2.2%)	10	(22.2%)	
Glycemia†	7.18 ± 2.29		9.44 ± 11.05		0.812[3]
Fibrinogen†	5.45 ± 1.81		5.05 ± 1.28		0.453[3]
D-dimer†	1824.24 ± 1882.86		1917.93 ± 2925.19		0.245
CRP†	33.5 ± 37.63		24.45 ± 31.46		0.188[3]
PCT†	0.23 ± 0.39		0.24 ± 0.37		0.616[3]
Se†	19.49 ± 16.11		20.56 ± 18.93		0.716[3]
Uric acid†	292.69 ± 111.35		279.45 ± 100.99		0.704[3]

CRP – C-reactive protein; PCT – procalcitonin; Se – sedimentation;
[1]t-test;
[2]the χ^2 test;
[3]Mann–Whitney test;
†data are presented as mean ± standard deviation;
‡data are presented as count (%)

The values of fibrinogen, IL-6 and CRP on the second day were significantly higher in patients with PC after rib fractures in BCT ($p = 0.029$, $p = 0.017$, and $p = 0.025$, respectively). The values of fibrinogen and CRP on the third day were significantly higher in patients with PC after rib fractures in BCT ($p = 0.008$, $p = 0.008$) (Table 2).

The value of IL-6 on the second day was shown to have a good discriminative ability in assessing PC after rib fracture in BCT (AUC 0.782, $p = 0.029$). The cutoff value was estimated at 21.33 pg/mL (Table 3) (Figure 1).

DISCUSSION

This is the first prospective study in which the association between PC after rib fracture in BCT and serum levels of fibrinogen, CRP and IL-6 is statistically linked and revealed.

Recognizing which of the patients with rib fractures in BCT will develop PC is important for preventing them, and our research follows that line of thinking.

Table 2. Levels of inflammation biomarkers in pleural complication and non-complication groups after ribs fracture in blunt chest trauma as a function of time data are presented as mean ± SD

	IL-6	Fibrinogen	CRP
Day I			
Complications	53.13 ± 35.9	5.45 ± 1.81	33.5 ± 37.63
Others	49.49 ± 83.5	5.05 ± 1.28	24.45 ± 31.46
p-value[1]	0.181	0.453[3]	0.188[3]
Day II			
Complications	**29.57 ± 22.52**	**6.26 ± 1.65**	**57.8 ± 44.8**
Others	**12.63 ± 7.83**	**5.46 ± 1.33**	**41.37 ± 49.51**
p-value[1]	**0.029**	**0.017**	**0.025**
Day III			
Complications	21.39 ± 14.38	**6.86 ± 1.69**	**59.16 ± 42.69**
Others	13.78 ± 10.14	**5.95 ± 1.47**	**39.19 ± 38.71**
p-value[1]	0.105	**0.008**	**0.008**
Day V			
Complications	15.48 ± 9.73	6.5 ± 1.69	39.99 ± 39.2
Others	13.16 ± 10.87	6,00 ± 1.4	31.01 ± 42.35
p-value[1]	0.439	0.065	0.094

CRP – C-reactive protein;
[1]Mann–Whitney test

Table 3. The area under receiver operating characteristic curve, cut-off value, sensitivity and specificity in pleural complications assessment

	AUC	95% CI	Cut off value	Sensitivity (%)	Specificity (%)
IL-6	0.782	0.582–0.982	21.33	60	90.9
Fibrinogen	0.627	0.379–0.875	5.68	60	63.6
CRP	0.645	0.401–0.890	17.90	70	54.5

CRP – C-reactive protein; AUC – the area under the receiver operating characteristic curve; CI – confidence interval

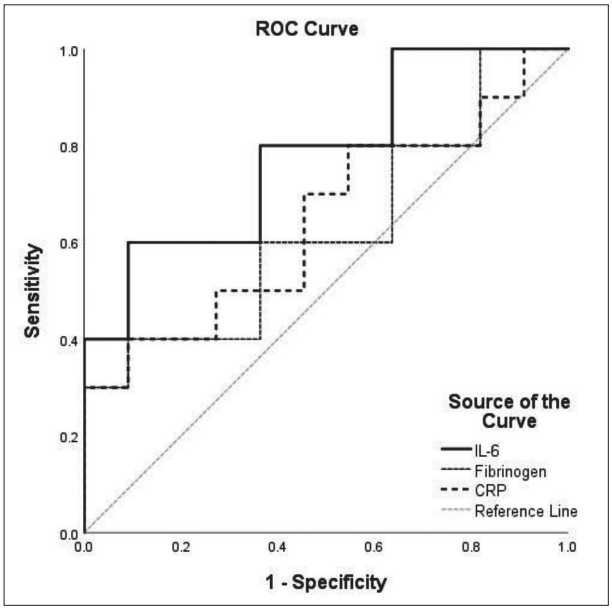

Figure 1. The receiver operating characteristic (ROC) curve of IL-6, fibrinogen, and C-reactive protein (CRP) on the second day in pleural complication assessment

Serum values of IL-6 on the second day and fibrinogen and CRP on the second and third day after injury in BCT were statistically significantly higher in patients with PC. This indicates that, as frequently used clinical markers of inflammation, fibrinogen, CRP and IL-6 can be used to predict the occurrence of PC after rib fractures in BCT, their timely repair, and that they can significantly replace clinical observation in these patients.

During our research we found out that there was an increase in blood fibrinogen values on the second and third day after injury in patients with PC in BCT with rib fracture, and not in the later period, which is in agreement with the results of the paper [24]. We believe that the role of fibrinogen as a DAMP molecule in this case is dominant in promoting the inflammatory reaction and in the process of coagulation in inflammation.

Our research has also shown that IL-6 levels were statistically significantly higher on the second day after injury in patients with PC after rib fractures in BCT. Moreover, our research has shown that there is a correlation between elevated levels of IL-6 in the early stages of trauma and the severity of the injury, which is in agreement with the results in the paper [25]. Also, our results are consistent with the view that IL-6 correlates with the severity of the injury, and not with the elapsed time since the injury, which is in agreement with the results in the paper [26]. All our patients who were exposed to violent BCT and who developed PC had elevated IL-6 values, which is in agreement with the previous findings [17].

The results of our research indicate that IL-6 can be used to predict the occurrence of PC after BCT with rib fracture, since serum levels of IL-6 on the second day after the injury are statistically significantly higher in patients with PC. The hypothesis that the level of IL-6 can be used in the stratification of patients for therapeutic intervention is confirmed by our finding of a good discriminative ability of IL-6 in the assessment of the occurrence of PC on the second day after rib fracture in BCT. Also, our results show that IL-6 levels are increased after injury and that IL-6 can be used as a biomarker in BCT, which is in agreement with other papers [10, 25].

In our research, we have come to the conclusion that in patients with PC and rib fracture in BCT, CRP values are statistically significantly higher on the second and third day after the injury. It was stated in agreement with the results that CRP values are highest on the second and third postoperative day, after orthopedic and abdominal surgery operations due to trauma [22, 27].

In traumatized patients, special attention should be paid to the cause of the increase in CRP levels, which can also be applied in patients with BCT [19]. Trauma and surgical intervention (due to tissue damage) cause a strong inflammatory response. All our patients with PC after rib fracture in BCT underwent surgical intervention – drainage of the chest, and we believe that the finding of the elevated CRP values in them is in agreement with the findings that the difference in peak CRP levels is partly a consequence of trauma, and partly a consequence of the surgical procedure after trauma [27]. Since an increase in the level of CRP also occurs after surgical procedures, and patients with PC in a large number of cases undergo therapeutic drainage of the chest, caution is needed in declaring CRP as a "marker of the occurrence of PC in BCT".

Some authors believe that low levels of CRP can be used to exclude the existence of complications in orthopedic surgery [27]. Our results show that normal CRP values significantly exclude the existence of PC in BCT. Regardless of that, we believe that additional research is needed in order to confirm with even greater certainty that a low level of CRP, analogous to the previous one, can be used to rule out PC after a rib fracture in BCT.

The results of our research are in agreement with similar results that can be found in the available literature related to trauma in orthopedics and abdominal surgery.

CONCLUSION

The available literature offers scarce data on the possibility of using fibrinogen, IL-6 and CRP as predictors of possible PC after rib fractures in BCT.

Based on the results of our research, it can be concluded that biomarkers of inflammation, fibrinogen, IL-6 and CRP can be used as predictors of PC after rib fractures in BCT.

The combination of fibrinogen, IL-6 and CRP after rib fracture in BCT can significantly replace clinical observation in these patients.

In patients with PC after rib fractures in BCT, fibrinogen has the highest values on the second and third day after the injury and as such can be used as a predictor of PC.

In patients with PC after rib fractures in BCT, IL-6 has the highest values on the second day after the injury. Due to its good discriminative ability in assessing the occurrence of PC on the second day after rib fracture in BCT, IL-6 can be used in stratifying patients for therapeutic intervention.

CRP in the prediction of PC is significant on the second and third day after a rib fracture in BCT. CRP values within the normal range largely exclude the existence of PC after rib fractures in BCT. If there is an increase in the level of CRP, special attention should be paid to searching for the cause of this increase.

Further prospective studies are needed to fully reveal the role of other inflammatory biomarkers in patients with rib fracture complications in BCT.

ACKNOWLEDGMENT

This research is a part of the PhD thesis to be defended this year: Pavlović M. Inflammatory biomarkers as predictors of pleuropulmonary complications after rib fracture in blunt chest trauma [dissertation]. Niš (Serbia): University of Niš; 2023.

Conflict of interest: None declared.

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Значај фибриногена, интерлеукина-6 и Ц-реактивног протеина као предиктора плеуралних компликација после прелома ребара у тупој трауми грудног коша

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САЖЕТАК

Увод/Циљ Преломи ребара су чести у тупој трауми грудног коша (ТТГК), а када су удружени са плеуралним компликацијама (ПК) – пнеумотораксом, хематотораксом и хематопнеумотораксом, лечење ових пацијента је продужено и отежано. Без могућности да се предвиде ПК након прелома ребара у ТТГК, већина лекара је приморана да иницијално у лечењу ових пацијената примени опсервацију и конзервативни третман.

Циљ истраживања је утврђивање који су од истраживаних биомаркера инфламације – фибриноген, ИЛ-6 и ЦРП у статистички значајној мери повезани са настанком ПК након прелома ребара у ТТГК, што би се користило у стратификовању пацијената за хоспитализацију и даље лечење.

Метод Проспективним истраживањем било је обухваћено 90 пацијената са преломима ребара изазваних ТТГК. Групу испитаника чинило је 45 пацијената са преломом ребара и присутним ПК, а контролну групу чинило је 45 пацијената са преломом ребара без ПК. Узорковање крви је вршено при пријему, другог, трећег и петог дана од повређивања, а праћење појаве ПК је било до седмог дана од повређивања.

Резултати Серумске вредности ИЛ-6 другог дана и фибриногена и ЦРП другог и трећег дана по повређивању биле су статистички значајно веће код пацијента са ПК, а ИЛ-6 је показао добру дискриминативну способност у процени настанка ПК другог дана по прелому ребара у ТТГК.

Закључак Испитивани биомаркери инфламације – фибриноген, ИЛ-6 и ЦРП могу се користити као предиктори ПК након прелома ребара у ТТГК и њихова примена у значајној мери може заменити клиничку опсервацију.

Кључне речи: тупа траума грудног коша; преломи ребара; плеуралне компликације; фибриноген; ИЛ-6; ЦРП

DOI: https://doi.org/10.2298/SARH221024075M
UDC: 616.366-089.878-074:577.1

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Insulin sensitivity and C-reactive protein levels after laparoscopic and open cholecystectomy – seven-day-follow-up

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SUMMARY

Introduction/Objective The development of acute insulin resistance after surgery intervention is associated with the type and magnitude of operation and tissue injury.
The aim of our study was to compare insulin sensitivity assessed by homeostatic model assessment of insulin resistance (HOMA-IR) and C-reactive protein (CRP) before and after laparoscopic and open cholecystectomy during seven days follow-up.

Methods In total, 92 patients were divided into two groups: laparoscopic cholecystectomy (Group 1) (n = 61) and open cholecystectomy (Group 2) (n = 31). Glucose, insulin and CRP levels were measured at day 0 and at postoperative days one, three and seven. Glucose, insulin and CRP were determined using commercial assay on Roche Cobas 6000 automated analyzer (Roche Diagnostics, Manheim, Germany).

Results There was no statistical difference between studied groups concerning age (p = 0.626), body mass index (p = 0.548), glucose (p = 0.947), insulin (p = 0.212), HOMA-IR (p = 0.390) and CRP (p = 0.546) at day 0. At day one, higher values of CRP were found in group 2 compared with group 1 (p = 0.046). At day three, significantly higher values of glucose and HOMA-IR were found in group 2 compared with group 1 (p = 0.025, p = 0.036, respectively).

Conclusion Increase in CRP precedes deterioration of insulin sensitivity measured by HOMA-IR after cholecystectomy. Impairment of insulin sensitivity was more pronounced at postoperative day three in group with open cholecystectomy. On the basis of our results, laparoscopic cholecystectomy induced less impairment in insulin sensitivity and lower inflammatory response.

Keywords: HOMA-IR; CRP; laparoscopic cholecystectomy; open cholecystectomy

INTRODUCTION

Development of perioperative hyperglycemia during surgery may result in appearance of insulin resistance [1]. Insulin resistance development during perioperative period may induce complications in major abdominal surgery [2]. It was shown that cholecystectomy may result in variety of metabolic changes [3].

Definition of postoperative insulin resistance is an effect of insulin below normal for the effect of insulin for glucose, protein, and/or fat metabolism in the period after the operation [4]. Acute insulin resistance development after elective surgery depends on the type and magnitude of operation and tissue injury [5, 6, 7]. It was observed that the increase in blood glucose after operation starts simultaneously with the decrease in peripheral glucose uptake due to development of insulin resistance [8]. Such postoperatively developed insulin resistance is temporary phenomenon and last approximately for at least five days after uncomplicated open cholecystectomy. After that period insulin sensitivity normalizes with the recovery of the patient [9]. Homeostatic model assessment of insulin resistance (HOMA-IR) is frequently employed method in everyday practice because of its convenience [7, 10]. HOMA-IR method has been used from practical standpoints as an alternative to the hyperinsulinemic normoglycemic clamp in studies of surgery induced insulin resistance which is established as a gold standard for the measurement of insulin resistance [2, 11]. Determination of insulin sensitivity by HOMA IR was therefore accepted as a simple and inexpensive alternative to more sophisticated techniques in the evaluation of in vivo insulin sensitivity in humans [7, 12]. A direct positive correlation between the concentrations of C-reactive protein (CRP) and the severity of postoperative inflammation was demonstrated [13, 14] as well as evidence about link between inflammation and insulin resistance [15, 16].

Hence, the aim of our study was to measure insulin sensitivity by HOMA-IR and CRP in a group of our patients after laparoscopic and open cholecystectomy in early perioperative period.

Received • Примљено: October 24, 2022
Revised • Ревизија: August 2, 2023
Accepted • Прихваћено: August 15, 2023
Online first: August 28, 2023

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METHODS

The non-randomized, prospective study on 92 patients with cholecystectomy was conducted at the Clinic for Emergency Surgery of the University Clinical Center of Serbia in Belgrade. Exclusion criteria were known diabetes Type I or II, liver, renal (serum creatinine over 150 mol/l) or heart failure, mental diseases, malignancy and severe infection. All the patients were divided into two groups: group with laparoscopic cholecystectomy and group with open cholecystectomy. Laparoscopic cholecystectomy was performed in 61 patients (Group 1) and open cholecystectomy in 31 patients (Group 2).

Fasting glucose, insulin and CRP were determined before operation (baseline, day 0) and one, three and seven days after the operation. Glucose was measured using commercial assay on Roche Cobas 6000 automated analyzer (Roche Diagnostics, Manheim, Germany). Reference range for glucose was 3.9–6.1 mmol/L. The serum CRP concentration was measured using commercial assays on Roche Cobas 6000 automated analyzer. Reference range for CRP was 0–10 mg/L. The serum insulin measurement was done by an electrochemiluminescence immunoassay on Roche Cobas 6000 automated analyzer. Insulin assay has a measurement range of 0.20–1000 μU/ml with a limit of detection of 0.20 μU/ml. The validation of the Roche Insulin assay in our laboratory revealed intra- and inter-assay coefficients of variation between 1% and 4.5%. Reference values for fasting insulin was < 25 μU/L. Homeostatic model assessment-insulin resistance (HOMA-IR) is based on fasting glucose and insulin levels and the index is calculated as follows: HOMA-IR = Go × Io /22.5, where Go = fasting glucose concentration (mmol/L), Io fasting plasma insulin concentration (μU/mL).

Data are expressed as mean ± standard deviation (SD). Student's t test was used for comparison between groups. Non-normally distributed data are presented as median and interquartile range (25^{th}, 75^{th} percentile) and compared by Mann–Whitney U-test. Pearson's χ^2 test was used comparison between groups for data presented as frequencies and percentages. Pearson correlation was used for testing the correlations between the examined variables. General linear model for repeated measures was used for evaluating the changes in measured variables from 0 to the first, third and seventh day and changes are presented by boxplot. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY, USA). In all test, p value < 0.05 was considered to be statistically significant.

The study protocol was approved by Ethics Committee of Faculty of Medicine, University of Belgrade (No 29/IV-11), and all patients gave informed consent to participate in the study.

RESULTS

Baseline anthropometric and laboratory characteristics of this study population are presented in Table 1. There was no statistical difference between studied groups concerning age (p = 0.626), body mass index (p = 0.548), glucose (p = 0.947), insulin (p = 0.212), HOMA-IR (p = 0.390) and CRP (p = 0.546) at day 0.

Table 1. Baseline characteristics of studied population

Variable	Group 1 (n = 61)	Group 2 (n = 31)	p
Age*, years	51.2 ± 15	57.5 ± 13.5	0.626
Male sex, n (%)	29 (48%)	16 (52%)	0.712
Body mass index*, kg/m^2	24.6 ± 1.2	24.7 ± 1.7	0.548
Glucose*, mmol/L	4.6 ± 0.91	4.63 ± 0.83	0.947
Insulin**, μU/mL	5.7 (7.7)	6.6 (5.3)	0.212
Homeostatic model assessment of insulin resistance**	1.3 (1.8)	1.2 (1.3)	0.390
High sensitivity C-reactive protein**	8 (9.8)	8 (1)	0.546

*Data are presented as mean ± standard deviation
**Data are presented as median with interquartile range

Table 2. Changes in glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and high sensitivity C-reactive protein (hs-CRP) during follow-up

Variable	Baseline	Day 1	Day 3	Day 7
Glucose*, mmol/L				
Group 1	4.60 ± 0.91	5.10 ± 1.09	4.70 ± 0.99	4.63 ± 0.72
Group 2	4.63 ± 0.83	5.80 ± 1.58	5.23 ± 1.19	4.71 ± 0.56
Insulin**, μU/mL				
Group 1	5.7 (7.7)	10.1 (10.7)	9.8 (4.8)	5.7 (6.2)
Group 2	6.6 (5.3)	12.1 (9)	10.6 (7.7)	6.9 (4.9)
HOMA-IR**				
Group 1	1.3 (1.8)	2.3 (3)	2 (1.3)	1.2 (1.4)
Group 2	1.2 (1.3)	2.9 (2.9)	2.2 (1.8)	1.3 (1)
CRP**, mg/L				
Group 1	8 (9.8)	36 (77.9)	43.5 (64.4)	23 (51.6)
Group 2	8 (1)	56 (39.6)	72.1 (55.2)	27 (45)

Group 1 – laparoscopic cholecystectomy; Group 2 – open cholecystectomy
*Data are presented as mean ± standard deviation
**Data are presented as median with interquartile range

Changes in glucose, insulin, HOMA-IR and CRP during the study period (from day 0 to day seven) are presented in Table 2.

There was significant difference in glucose over time in group 1 (p = 0.017) and group 2 (p < 0.001). In group 1, glucose levels were significantly higher the first day after operation compared with baseline 0 day (p = 0.024), continue to decrease significantly on day three and reach its lowest level at day seven, significantly lower than day one (p = 0.042). The glucose levels in group 2 follow the same trend, but with more significant increase of glucose the first day after operation (p < 0.001) and decrease of glucose values at day seven compared with day one (p = 0.001).

There was significant difference in insulin over time in group 1 (p < 0.001) and group 2 (p < 0.001). In group 1, insulin had its highest level at day one, decreased significantly at day three (compared with day1) (p = 0.001) and finally reached its lowest level at day seven compared with values measured at day three (p = 0.012). In group 2, the same trend was noticed: insulin increased significantly after operation compared with values at day 0 (baseline

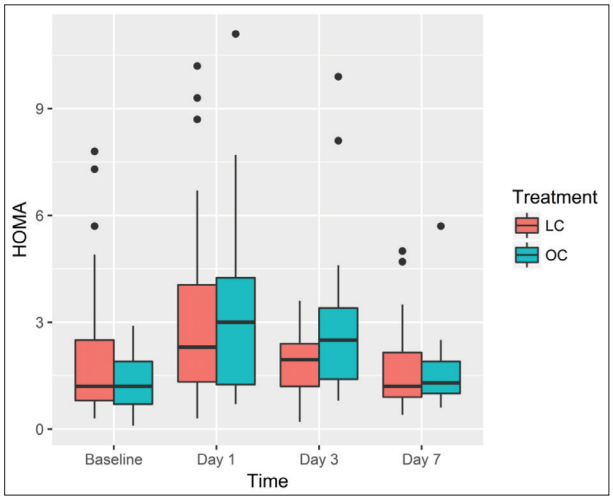

Figure 1. Homeostatic model assessment of insulin resistance (HOMA-IR) at day zero and one, three, and seven after laparoscopic cholecystectomy (LC) and open cholecystectomy (OC)

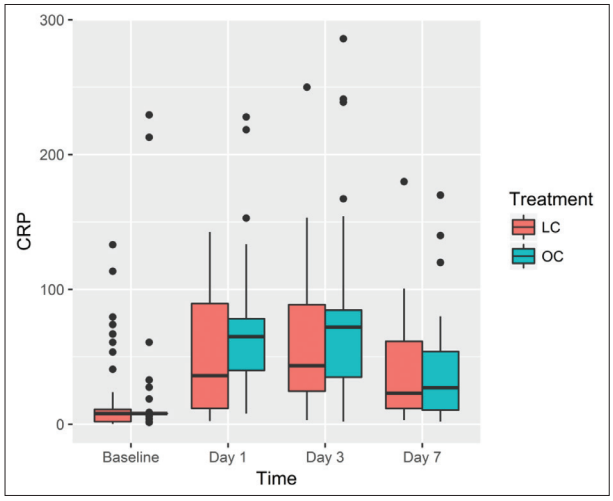

Figure 2. Changes in high sensitivity C-reactive protein (hs-CRP) at day zero and one, three, and seven after laparoscopic cholecystectomy (LC) and open cholecystectomy (OC)

value) ($p < 0.001$), and significantly decrease at day seven (compared with day three) ($p < 0.001$).

Changes of HOMA-IR at day 0 and one, three and seven after laparoscopic and open cholecystectomy are presented at Figure 2. In group 1, HOMA-IR values increased significantly at day one compared with day 0 ($p < 0.001$) and significantly decreased at day seven compared with day three ($p = 0.012$). In group 2, HOMA-IR was significantly higher at day one (after operation) compared with baseline and it significantly decrease at day seven compared with day three ($p < 0.001$).

There is significantly higher values of glucose and HOMA-IR at day three ($p = 0.025$, $p = 0.036$, respectively) in group 2 in comparison with group 1.

Changes of CRP at day 0 and one, three and seven after laparoscopic and open cholecystectomy are presented at Figure 2. CRP increased significantly at day one, three, and seven in comparison with day 0 ($p < 0.001$) in both groups. At day one, CRP was significantly higher in group 2 (56.0 ± 39.6 *vs*. 36.0 ± 77.9; $p = 0.046$) in comparison with group 1 (Figure 2).

DISCUSSION

Stress response to surgery depends on the extent of the injury. Insulin resistance during the surgery may be associated with increased inflammation, organ dysfunction and mortality [17, 18]. It was demonstrated that cholecystectomy may increase insulin resistance and diabetes, although mechanisms of connections between cholecystectomy and insulin release and sensitivity are still not clear [19]. It was suggested that abnormal metabolic consequences may be generated by abnormal transintestinal flow of bile acids that produce metabolic signals that are performed without gallbladder rhythmic function [20].

Insulin resistance develops after surgery as a part of the metabolic response to stress [21]. The degree of insulin resistance is related to the magnitude of operation [10, 22]. Postoperative insulin resistance is mainly developed due to two reasons – perioperative starvation and release of stress hormones and inflammatory cytokines, including CRP among them. Development of insulin resistance among elective surgical patients in modern surgical practice may be harmful since it prolongs recovery and leads to postoperative complications [21, 22]. Earlier published data indicate that the decrease in insulin sensitivity lasts over a week even after moderate surgical stress [23]. In clinical practice, different methods were used for the measurement of perioperative changes of insulin sensitivity, from simple methods based on fasting plasma glucose and insulin, like HOMA-IR, up to more laborious ones, like minimal model (intravenous glucose tolerance test with frequent sampling of glucose and insulin) up to gold standard for the measurement of insulin sensitivity, like hyperinsulinemic euglycemic clamp [7, 21]. Based on the experience of the investigators and the equipment which they used, different proposals were published – from one that the static simple methods are suitable for clinical studies, up to the claims that clamp method is superior to all the others, and that it measures changes in insulin sensitivity, while HOMA-IR measures something different [2, 24]. Previously, it was suggested that HOMA-IR can be used to assess the effects of treatment [25]. It was suggested that HOMA-IR estimates of insulin sensitivity are usually not normally distributed [25]. Our findings confirmed this statement and we used medians with interquartile ranges to present data without normal distribution (Table 1). Our results demonstrated that HOMA-IR, as marker of insulin resistance, significantly increased in a group with open cholecystectomy. Similar results with the increase in insulin resistance in the first day after surgery was demonstrated by others [26]. There was no significant difference in HOMA-IR between day 0 and day seven ($p > 0.05$). Previous studies have shown that administration of different forms of oral carbohydrate supplementation before the cholecystectomy resulted in lower values of postoperative HOMA-IR [26, 27]. In a study with a hyperinsulinemic normoglycemic

clamp the fall in insulin sensitivity after surgery was lower in patients after laparoscopic cholecystectomy (22 +/- 2%) compared with patients after open cholecystectomy (49 +/- 5%) [28]. Different results were reported concerning postoperative levels of CRP – from lack of significant difference in the CRP levels between open and laparoscopic cholecystectomy [29], to a significantly higher increase in serum CRP levels in patients following open cholecystectomy in comparison to laparoscopic cholecystectomy [13]. Our study indicates that the level of CRP increased significantly during early postoperative period in both groups in comparison with day 0, but significantly higher increase of CRP was established at day one in the group with open cholecystectomy in comparison with the group with laparoscopic cholecystectomy. This result is consistent with findings of other investigators and support assumption that minimal invasive surgical procedures such as laparoscopic cholecystectomy impairs inflammatory response less [30].

CRP is a protein of acute phase and starts to increase 4–6 hours after tissue trauma and reaches its peak at 48 hours and starts to fall gradually after 72 hours after surgery without complications [16]. In our study CRP increased at first and third days after operation in both groups and gradually falls at day seven. Peak CRP values were achieved in both groups at day three. CRP peak values were higher in a group with open cholecystectomy. In early postoperative period we observed a decrease in insulin sensitivity, measured through an increase in HOMA-IR index. Values of HOMA-IR were higher in a group with open cholecystectomy than in a group with laparoscopic cholecystectomy, indicating a greater magnitude of surgical trauma. Previously it was shown that insulin resistance during surgical trauma is produced by elevated fatty acid concentration, decreased uptake of glucose in muscled and increased production of glucose in liver. In our study we detected insulin increase in the circulation in both group at days one and three. Insulin values were higher at respective days (days one and three) in a group where open cholecystectomy were performed. In our previous investigation we demonstrated a correlation between CRP and HOMA-IR in some surgical operation, indicating a possible interrelation between increase in cytokines impairment in insulin sensitivity [16]. In our study, comparison between open and laparoscopic cholecystectomy demonstrated less postoperative reduction in insulin sensitivity in a group with laparoscopic cholecystectomy. Such findings may indicate that this could be one of factor for faster recovery after laparoscopic cholecystectomy.

CONCLUSION

Change in insulin resistance during the early postoperative period after cholecystectomy is one of the most fundamental reactions to injury and stress. Increase in CRP precedes deterioration of insulin sensitivity, indicating the role of inflammation in the development of insulin resistance after surgical procedures. On the basis of our results, laparoscopic cholecystectomy causes less impairment in insulin sensitivity and inflammatory response then open procedure. The use of HOMA-IR may be useful for fast and easy determination of insulin sensitivity changes in perioperative period in abdominal surgery patients. Keeping metabolism under optimal control should be one of the priorities for the benefit of the surgical patients, allowing early implementation of preventive measures against further deterioration of insulin sensitivity.

Conflict of interest: None declared.

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Инсулинска сензитивност и вредности Ц-реактивног протеина после лапароскопске и отворене холецистектомије у току првих седам постоперативних дана

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САЖЕТАК

Увод/Циљ Развој акутне инсулинске резистенције после хируршке интервенције је повезан са типом и величином операције и оштећењем ткива.

Циљ наше студије је поређење инсулинске сензитивности процењене применом хомеостатског модела за процену инсулинске резистенције (ХОМА-ИР) и Ц-реактивног протеина (ЦРП) пре и после лапараскопске и отворене холецистектомије током првих седам постоперативних дана.

Методе Испитана су 22 болесника који су подељени у две групе: група са лапараскопском холецистектомијом (група 1) ($n = 61$) и група са отвореном холецистектомијом (група 2) ($n = 31$). Гликемија, инсулин и ЦРП су мерени у нултом дану и постоперативно у првом, трећем и седмом дану. Гликемија, инсулин и ЦРП су одређивани коришћењем комерцијалног прибора на аутоматском анализатору *Roche Cobas* 6000 (*Roche Diagnostics*, Манхајм, Немачка).

Резултати Није било статистички значајне разлике између испитиваних група у погледу старости ($p = 0,626$), индекса телесне масе ($p = 0,548$), гликемије ($p = 0,947$), инсулина ($p = 0,212$), ХОМА-ИР ($p = 0,390$) и ЦРП ($p = 0,546$) у нултом дану. Првог дана, више вредности ЦРП нађене су у групи 2 у поређењу са групом 1 ($p = 0,046$). Трећег дана, значајно више вредности гликемије и ХОМА-ИР нађене су у групи 2 у поређењу са групом 1 ($p = 0,025$, $p = 0,036$, респективно).

Закључак Повишење ЦРП претходи погоршању инсулинске сензитивности измерене помоћу ХОМА-ИР после холецистектомије. Оштећење инсулинске сензитивности је било израженије трећег постоперативног дана у групи са отвореном холецистектомијом. На основу наших резултата, лапараскопска холецистектомија изазива мање оштећење инсулинске сензитивности и нижи инфламаторни одговор.

Кључне речи: ХОМА-ИР; ЦРП; лапараскопска холецистектомија; отворена холецистектомија

DOI: https://doi.org/10.2298/SARH230110078P
UDC: 618.5-089.888.61-089.5(497.11)"2021/2022"

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Evaluation of patient satisfaction with provided spinal anesthesia for Cesarean delivery – a survey in Leskovac General Hospital, Serbia

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SUMMARY

Introduction/Objective To ensure that all patients receive the best possible anesthetic care, it is essential to continuously evaluate our practices and strive for improvement.
The objective of this study was to internally assess the anesthesia services provided during the peripartum period.

Methods The Anesthesiology Department of Leskovac General Hospital, Serbia (LGH) aimed to evaluate patient satisfaction with spinal anesthesia (SA) for Cesarean delivery (CD) using a questionnaire consisting of four open-ended questions. Following Institutional Review Board approval, an institutional-based survey was conducted from August 2021 to July 2022. During the study period, 624 (40.6%) of the total 1535 deliveries in LGH were CDs, with 311 (49.8%) of them performed under SA. Of the patients who underwent CD under SA, 87 agreed to anonymously complete the questionnaire.

Results Although patients had sufficient space to provide detailed responses, the majority of participants opted for brief answers, often limited to "yes" or "no". Of the surveyed participants, 78% were informed about SA for CD before delivery, and 96.6% expressed satisfaction with the information provided during the preoperative anesthesiologist's visit. Additionally, the majority of participants (94.3%) reported satisfaction with the postoperative analgesia they received.

Conclusion Our patients expressed high levels of satisfaction with the preoperative anesthesiologist's visit and the SA provided for CD. However, there is a need to improve antenatal education for expectant mothers in the field of anesthesia. Conducting a new and more detailed survey would be necessary to further explore the influence of patient education and socio-economic status on patient satisfaction.

Keywords: spinal anesthesia; cesarean delivery; patient satisfaction; quality improvement

INTRODUCTION

To ensure that all patients receive the best possible anesthetic care, it is necessary to continually examine our practices, methods, and opportunities for improvement. This quality improvement strategy should be an integral part of everyday anesthesia practice, where we evaluate what we do, how we do it, and how we can do it better. The Society for Obstetric Anesthesia and Perinatology has published guidelines and recommendations for peripartum care, which we have implemented to the best of our ability [1].

The measurement of anesthesia patient experience is an emerging public and academic focus [2]. The patient experience has a direct effect on the patient's opinion of the quality of care that was received. The purpose of this study is to internally evaluate the anesthesia services we provide during the peripartum period at the Leskovac General Hospital, Serbia (LGH). We hope to improve on areas requiring assistance and acknowledge our team for its success. This is the first study of its kind in the obstetric anesthesia in Serbia to our knowledge.

METHODS

The Anesthesiology Department of LGH wanted to evaluate the patient satisfaction with provided anesthetic care for Cesarean delivery (CD) via a questionnaire. Following the Institutional Review Board approval (approval no. 6528/2), an institutional-based survey was conducted from August 2021 to July 2022. Every patient who had CD done under SA was offered to participate in the survey. Consent was obtained after explaining all the study details, including voluntary inclusion and data confidentiality. The inclusion criteria included patients at least 18 years of age, and the ability to complete a questionnaire. The exclusion criterion was a rejection of participation in the survey. We interviewed the patients on the second postoperative day.

During the study period (from August 2021 to July 2022), there were 1535 deliveries in LGH,

Received • Примљено: January 10, 2023
Revised • Ревизија: July 1, 2023
Accepted • Прихваћено: August 20, 2023
Online first: August 30, 2023

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and 624 (40.6%) of them were CDs. There were 311/624 (49.8%) CDs done under SA (Table 1). In total, 87 patients who had CD done under SA accepted to fill out the questionnaire anonymously and were enrolled in the study.

Table 1. The total number of deliveries at Leskovac General Hospital during the study period

Type of delivery	Number of patients	Percentage
Total	1535	100
Vaginal delivery	911/1535	59.4
CD	624/1535	40.6
CD done under GA	313/624	50.2
CD done under SA	311/624	49.8
Survey participants	87/311	28

CD – Cesarean delivery; SA – spinal anesthesia; GA – general anesthesia

The questionnaire was printed on a card in an envelope containing four open-ended questions (Figure 1). The first question was: "Did you have any information or knowledge about spinal anesthesia or labor analgesia before your procedure?" The second was: "Did your anesthesiologist explain the procedure and communicate with you so that you could understand the procedure?" The third was: "Was your pain well-controlled during your stay in the hospital?" And the fourth was: "Would you use the same anesthesia technique again?" There were no offered answers. Patients were able to write what they wish, on their own.

In LGH, SA for CD is performed using 12.0–15.0 mg of 0.5% bupivacaine/levobupivacaine, along with 15–25 mcg of fentanyl (based on the patient's body habitus). Efforts to implement intrathecal (IT) morphine use were not successful. Only several anesthesiologists use it occasionally. However, we use exclusively pencil-point needles 25 G (Pencan®, BBraun Melsungen AG, Melsungen, Germany).

This study, done according to the Declaration of Helsinki, was approved by the Ethical Committee of LGH (approval no. 6528/2).

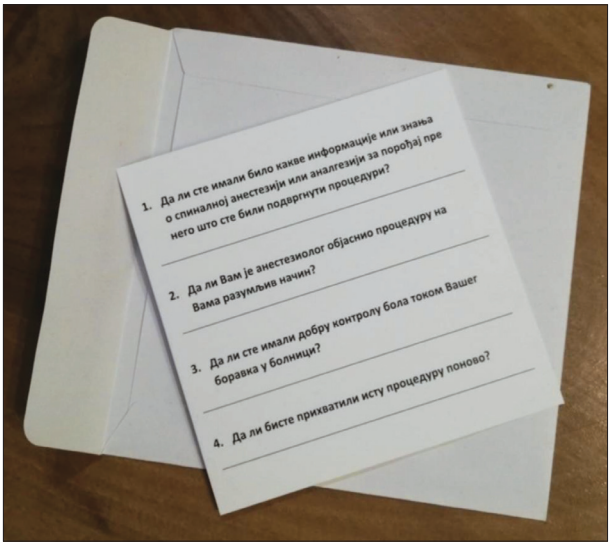

Figure 1. Questionnaire (printed card in the envelope)

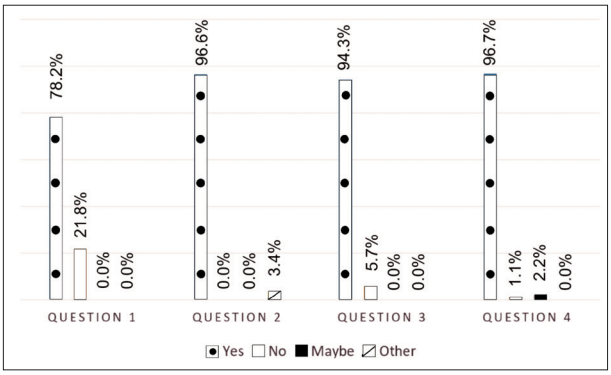

Figure 2. Patients' answers to the questions

RESULTS

The majority of patients provided brief answers, often limited to "yes" or "no", even though they had the option to write longer sentences (Figure 2).

In total, 68 of 87 patients (78.2%) were informed about the usage of SA for CD before their hospital admission. During the preoperative visit, the approach of the anesthesiologist was deemed satisfactory by most patients (96.6%). Only three out of 87 patients (3.4%) had difficulty fully understanding the anesthesiologist's explanation of the SA procedure.

A significant majority of patients (94.3%) reported good postoperative analgesia. However, five out of 87 patients (5.7%) expressed dissatisfaction with the provided postoperative analgesia at times during their hospital stay. These patients experienced periods of well-controlled pain followed by breakthrough pain that lasted longer than expected.

Almost all surveyed patients expressed high levels of satisfaction with SA for CD. Only one patient (1.1%) stated that she would never accept SA for CD again. Two patients (2.2%) had some doubts about their experience, responding 'maybe' when asked if they would accept SA for their next CD.

DISCUSSION

As early as the 1960s, the fields of marketing and healthcare began collaborating to understand patient satisfaction [3]. Patient satisfaction is a subjective, complex, and multi-dimensional measure of healthcare system functioning influenced by cultural, socio-demographic, cognitive, and affective factors [4]. It is a concept in healthcare system evaluation that quantifies and scores specific services based on subjective experiences and affective reactions [3, 5]. Patient satisfaction is the result of patients' expectations and experiences after receiving services from healthcare providers [5]. If patients receive lower or weaker service than their expectations, they may be dissatisfied. Conversely, if the received service meets or exceeds their expectations, patient satisfaction will be higher [5].

Improving the quality of healthcare provision involves identifying current problems. One way to recognize such issues is by assessing patient satisfaction [3]. Considering patients' opinions helps establish appropriate policies,

administrative practices, and resource allocation priorities [3].

Some studies [5–8] identified a range of non-modifiable factors affecting patient satisfaction, such as socio-demographic characteristics like age, sex, education, occupation, and marital status. Furthermore, patient satisfaction is associated with many modifiable factors, such as convenience, including the availability of services (drugs, ordered labs, and X-ray in the hospital), accessibility of services (waiting time, cost of services, transport to the service), and clinician-patient communication [5, 7]. Many anesthesiologists and surgeons believe that patient satisfaction with their perioperative experience is a function of technical variables such as surgical and anesthetic techniques. However, patients may not always have the comprehensive perspective or expertise required to make such evaluations. Furthermore, their satisfaction reflects their subjective impressions regarding staff hospitality, physician-patient communication, nurse-patient communication, provided information about the perioperative course, and overall perioperative experience [7, 8, 9]. Involvement in decision making significantly increases patient satisfaction [10].

It was found that older patients, poor patients, female patients, patients with lower levels of education, patients not working for private enterprises (or foreign enterprises), and patients in rural parts of countries with limited healthcare resources and ongoing healthcare reforms reported higher levels of overall satisfaction [6]. On the contrary, Endale Simegn et al. [8] showed that males and patients from urban neighborhoods had higher satisfaction.

Factors associated with women's satisfaction with skilled delivery care were wanted pregnancy, planned delivery at a health facility, ambulance service, privacy, short waiting time and duration of labor, proper management of labor pain, healthy newborn outcomes, and the opportunity to breastfeed the baby within the first hour of life [11,12]. Implemented enhanced recovery after surgery and CD also improves patient satisfaction [13]. Involvement in decision making, and fulfilment of expectations are better predictors of a positive birth experience than factors such as pain and medical intervention [14]. An inverse relationship between preoperative anxiety and maternal satisfaction in patients undergoing CD is well known [15]. However, a recently published randomized controlled trial by Singh and Heralal [16] showed that the use of a simple educational anesthetic video might be associated with reduced anxiety and improved maternal satisfaction in patients scheduled for elective CD under regional anesthesia (RA).

A higher level of satisfaction with the childbirth experience is also related to satisfactory antenatal care [12, 14]. Brinkler et al. [14] have shown that good quality antenatal information on analgesia and anesthesia significantly influences parturients' confidence in making decisions about analgesia and their satisfaction with the analgesia used. Good antenatal preparation may reduce the time an anesthesiologist spends obtaining consent for interventions. Improvements in information provision and retention require a coordinated approach with the services that women already use and trust, such as their obstetricians, midwives and antenatal classes. As anesthesiologists, we can offer support to these colleagues to promote antenatal delivery of information regarding peripartum anesthesia care [14].

Maternal satisfaction had immediate and long-term effects on their health. Women who feel a lack of control during the delivery, those who are dissatisfied with their pain relief, and those who undergo unplanned procedures are more likely to develop a negative birth experience. Such experience puts them at an increased risk of postnatal depression, and post-traumatic stress disorder [14]. Dissatisfied parturients decrease the use of maternal health services, which influences an increasing rate of maternal morbidity and mortality [11]. Disrespect and abuse of women during childbirth are decisive factors in skilled delivery care utilization, especially in low- and middle-income countries. The birth experience in one labor has a lasting effect on subsequent labors. Both CD and the use of non-pharmacological analgesia (such as water, transcutaneous electrical nerve stimulation, hypnobirthing) in a previous labor were associated with less confidence in the current delivery [14]. The World Health Organization recommends monitoring and evaluating maternal satisfaction to improve the quality and efficiency of skilled delivery care [11].

Good patient-staff communication and effective pain control during a hospital stay may improve overall patient satisfaction [4, 17]. The absence of pain immediately after anesthesia recovery, the absence of postoperative nausea and vomiting, and the postoperative anesthesiologist's visit are the main factors significantly contributing to higher patient satisfaction with perioperative anesthesia services [8, 9]. Furthermore, patients who underwent surgery under SA had higher satisfaction scores than those under general anesthesia (GA) [8, 9]. The level of satisfaction with RA was higher in the of 18–25 age group, male gender, patients with previous RA experience, and patients who received comprehensive information about RA during the preoperative anesthetic evaluation. Dissatisfaction with RA was influenced by failed SA during surgery [18].

It has been observed that patients evaluated the care received during their hospital stay differently at different time points. Joseph at al. [19] compared the orthopedic patient satisfaction scores given two days after admission to an academic hospital with their satisfaction scores obtained four to six weeks after discharge via email or phone call. They reported that patient satisfaction after discharge was discordant with their inpatient experience. Patients had a better impression of the care they had received during the hospital stay several weeks following their discharge compared to the impression expressed in a survey conducted two days after hospital admission. However, Berning et al. [4] concluded in their prospective observational cohort study that the quality of recovery had only a marginal additional effect on total patient satisfaction with anesthesia and surgery. Based on expert opinion, the American Society of Anesthesiologists (ASA) and its Committee on Performance and Outcomes measurement (CPOM) determined that the survey should be administered within two weeks of discharge [20].

For accurate evaluation of patient satisfaction that may assist in quality improvement in clinical practices, validated

tools should be used [10]. The Consumer Assessment of Healthcare Providers and Systems (CAHPS) surveys belong to a family of validated tools. These questionnaires capture self-reported patient assessments of multiple points of contact during the healthcare experience, which can then be used to compare facility performance [21]. Covering multiple clinical settings, some of these surveys include several questions relevant to anesthesia care, but in general do not include questions related specifically to patient satisfaction for anesthesia services and thus may not be suitable for benchmarking.

The ASA recognized the importance of assessing and measuring patient satisfaction and experience with anesthesia. ASA CPOM had reviewed the existing literature on the assessment of the patient experience with anesthesia and developed an ASA recommended set of survey questions to be used to evaluate the patient experience with anesthesia care in 2013 [22]. Furthermore, the ASA recommended that anesthesia practices report the results of this survey to the Anesthesia Quality Institute. These data could help in improving anesthesia services and compare the anesthesia facilities throughout the country. The survey includes some general questions such as the time of survey, the surgical procedure, and patient demographic information. There are also a set of questions from the following dimensions: provided information, involvement in decision making, pain management, attention, practitioner-patient relationship, and anesthesia related sequelae. Three questions reflect global satisfaction with anesthesia. One question reflects global satisfaction with the facility. Response to questions was standardized to a five-point Likert Scale as this has been shown to be optimal for surveys of patient satisfaction [22].

The last update from the ASA on patient satisfaction measures relevant to anesthesia services was conducted in 2019 [20]. The update includes a list of available facility-based and practice-based tools. Facility-based surveys are well-validated surveys that are customized to specific service lines and care settings. They incorporate the official CAHPS program questions and serve as a good benchmark at the national level. However, these surveys usually require a third party to administer them, collect patient responses, and provide reports to anesthesia services, which results in additional costs.

Anesthesia practice-based surveys are newer and may have less established scientific rigor compared to facility-based surveys. These questionnaires specifically focus on anesthesia care. Anesthesia practice-based surveys can be administered either by vendors or locally without the involvement of vendors. While locally-instituted practice-based surveys can only be used to assess performance, they are less expensive.

We live in a country with limited healthcare resources and ongoing healthcare reforms. In our setting, patients are rarely prepared to complete complex surveys. Furthermore, analyzing and interpreting the surveys can be challenging. However, we have taken the first steps in communicating with our patients using a simple questionnaire. Although it does not allow us to compare our service with other anesthesia facilities, it provides us with valuable patient feedback. The answers from patients can highlight the main issues related to perioperative anesthesia services.

Our patients were primarily young females who expressed a high level of satisfaction. We did not analyze their social, economic, and educational backgrounds. More than 20% of our patients had no information about SA for CD before their preoperative visit with an anesthesiologist. This statistic suggests that anesthesiologists should play a role in educating expectant mothers during the antenatal period. However, 96.6% of the surveyed parturients had appropriate communication with an anesthesiologist prior to their surgery. This indicates that the approach of our anesthesiologists to patients is well-received.

Our survey has certain limitations. The answers to the questions are descriptive and qualitative in nature. The majority of patients (94.3%) expressed satisfaction with the treatment of postoperative pain during their hospital stay. However, there are no quantitative measurements of the care provided. We did not differentiate the duration of the postoperative hospital stay based on the number of postoperative days. Typically, post-Cesarean hospital stays range from four to five days. Nevertheless, it remains unclear what level of analgesia was provided immediately after anesthesia recovery, as well as the analgesic levels given after the day of surgery. To assess the influence of patient demographics (education and socio-economic status) on patient satisfaction, further follow-up studies are needed.

Although SA with IT morphine use has been recommended as the preferred anesthesia choice for CD [1], we had a low rate of IT morphine use and a significantly higher rate of CD performed under GA. It would be interesting to compare the satisfaction scores of patients who received IT morphine during SA to those who underwent SA without IT morphine. Furthermore, we could also compare the satisfaction scores of patients who underwent SA to those who had GA.

CONCLUSION

The patient feedback plays a crucial role in identifying communication gaps between the patients and hospital staff, and it can influence strategies to improve patient care. Our patients have expressed high levels of satisfaction with the preoperative visit by an anesthesiologist and the SA provided for CD. It is imperative for us to enhance antenatal education for expectant mothers in the realm of anesthesia by involving an anesthesiologist in the antenatal education team.

Conducting a new and more comprehensive survey would be necessary to elucidate the impact of patient education and socio-economic status on patient satisfaction. Additionally, a more detailed analysis of postoperative pain control could be conducted.

Conflict of interest: None declared.

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Евалуација задовољства пацијенткиња спиналном анестезијом за царски рез – истраживање у Општој болници „Лесковац“, Србија

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САЖЕТАК

Увод/Циљ Када настојимо да сви пацијенти буду што боље збринути, неопходно је стално преиспитивање како радимо и да ли је могуће да своје поступке унапредимо.
Циљ ове студије је унутрашња евалуација анестезиолошких техника пружаних током порођаја.

Методе Одељење анестезиологије Опште болнице „Лесковац“ у Србији желело је да процени задовољство пацијенткиња примљеном спиналном анестезијом (СА) за царски рез (ЦР) путем испитивања (тако што ће пацијенткиње попунити упитник од четири питања отвореног типа). Након сагласности Етичког одбора Опште болнице „Лесковац“, спроведено је испитивање током периода од августа 2021. до јула 2022. године. Током испитивања, од укупно 1535 порођаја 624 (40,6%) завршена су ЦР-ом, а од тога је било 311 (49,8%) порођаја са СА. Попуњавањем упитника у истраживање се укључило 87 пацијенткиња које су добиле СА за ЦР.

Резултати Највећи број пацијенткиња је дао одговор у краткој форми – „да“ или „не“, без додатних појашњења, без обзира на то што је било довољно простора за детаљнији одговор. Укупно 78% испитаница је одговорило да су биле претходно информисане о планираној техници анестезије и разлозима за извођење СА за ЦР, а 96,6% је било задовољно оствареним дијалогом с анестезиологом током преоперативне посете. Већина пацијенткиња (94,3%) била је задовољна и постоперативном контролом бола.

Закључак Наше пацијенткиње су врло задовољне преоперативним анестезиолошким прегледом и СА за ЦР. Неопходно је да се анестезиолог укључи у антенатално саветовалиште за труднице како би биле боље информисане о питањима везаним за анестезију. Неопходно је ново, детаљније испитивање како би се разјаснио утицај образовања и социоекономског статуса породиља на њихово задовољство као пацијенткиња.

Кључне речи: спинална анестезија; царски рез; задовољство пацијента; унапређење квалитета лечења

DOI: https://doi.org/10.2298/SARH230306076B
UDC: 616.31-006.6:575.22

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Impact of epidermal growth factor receptor gene rs1468727 polymorphism on survival of the patients with oral squamous cell carcinoma

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SUMMARY

Introduction/Objective Genetic aberrations and environmental factors are known to play an important role in oral squamous cell carcinoma (OSCC). The aim of the study was to clarify the association of epidermal growth factor receptor (*EGFR*) gene polymorphism rs1468727 with overall survival (OS) in patients with OSCC.

Methods The study comprised a total of 61 patients diagnosed with OSCC. The follow-up period for each patient was three years from the date of surgery and during that period their genotypes for rs1468727 polymorphism of the *EGFR* gene were identified using real-time polymerase chain reaction. Binary logistic regression was used to investigate the influence of various variables on survival. Additionally, the χ^2 test of independence and Man–Whitney U test were done to examine the interplay between two categorical variables and two independent samples.

Results Two variables demonstrated a statistically significant influence on OS: the TNM Classification of Malignant Tumors (TNM) stage and *EGFR* genotype. At the end of the follow-up period, 39 patients survived, with a noteworthy observation that more than half of the survivors had the *EGFR* rs1468727 CC genotype. The distribution of CC and CT genotypes was equal ($\chi^2 = 0.397$, df = 2, $p = 0.820$) among patients who deceased, indicating that no statistically significant correlations were found between OS and demographic or tumor-related characteristics.

Conclusion *EGFR* rs1468727 homozygote (genotype CC) and TNM stage showed statistically significant influence on OS in the follow-up period. This study highlights the potential significance of homozygote *EGFR* rs1468727 CC in assessing the prognosis and treatment outcomes of patients undergoing surgery for OSCC.

Keywords: oral squamous cell carcinoma; epidermal growth factor receptor; polymorphisms

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is a malignant head and neck tumor that affects the oral cavity, posing high morbidity and mortality risk [1]. OSCC is one of the most prevalent types of malignancies. It accounts for approximately 90% of all oral cavity cancers, signifying its prevalence and clinical relevance in the field of oncology [2, 3]. In Serbia, malignant tumors of the oral cavity account for approximately 1.1% of all malignant neoplasms [2].

OSCC is localized in various regions of the oral mucosa, including buccal mucosa, mobile tongue, gingiva, and mucosae of the floor of the mouth. Clinically, it can manifest as ulceration, infiltration, or vegetation, with leukoplakia or erythroplakia being precancers important for its development [4].

Numerous risk factors, including cigarette smoking, alcohol consumption, poor dental hygiene, persistent irritability, and genetic abnormalities, have been linked to OSCC [4]. The synergistic consumption of alcohol and cigarettes showed increased odds of the occurrence of OSCC [4]. Recent research indicates a higher prevalence of OSCC in males compared to females, and older adults are thought to be at the highest risk of developing OSCC [5, 6].

Management of the OSCC involves a multidisciplinary team approach. Surgery presents the cornerstone in OSCC treatment in combination with adjuvant radiotherapy and chemoradiation for high-risk patients, while systemic therapy can be used in neoadjuvant settings for advanced-stage disease or as a palliative setting [7, 8].

The complex behavior of malignant neoplasm is closely linked to genetic instability [9, 10].

Received • Примљено: March 6, 2023
Revised • Ревизија: August 17, 2023
Accepted • Прихваћено: August 20, 2023
Online first: August 28, 2023

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OSCC has been linked to abnormalities in a number of oncoproteins, including EGFR, K-ras, c-myc, FGF3, and cyclin D1 [11].

The *EGFR* gene encodes a transmembrane glycoprotein EGFR, belonging to ErbB (epidermal growth factor receptor) family [12]. Upon ligand binding, receptor autophosphorylation follows, triggering a chain of intracellular signaling events [12]. The EGFR signaling pathway is frequently dysregulated in cancer cells, promoting their proliferation, resistance to apoptosis, enhancing capacity for metastasis, and facilitating angiogenesis [12].

Neoplastic cells must evade the effective cell cycle checkpoint regulatory system. The most frequent genetic change observed in all human malignancies is the inactivation of *p53*, leading to persistent cell proliferation and suppression of apoptotic signaling [11]. The *CDKN2A* gene is the second most frequently mutated gene in OSCC. During the G1 to S phase transition of the cell cycle, the *CDKN2A* gene encodes a protein called p16, which promotes cell cycle progression [13].

Single nucleotide polymorphisms (SNPs) within the *EGFR* gene have been identified as potential factors influencing the clinical outcomes and survival of cancer patients. SNPs can impact *EGFR* gene expression, protein levels, and signaling, thereby affecting the response to treatment and overall prognosis. Extensive research has been conducted to investigate the predictive and prognostic utility of *EGFR* SNPs, with a particular focus on small-molecule tyrosine kinase inhibitors (TKIs) and anti-EGFR monoclonal antibodies (mAbs). SNPs can influence the efficacy of TKIs and mAbs by altering the binding affinity of the inhibitors to EGFR, modulating downstream signaling pathways, or influencing the expression levels of EGFR itself [14].

The objective of this study was to determine the association between *EGFR* rs1468727 gene polymorphism, TNM Classification of Malignant Tumors (TNM) stage, demographic factors, and tumor characteristics with overall survival in patients diagnosed with OSCC.

METHODS

The tissue samples were collected from 61 patients between 2014 and 2018 by maxillofacial surgeons at the Clinic for Maxillofacial Surgery of the University Clinical Center of Vojvodina, Serbia. Each tissue block, originating from the central part of the tumor from OSCC patients, was paraffin-embedded. Before surgery, all patients underwent biopsy to confirm the presence of OSCC. As part of the preoperative preparation, a computerized tomography (CT) examination of the head, neck, and chest was performed, and the stage of the disease was determined by the TNM classification based on clinical examination and CT diagnostics, as well as clinical parameters of tumor dimensions [15].

The inclusion criteria were the following: newly pathohistologically diagnosed patients of any sex with untreated resectable OSCC, aged 18 years or older, with no radiologically diagnosed distant metastasis.

The exclusion criteria were as follows: patients with a history of a prior malignancy other than basal cell carcinoma of the skin, with recurrent oral carcinoma, a history of therapeutic irradiation, with autoimmune disease or HIV infection, as well as those with distant metastasis.

All patients included in the study were also HPV-negative. The follow-up period for each patient was three years, measured from the date of surgery until the last consultation with the operator.

The Faculty of Medicine Ethics Committee of the University of Novi Sad approved this study, which was carried out in accordance with the Declaration of Helsinki. All the patients signed an informed consent and underwent standardized preoperative and operative surgical procedures.

Clinical data including age, sex, alcohol consumption, cigarette consumption, TNM stage and the survival rate during the follow-up period were determined for all the patients. The pathohistological data were the following: tumor size, the depth of tumor invasion, and the existence of lymph node metastases.

DNA isolation and rs1468727 EGFR polymorphism genotyping

By using QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany), genomic DNA was extracted from tissue blocks

The *EGFR* polymorphism rs1468727 was genotyped using TaqMan SNP Assays MTO Human SM 10 (Applied Biosystems, Foster City, CA, USA). Polymerase chain reaction (PCR) reaction contained 50 ng DNA, 1 μl of assay, and 12.5 μl of Taq DNA polymerase master mix (TaqMan) and water to reach the final volume of 25 μl.

PCR was carried out with the following temperature profile: initial denaturation step (95°C for five minutes), followed by 30 cycles of denaturation (95°C for one minute), annealing (69°C for one minute) and extension step (72°C for one minute), with the final extension step (72°C for five minutes). The assay was performed in a 96-well plate and the fluorescence was measured in the Applied Biosystems 7500 Fast Real-Time PCR System instrument. All necessary PCR control reactions were set up and performed in each run.

Summary statistics, including the mean, median, and standard deviation for numerical variables, and frequencies for categorical variables, were presented to provide an overview of the data.

We employed binary logistic regression to investigate the impact of various variables on survival outcomes. This modeling approach is well-suited for Bernoulli-distributed dependent variables, which take binary values (0 or 1) based on the presence or absence of a specific criterion, in our case overall survival. The results of the binary logistic regression analysis were reported in terms of coefficients (B), standard errors (S.E.), significance tests (Wald, degrees of freedom, p-values), and odds ratios.

An odds ratio greater than 1 indicates a positive association between independent and dependent variables, implying an increase in the likelihood of the outcome of the dependent variable with the predictor's presence. Conversely, an odds ratio below 1 describes a negative association.

We employed the χ^2 test of independence to assess relationships between categorical variables. It allowed us to explore potential dependencies between various categorical factors and the survival outcome.

We used the Mann–Whitney U test to compare numerical variables between two independent groups. This test was appropriate for our study as it does not assume a normal distribution of data and is robust against outliers.

We set the significance level at $p < 0.05$ for all statistical tests.

All statistical analyses were conducted using IBM SPSS Statistics, Version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

In the three-year follow-up period after surgery, a total of 22 patients deceased (36.1%). The analysis was conducted to determine the potential statically significant difference between survival outcomes and collected characteristics. Summary statistics of demographic data, patients, and cancer characteristics are presented in Table 1.

Table 1. Summary statistics for analyzed variables in the total group of patients; results are presented for the total sample of patients and are further stratified into two groups based on survival outcomes: survived and deceased patients

Characteristics	Total mean ± SD or n (%)	Survived mean ± SD or n (%)	Deceased mean ± SD or n (%)	Survival differences p-values
Demographic characteristics				
Age	65.4 ± 10.1	65.5 ± 8.9	65.3 ± 12.3	0.636
Males	47 (77)	29 (74.4)	18 (81.8)	0.728
Alcohol consumers	40 (65.6)	27 (69.2)	13 (59.1)	0.603
Cigarette consumers	50 (82.0)	35 (89.7)	15 (68.2)	0.079
Tumor-associated characteristics				
With lymph node metastases	25 (41)	13 (33.3)	12 (54.5)	0.108
Largest tumor dimension (cm)	1.3 ± 0.5	1.2 ± 0.5	1.5 ± 0.5	0.027
PH depth of tumor invasion (mm)	8.9 ± 5. 7	7.7 ± 5. 8	10.8 ± 5.17	0.016
TNM stage				0.052
I	5 (8.2)	4 (10.3)	1 (4.5)	
II	17 (27.9)	13 (33.3)	4 (18.2)	
III	19 (31.1)	13 (33.3)	6 (27.3)	
IVa	16 (26.2)	13 (33.3)	7 (31.8)	
IVb	4 (6.6)	9 (23.1)	4 (18.2)	

At the end of the follow-up period, 39 patients survived and more than half of them had genotype CC. An equal distribution between CC and CT genotypes ($\chi^2 = 0.397$, df = 2, $p = 0.820$) was observed among patients who deceased.

A binary regression model was used in this study to explain the survival of the patients by entering the following variables as independent ones: age, sex, alcohol consumption, cigarette consumption, presence of lymph node metastases, tumor size, depth of tumor invasion, as well as *EGFR* genotype.

The omnibus test of model coefficients confirmed that the model fit the data significantly better than the model without any independent variables ($\chi^2 = 14.276$, df = 1, $p = 0.032$). The Nagelkerke R^2 value amounted to 36%, while the overall classification percentage was 75.9%.

Forward selection based on likelihood ratio was used to perform a stepwise selection method and chose statistically significant determinants of overall survival. According to the results, two variables significantly influenced overall survival: the TNM stage and *EGFR* CC genotype.

The odds ratio, often denoted as Exp (B) in logistic regression output, provided an insight into the relationship between the independent variables and the likelihood of the dependent variable outcome. A person with genotype CC is more likely to survive (Table 2). The odds ratio of 3.118 suggests that, while keeping other variables constant, each unit increase in the TNM stage results in approximately 3118 times higher odds of not surviving. This indicates a positive association between the TNM stage and the likelihood of not surviving, implying that higher TNM stage is associated with higher odds of not surviving (Table 2).

Table 2. Logistic regression results

	B	S.E.	Wald	Df	Sig.	Exp (B)
TNM Stage	1.137	.360	10.006	1	0.002	3.118
rs1468727 EGFR Genotype CC	-2.794	1.438	3.773	1	0.050	0.061
Constant	-5.502	1.701	10.468	1	0.001	0.004

B – coefficients; S.E. – standard errors; Df – degrees of freedom; Sig. – tests for significance

The odds ratio of 0.061 indicated a statistically significant association between the genotype *EGFR* rs1468727 CC and lower odds of not surviving. Specifically, individuals with genotype *EGFR* rs1468727 CC had approximately 0.061 times lower odds of mortality compared to individuals with the reference genotype. This indicates a negative association between genotype *EGFR* rs1468727 CC and the likelihood of death, implying that having genotype *EGFR* rs1468727 CC decreases the likelihood of not surviving.

DISCUSSION

EGFR-mediated signaling pathways play a crucial role in facilitating tumor cell growth and survival, providing tumor cells with significant advantages that lead to uncontrolled proliferation. Consequently, this unregulated cell division results in increasing the number of cancerous cells and acceleration of tumor growth [16].

Several mechanisms have been proposed to explain how the *EGFR* SNPs might affect survival or treatment outcomes in cancer patients: the *EGFR* SNPs can influence the expression level of the *EGFR* gene, which could potentially impact the responsiveness of cancer cells to certain treatments or influence disease progression [17]. The *EGFR* rs1468727 SNP might interact with other genetic factors to collectively influence survival outcomes [18]. It is extremely challenging to isolate the specific effect of a single SNP on a given phenotype when other related SNPs

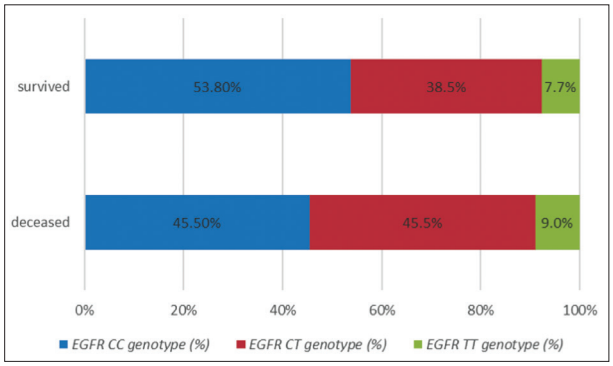

Figure 1. Comparative overview of EGFR rs1468727 genotype frequencies in groups of survived and deceased patients*

*Distribution of CC, CT, and TT genotype frequencies in survived and deceased patients

may do the same through linkage disequilibrium and other mechanisms [19]. Certain *EGFR* genotypes could potentially influence drug efficacy, toxicity, or overall treatment response [17, 20].

EGFR signaling interacts with numerous other pathways involved in cell proliferation, apoptosis, angiogenesis, and DNA repair. Consequently, the *EGFR* polymorphisms may influence the activity of these pathways indirectly, thus potentially affecting survival outcomes [16].

In this study, we examined the associations between demographic characteristics, *EGFR* SNP rs1468727 and tumor-associated characteristics with survival in OSCC patients. The results showed that TNM stage and *EGFR* CC genotype had a statistically significant influence on overall survival. In contrast, no statistically significant correlations were identified between overall survival and each of the following variables: age, sex, alcohol and cigarette consumption, presence of metastases, tumor size and histopathological depth of tumor invasion.

Our data indicated that individuals with *EGFR* rs1468727 CC genotype and OSCC were more likely to survive. Su et al. [21] reported the predictive significance of *EGF* and *EGFR* polymorphisms in a group of locally progressed head and neck squamous cell carcinoma patients undergoing post-operative chemotherapy-radiotherapy. Additionally, Saravani et al. [22] evaluated the potential impact of three polymorphisms: rs2227983, rs2227984, and rs2293347 in OSCC patients in southeast Iran. Their study showed that the *EGFR* G>A (rs2227983) polymorphism contributes to OSCC susceptibility. Specifically, patients with the *EGFR* R521K G/G (11.1%) and G/A (15.9%) genotypes exhibited poorer five-year overall survival rates compared to those with the A/A (62.5%) genotype. The prognostic value of the R521K polymorphism was further investigated in the study by Bandrés et al. [23]. The R497K variant was associated with a poorer prognosis than the other variants. Patients with the R521K polymorphism and the G/G genotype in exon 13 had the highest chance of disease-related mortality.

In contrast, the (CA)n polymorphism in intron 1 was not associated with overall survival in the same patient group. No other references regarding the connection between *EGFR* rs1468727 CC genotype and OSCC were found. Nonetheless, Li et al. [18] discovered that the overall survival in Chinese population of patients with glioma and *EGFR* rs1468727 CC genotype was much shorter, indicating different effect in different tumor types.

On the contrary, our research suggested that individuals with *EGFR* rs1468727 CC genotype were more likely to survive. The conflicting result could be attributed to variations in the sample size, differences in tumor type or geographical locations.

Metadata analysis conducted by de Morais et al. [24] involved a review of 14,746 papers and focused on 11 relevant studies, which matched the criteria, to identify clinical and pathologic factors related to the prognosis of OSCC in young patients. The analysis included a total of 2317 patients with OSCC, with men comprising the majority of the sample. Regarding the tumor-node-metastasis stage, the majority of research indicated that cases were typically detected in their early stages (I and II). The studies also revealed considerable variation in locoregional recurrence rates and histologic grade of malignancy. Regional lymph node metastases decreased both the overall and individual survival rates which is consistent with our findings.

Kaminagakura et al. [25] reported that younger patients had a greater relapse rate ($p = 0.02$), but there was no difference in overall survival ($p = 0.86$) that was statistically significant. The clinical stage of the tumors in the younger patients was less advanced, and there was an increased utilization of surgery, radiation, and chemotherapy, leading to improved overall survival.

This study emphasized the significance of early detection and vigorous treatment of OSCC [25]. Zhang et al. [26] discovered that there was no statistically significant difference between the youngest and oldest patient groups in both disease-free survival or disease-specific survival ($p = 0.605$ and $p = 0.520$, respectively). Costa et al. [27] discovered a higher incidence of OSCC among men, Caucasians, smokers, and alcohol consumers. In our study, the mean age of patients was 65.4 ± 10.1 with the majority of patients (47, 77%) being male.

Tsou et al. [28] presented molecular evidence demonstrating how acrolein-containing cigarette smoke contributed to EGFR amplification and activation of downstream signaling in OSCC. Shahsavari et al. [29] showed that the age, sex, grade, and stage of OSCC patients did not exhibit any statistically significant relationships with EGFR expression ($p > 0.05$). However, in the group of esophageal squamous-cell carcinoma patients, there was a statistically significant connection between EGFR expression and stage ($p = 0.006$) [29].

The study by Costa et al. [27] found no associations between EGFR expression and alcohol or tobacco use. Similarly, our study did not discover any statistically significant correlations between age, sex, alcohol and cigarette consumption, genotype, and overall survival of the patients. Costa et al. [27] reported that the disease development and survival rates were adversely impacted by tumors with positive margins, larger size, and stronger EGFR expression and our data indicates that the TNM stage of illness and *EGFR* genotype impacted the survival of the patients.

Bandrés et al. [23] demonstrated that *EGFR* genotypes might be useful indicators in predicting the survival of OSCC patients with metastatic or recurrent disease. In addition, their research indicated that *EGFR* polymorphisms could be advantageous for EGFR-targeted antibody therapy [23]. EGFR, a cell-surface receptor and a druggable kinase, can be targeted by drugs to modulate its activity [20]. In a subset of malignant neoplasms, the *EGFR* gene is abnormally amplified, rearranged, and mutated, contributing to the development and progression of cancer. As a result, targeting the abnormal *EGFR* has become a major focus in signal blockade strategies for treating various cancers, including OSCC. Onda et al. [30] conducted flow cytometry analysis to evaluate the expression levels of *EGFR* in OSCC cell lines, revealing high expression levels in all tested OSCC cell lines. This finding suggests that *EGFR* may have a significant role in the development and progression of OSCC.

By targeting abnormal *EGFR*, researchers aim to inhibit its activity and disrupt the signaling pathways that promote cancer growth [30].

Despite these insights, our data cannot conclusively highlight the significance of *EGFR* rs1468727 gene variants.

CONCLUSION

According to the results, two variables had a statistically significant influence on OS: the TNM stage and *EGFR* rs1468727 CC genotype. Higher TNM stage was associated with a decreased likelihood of survival, while individuals with *EGFR* rs1468727 CC genotype were more likely to survive. This study underscores the potential significance of genetic factors, particularly homozygote *EGFR* rs1468727 CC, in assessing the prognosis and treatment outcomes in OSCC. Ongoing research of genetic factors and OSCC is crucial to uncover novel avenues for medical care and improve patient outcomes.

ACKNOWLEDGEMENT

This work constitutes a part of the doctoral dissertation: Bačulov K. Epidermal growth factor receptor and vascular endothelial growth factor gene polymorphisms in patients with oral squamous cell carcinoma [PhD thesis]. Novi Sad: University of Novi Sad.

Conflict of interest: None declared.

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Утицај полиморфизма гена за рецептор епидермалног фактора раста rs1468727 на преживљавање болесника са оралним планоцелуларним карциномом

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САЖЕТАК

Увод/Циљ Познато је да генетичке аберације заједно са факторима средине играју важну улогу у настанку оралног планоцелуларног карцинома (ОПК).

Циљ истаживања је да се разјасни могући утицај полиморфизма гена за рецептор епидермалног фактора раста (*EGFR*) *rs*1468727 на укупно преживљавање код болесника са ОПК.

Методе У студију је био укључен 61 болесник са дијагнозом ОПК. Период праћења за сваког болесника био је три године од датума операције. Генотип сваког болесника за *rs*1468727 полиморфизам гена *EGFR* детектован је коришћењем *PCR* методе у реалном времену. Како би се истражило која варијабла утиче на преживљавање, коришћена је бинарна логистичка регресија. За испитивање односа категоричких варијабли коришћени су тест независности χ^2 и Ман–Витнијев *U* тест.

Резултати Две варијабле су показале статистички значајан утицај на укупно преживљавање: стадијум класификације малигних тумора (*TNM*) и *EGFR* генотип. Три године после операције (праћења) међу 39 преживелих болесника више од половине имало је генотип *EGFR rs*1468727 *CC*. Међу болесницима који нису преживели, дистрибуција генотипова *CC* и *CT* била је једнака ($\chi^2 = 0,397$, $df = 2$, $p = 0,820$). Нису идентификоване статистички значајне корелације између укупног преживљавања и демографских или туморских карактеристика.

Закључак *EGFR rs*1468727 хомозигот (генотип *CC*) и стадијум *TNM* показали су статистички значајан утицај на укупно преживљавање у периоду праћења болесника. Ова студија наглашава могући значај разматрања генетских фактора, као што је хомозиготни *EGFR rs*1468727 генотип *CC*, приликом процене прогнозе и исхода лечења болесника који су били подвргнути операцији у циљу лечења ОПК.

Кључне речи: орални планоцелуларни карцином; рецептор епидермалног фактора раста; полиморфизми

DOI: https://doi.org/10.2298/SARH220911088K
UDC: 343.61:616.89-008

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Psychiatric characteristics of homicide perpetrators in Serbia

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SUMMARY
Introduction/Objective Homicide, a major public concern, has always attracted the attention of criminology, psychiatry, psychology, and other related disciplines.
The objective of this study was to determine the frequency and type of mental disorders in 94 attempted/committed homicide perpetrators.
Methods The authors conducted a psychiatric assessment of all perpetrators based on psychiatric interviews, psychological testing, and the examination of available medical records.
Results The key findings of this study imply that there is a large percentage of violent crime perpetrators with mental disorders (62%). When we excluded people with personality disorders from this group, we found that the most common major mental disorders among the perpetrators were psychosis and alcohol use disorders (approximately 10% each).
Conclusion The results highlight the importance of the early identification and treatment of people with mental disorders in the general population, as this could reduce the possibility of criminal behavior. The high overall incidence of mental disorders in the group of homicide perpetrators indicates the need for a reform of psychiatric services in Serbia and the promotion of psychiatry in the community, which would contribute to bringing professionals closer to people with mental disorders and thus, timely recognition and treatment of these patients.
Keywords: homicide; mental illness; psychosis; alcohol use disorders; personality disorders

INTRODUCTION

Homicide, a major public concern, has always attracted the attention of law, criminology, psychiatry, psychology, sociology, and other related disciplines. According to the United Nations' data, the overall number of people killed in homicides increased from 362,000 in 1990 to 464,000 in 2017 [1]. The same source states that the global homicide rate was 6.1 per 100,000, the American continent had the highest rate of 17.2, while the rate in Europe was 3 in 2017 [1]. For people aged 5–29, one of the top five causes of death is homicide [2].

Studying the phenomenon of homicide certainly requires taking into consideration human aggression which is defined as the deliberate use of force against another person. Aggression is the result of complex interactions between neurobiological, psychological, and environmental factors. It has been shown that the male sex is associated with a higher frequency of aggressive behavior. However, sex differences in aggression are less pronounced in individuals with mental disorders [3]. Aggression in the population with mental disorders has not been sufficiently explored, despite its obvious importance [4]. The opinion of earlier experts that the risk of aggressive behavior in the population of psychiatric patients is no greater than in the general population was replaced by research data indicating that there is an increased risk of aggression in people with certain psychiatric diagnoses [5]. In other words, mental disorders, regardless of other factors, are associated with an increased rate of aggressiveness, with an estimated risk of approximately 4% [6]. The risk of aggressive behavior is even greater when there is comorbidity of a mental disorder with the abuse of psychoactive substances [7, 8].

Schizophrenia, the most prevalent psychotic disorder, increases the risk for aggression [9]. Studies suggest that individuals with schizophrenia are four to seven times more likely to commit violent crimes, and four to six times more likely to exhibit general aggressive behavior, compared with the general population [10]. Flynn et al. [11] concluded that 90% of the homicide offenders with schizophrenia experienced psychotic symptoms at the time of the offence. Furthermore, previous research reported that 10% of homicide perpetrators were described in psychiatric reports as being mentally ill at the time of their offence, 4% of whom were thought to have schizophrenia [12]. A significant part of increase in the risk of aggression in people with schizophrenia is caused by comorbid psychiatric disorders caused by psychoactive substance use [4, 9]. Research on bipolar disorder has revealed a higher risk of violence during acute manic episodes even when controlling for psychoactive substance use [4].

Received • Примљено: September 11, 2022
Revised • Ревизија: August 31, 2023
Accepted • Прихваћено: September 26, 2023
Online first: October 2, 2023

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A diagnosis of depression has also been associated with an increase in violent crimes, including homicide [13]. In addition, the interaction between personality traits and aggressive behaviors has drawn the attention of researchers who identified people with personality disorders (PDs) as high-risk population [14, 15]. And finally, it is important to note that substance abuse has shown to have a negative effect on inhibition or impulse control, supporting the hypothesis of a biological link between psychoactive substance use disorders and aggression [16, 17].

The only available study conducted in the Republic of Serbia on 154 homicide perpetrators found that 55% had been diagnosed with mental disorders. The most frequent diagnosis was PD (63%), followed by psychosis (13%) and alcohol dependence (14%). It is also interesting that the aforementioned study indicated that as many as 45% of people with mental disorders from a group of perpetrators were diagnosed for the first time in forensic services following the offence [18].

The primary objective of this study was to determine the frequency and types of mental disorders among homicide perpetrators to underline the need for adequate psychiatric treatment of individual patients prone to aggressive behavior.

METHODS

We examined forensic psychiatric reports conducted at the Clinic for Psychiatry in Novi Sad, Serbia from 2001 to 2018, that assessed 94 attempted or committed homicide perpetrators. The authors conducted a psychiatric assessment of all perpetrators based on psychiatric interviews, psychological testing, and the examination of available medical records. Diagnoses of mental disorders were made based on official diagnostic criteria from the International Classification of Diseases (ICD-10), and relevant perpetrator characteristics were determined using the Minnesota Multiphasic Personality Inventory [19, 20]. To compare our results with the literature data, we also used the diagnostic category of major mental disorder (MMD) which is frequently used in research exploring the mental state of murderers. This category includes psychotic disorders, mood disorders, psychoactive substance use disorders, and excludes PDs, as well as mental retardation [21]. According to ICD-10, a specific PD is a severe disturbance in the characterological constitution and behavioral tendencies of the individual, usually involving several areas of personality, and is nearly always associated with considerable personal and social disruption. All PDs must meet the following criteria:

a) markedly disharmonious attitudes and behavior, usually involving several areas of functioning;

b) the abnormal behavior pattern is enduring, long-standing, and not limited to episodes of mental illness;

c) the abnormal behavior pattern is pervasive and clearly maladaptive to a broad range of personal and social situations;

d) the above manifestations always appear during childhood or adolescence and continue into adulthood;

e) the disorder leads to considerable personal distress, but this may only become apparent late in its course;

f) the disorder is usually, but not invariably, associated with significant problems in occupational and social performance.

Specific PDs include paranoid, schizoid, dissocial, emotionally unstable, histrionic, anankastic, anxious, dependent, mixed, and other. To diagnose most of the subtypes listed below, clear evidence is usually required for the presence of at least three traits or behaviors given in the clinical description [19].

All forensic records are properties of the Clinical Centre of Vojvodina, and their use was authorized by the Institutional Ethics Committee in 2017. We emphasize that local court rules require that all individuals charged with attempted or committed homicide receive psychiatric evaluations during trial to assess their mental competence. This is because Serbian criminal legislation determines that a perpetrator is guilty only if he is mentally competent at the time of the offence. If the perpetrator was unable to understand the significance of his criminal act or was unable to control his actions because of his mental disorder at the time of the offence, he was said to be mentally incompetent. Mentally incompetent perpetrators are not considered guilty and are not being sentenced to sanctions. Instead of sanctions, mentally ill perpetrators receive compulsory psychiatric treatment to reduce the risk of recidivism due to psychiatric illnesses [22].

The sample baseline characteristics were summarized using means or frequencies as appropriate. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY, USA), and the results are presented in the text and figures. Descriptive statistics were used for data processing. Numerical features were presented through measures of central tendency (arithmetic mean), variability (range of values), and attributive features using frequencies and percentages [23].

RESULTS

The sample was mostly male (85%) and relatively young (median age: 37 ± 4.1, ranging: 15–80 years). In total, 41% of the study group completed elementary education, 45% secondary education, and 14% university education. As many as 27% of the study group had mental disorders among their close relatives, mainly alcoholism (68%), schizophrenia (12%), and depression (8%).

In total 26% percent of perpetrators had a history of criminal offences, with violent crimes being the most frequent (60.87%).

Of the sample 32% had a lifetime history of psychiatric illnesses. Among perpetrators who had received psychiatric treatment before the violent act, the most frequent diagnoses were PDs and psychoactive substance use disorders (27.9% each), followed by psychotic disorders (14%), mood disorders, neurotic, and stress-related disorders (9.3% each), organic mental disorders (7%), and mental retardation (4.6%). The most common psychiatric

comorbidities were substance use, PDs (40%), and psychotic disorders (12%).

According to the forensic psychiatric evaluation, 62% of the sample had a certain form of mental disorder. The results showed that 25% of the study population had MMDs such as schizophrenia, non-schizophrenic psychosis, mood disorders, or psychoactive substance use disorders. The types and frequencies of the MMDs in the study group are shown in Figure 1.

Interestingly, schizophrenia was recognized and treated before attempted or committed homicide in only 12% of patients with schizophrenia.

PD was diagnosed in 41% of patients. The types and frequencies of PD are shown in Figure 2.

As many as half of the perpetrators were under the influence of psychoactive substances at the time of the offence, and alcohol was the most commonly used substance (95.74%).

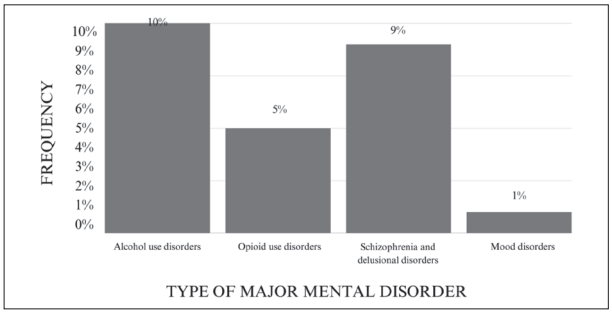

Figure 1. Major mental disorders in perpetrators

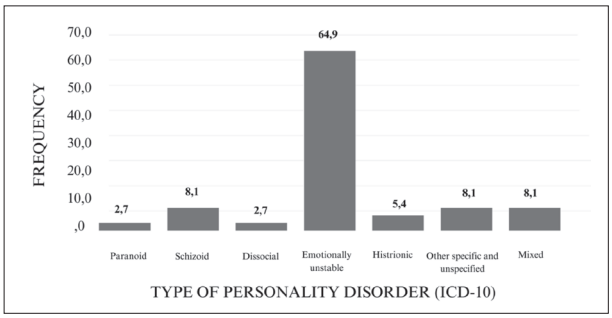

Figure 2. Types of personality disorders in perpetrators

DISCUSSION

The characteristics of our sample, in terms of sex, age, educational level, employment status, and previous criminal offences, are consistent with the literature. Previous research has described a male predominance in the population of killers, and this was confirmed by our finding that there were 85% of men in the study group [24]. The average age of the perpetrators in our sample was 37 ± 4.1, which is consistent with the literature describing murderers as young or middle-aged adults [25, 26]. High school education was the most common (45%) in our sample, followed by elementary school (41%), and university (14%). Statistical analysis showed that none of the educational categories were significantly more frequent in the investigated population. However, a study of homicide statistics between 1990 and 2005, from a range of countries similarly showed that homicide was more likely to decline in countries that invested more heavily in education [1]. Although some authors state that a lower educational level could be a factor contributing to aggression, our results do not indicate this association [27]. As many as 65% of the perpetrators in our study were unemployed at the time of the offence. The correlation between the prevalence of murders and unemployment is present in the literature, but we must emphasize that unemployment is also linked to mental disorders in general, which is why we cannot say that our results confirm this connection [27].

About a quarter of the sample (27%) had a close relative with a mental disorder. The most frequent diagnoses among perpetrators' relatives were alcoholism (68%), schizophrenia (12%), depression (8%), opiate dependence (4%), mental retardation (4%), and PD (4%). The significance of this result comes from the fact that previous research suggests that a family history of mental disorders is a significant independent risk factor for homicide [28].

It is well known that a history of violence is one of the most important predictors of future violence [29]. High rates of criminal recidivism are confirmed by our results, which show that 26% of the sample had been previously prosecuted, most frequently because of violent crimes (61%).

Almost one third of our sample (32%) was diagnosed and treated psychiatrically before committing a criminal act. This result must be taken seriously in the context of the prevention of crimes that may stem from untreated or inadequately treated mental disorders. In this context, it is important to mention the literature on the increased risk of homicides in mental disorders. Available evidence suggests that persons with serious forms of mental illness are 4–10 times more likely to commit homicide as compared to non-affected members of the general population [30].

The authors used the diagnostic category MDD which is frequently used in international research and Serbian practice, to explore the mental state of murderers to compare the presented results with the literature data. MMD includes psychotic disorders, mood disorders, and psychoactive substance use disorders, and excludes PDs and mental retardation [31].

Psychiatric forensic evaluation of our sample revealed that 25% of perpetrators had MMDs. We must emphasize that the literature data is inconsistent with regard to the frequency of mental disorders in the group of homicide perpetrators, and this percentage ranges from 10% to 91% [21, 31]. When we considered the distribution of individual MMDs in our study group, the most frequent was alcohol use disorder (10%), followed by psychosis (9%) and opioid use disorder (5%). Literature suggests that between 4% and 6.5% of homicide perpetrators suffer from psychotic disorders, mainly schizophrenia [32]. In this context, it has been reported that as many as 5.2% of extremely violent acts are committed by psychiatric patients, most commonly with schizophrenia [11]. As the proportion of perpetrators with psychosis in our sample

is almost twice as high as that in the literature, and as many as 88% of perpetrators with psychosis have not been diagnosed prior to the offence, we must wonder about the quality of psychiatric screening and treatment programs in Serbia. We emphasize that untreated psychosis contributes to the risk of violence [11]. It must be noted that psychiatric comorbidity significantly increases the risk of aggression, and the most frequent co-morbid mental disorders are psychoactive substance use disorders [4, 9]. It is important to note that schizophrenia *per se* increases the risk of homicide ten times, while its comorbidity with the use of psychoactive substances increases this risk by as much as 17 times [8].

When we examined diagnoses that were not included in the category of MMDs (non-MMD diagnoses), 6% of our sample had mental retardation, while PD was present in 41% of all subjects. The most frequent type of PD was emotionally unstable (64.9%), followed by schizoid (8.1%), other-specific (8.1%), mixed (8.1%), histrionic (5.4%), dissocial (2.7%), and paranoid (2.7%). The frequency of PDs in our study group was significantly higher than that described in the literature, ranging from 13% to 24% in people convicted of a murder [32]. This result may indicate a lower threshold for diagnosing PD in our country, or that there is a higher incidence of murders resulting from impulsiveness as one of the characteristics of emotionally unstable PD. It is estimated that prisoners have PDs several times more frequently than the general population, indicating that this disorder is a risk factor for committing criminal offences [33]. This is also supported by the fact that aggression is a defining characteristic of borderline and antisocial PDs.

Exactly half of all perpetrators were under the influence of psychoactive substances at the time of the offence, most often alcohol (96%). This result is compatible with the results of similar research, where it is stated that 37–59% of men who committed offences were under the influence of psychoactive substances, most often alcohol [1].

The findings of the present research have to be interpreted with several limitations in mind. First, the sample sizes in this study are larger than in most previous clinical studies of homicide, but still insufficient to be generalized. Second, we obtained only data from a single center, thereby limiting general transferability. Finally, much of the information and the diagnostic assessment were based on the report of subjects who were interviewed after arrest in a pretrial evaluation, and these reports may have been biased by perceived self-interest.

CONCLUSION

We found that a significant number of perpetrators had mental disorders, suggesting that psychiatry could contribute to reducing the unacceptably high homicide rates.

The high overall incidence of mental disorders, as well as almost twice the incidence of psychoses and PDs in our sample when compared to the literature data, requires significant improvement in the existing health care system in Serbia because mental health strategies include identifying persons who are at high risk of aggression. This important task can be carried out by improving the recognition and treatment of mental disorders, especially in terms of secondary prevention, considering the high rates of criminal recidivism. Timely and adequate psychiatric treatment is a well-known factor in reducing crime rates in psychiatric patients. Improvement of the psychiatric care system in Serbia could be achieved through the reform of psychiatric services, which has already been suggested by experts and the state policy [34, 35]. This should include promotion of psychiatry in the community, person-centered care, as well as humanization and individualization of treatment which would contribute to bringing professionals closer to people with mental disorders, and thus, timely recognition and treatment of these patients.

Conflict of interest: None declared.

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Психијатријске карактеристике починилаца хомицида у Србији

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САЖЕТАК

Увод/Циљ Хомицид је као значајан друштвени проблем одувек привлачио пажњу криминологије, психијатрије, психологије и других сродних дисциплина.

Циљ овог истраживања био је да се утврде учесталост и врста менталних поремећаја код 94 извршиоца убиства или убиства у покушају.

Методе Аутори су извршили психијатријску евалуацију извршилаца кривичних дела на основу психијатријског интервјуа, психолошког тестирања и увида у доступну медицинску документацију.

Резултати Најзначајнији резултат овог истраживања је да постоји велики проценат починилаца насилних кривичних дела који задовољавају критеријуме за постављање дијагнозе менталног поремећаја (62%). Када смо из ове групе искључили особе са поремећајима личности, установили смо да су међу учиниоцима најагресивнијих кривичних дела најчешћи психотични поремећаји и ментални поремећаји настали због употребе алкохола (сваки по око 10%).

Закључак Резултати указују на значај раног дијагностиковања и третмана особа са менталним поремећајима у општој популацији, јер би то могло да доведе до редукције ризика од насилног понашања. Висока укупна инциденца менталних поремећаја у групи извршилаца убистава указује на потребу да се реформише психијатријска здравствена заштита у Србији. У прилог благовременом препознавању и лечењу менталних поремећаја, а самим тим и редукцији ризика од насилног понашања, потребно је унапредити концепт психијатрије у заједници који би допринео приближавању професионалаца особама са менталним поремећајима.

Кључне речи: хомицид; ментални поремећај; психоза; алкохолизам; поремећај личности

DOI: https://doi.org/10.2298/SARH220529081B
UDC: 616.72-002.77-079.4

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Atypical clinical presentation of rheumatoid arthritis

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SUMMARY

Introduction Rheumatoid arthritis is a systemic autoimmune disease with inflammation of the joints as its hallmark. Extra-articular manifestations affect nearly half of the patients either at the onset of disease or later during the disease course.

Case outline A 43-year-old man complained of chest pain, dry cough, and fatigue. Diagnosis of pericarditis was made based on echocardiography findings. Due to worsening of respiratory symptoms, he was admitted to the hospital. Initial diagnostic workup revealed elevated concentrations of acute phase reactants, pericardial effusion, and bilateral pulmonary nodules. Pathohistological analysis of lung nodules ruled out malignancy and tuberculosis. He was treated with colchicine, which led to a regression of a pericardial effusion. Afterwards, due to arthritis of the right wrist, high erythrocyte sedimentation rate, and C-reactive protein, positive immunoserology and bone erosion at the distal ulna diagnosis of seropositive rheumatoid arthritis was established. He was treated with antimalarial, methotrexate, and glucocorticoids until he suffered from COVID-19 pneumonia, which triggered arthritis flare. Owing to the loss of efficiency of combination therapy with methotrexate and glucocorticoid, baricitinib was added to the treatment. Low disease activity was achieved after three months of administering baricitinib and methotrexate, and no adverse events occurred during 20-month-long therapy.

Conclusion Every patient with pericarditis of unknown etiology should be diagnostically evaluated in term of connective tissue disease including rheumatoid arthritis, because the initial clinical presentation in some group of patients could lack characteristic synovitis.

Keywords: pericarditis; lung nodules; rheumatoid arthritis; COVID-19 pneumonia; flare; baricitinib

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease with articular inflammation as the main feature. Inflammatory processes can also affect other tissues and these extra-articular manifestations are associated with a higher risk of morbidity and mortality in patients with RA [1].

The objective of this article was to present a case of atypical clinical manifestation of RA.

CASE REPORT

In December 2014, a 43-year-old man complained of chest pain that worsened with deep inspiration and in supine position, dry cough, and fatigue. These symptoms were present for one month prior to the medical appointment. Electrocardiogram was normal, laboratory test results were within the reference range except low levels of red blood cells (RBC) indices. Echocardiography (ECHO) revealed circular separation of pericardium layers up to 3.1 mm with adhesions along the lateral wall and apex of the heart. The pericarditis was treated with nonsteroidal anti-inflammatory drug in combination with a proton pump inhibitor, which the patient stopped on his own initiative due to the onset of black stool after two days of taking these medications. In January 2015, owing to symptoms progression, the patient was admitted to the hospital with dyspnea, dry cough, and malaise. Physical examination was unremarkable. Laboratory findings showed a slight increase in acute phase reactants concentration (C-reactive protein (CRP) 13.9 mg/L, erythrocyte sedimentation rate (ESR) 24 mm/h) and iron deficiency (5 μmol/L). On the other hand, the results of the complete blood count and the biochemical panel were within the normal range. Remaining laboratory results are presented in Table 1. ECHO assessment demonstrated pericardial effusion up to 16.6 mm with the right atrium collapse (Figure 1). During the hospitalization, a computed tomography (CT) scan of the thorax detected bilateral soft tissue density nodules with 5 mm in diameter localized in the lower lobes and in the middle lobe of the lung along with mediastinal lymphadenomegaly. Pathohistological analysis of pulmonary nodules (PNs) ruled out malignancy, furthermore all performed tests indicative of *Mycobacterium tuberculosis* infection were negative. Characteristic pathohistological features regarding rheumatoid lung nodule were not present in taken samples. The patient was treated with colchicine and administration of this therapy led to a resolution of pericardial

Received • Примљено: May 29, 2022
Revised • Ревизија: July 23, 2023
Accepted • Прихваћено: August 28, 2023
Online first: September 5, 2023

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Table 1. Laboratory findings during hospitalization

Parameter	Value	Reference range
CMV IgG EBV IgG	1/160 1/160	Positive titer Positive titer
C3 (g/L)	1.717	0.9–1.7
C4 (g/L)	0.491	0.12–0.36
ANA/AMA/ASMA/APA IgG EMA IgA	negative	–
CA-125 (U/mL)	42	0–21
CA 19-9 (U/mL)	2.9	0–34
CA 72-4 (U/mL)	3.4	0–6
CEA (ng/mL)	0.1	0–5.5
NSE (ng/mL)	2.7	0–17
PSA (ng/mL)	0.8	0–4.1
AFP (ng/mL)	1.5	0–7.08

CMV – cytomegalovirus; EBV – Epstein–Barr virus; IgG – immunoglobulin G; C3 – complement component 3; C4 – complement component 4; ANA – antinuclear antibodies; AMA – anti-mitochondrial antibody; ASMA – anti-smooth muscle antibody; APA – antiphospholipid antibody; EMA – anti-endomysial antibody; IgA – immunoglobulin A; CA-125 – cancer antigen 125; CA 19-9 – cancer antigen 19-9; CA 72-4 – cancer antigen 72-4; CEA – carcinoembryonic antigen; NSE – neuron-specific enolase; PSA – prostate-specific antigen; AFP – alpha fetoprotein

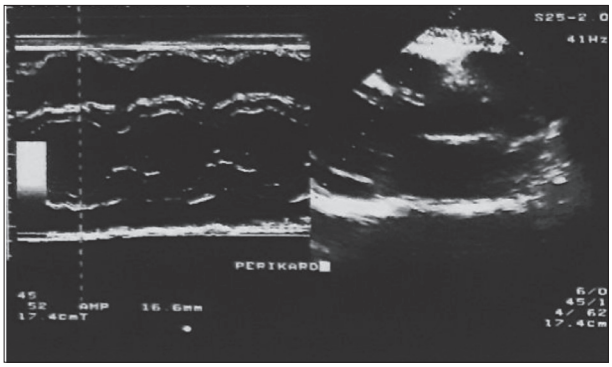

Figure 1. Echocardiogram showing pericardial effusion up to 16.6 mm, with right atrium collapse

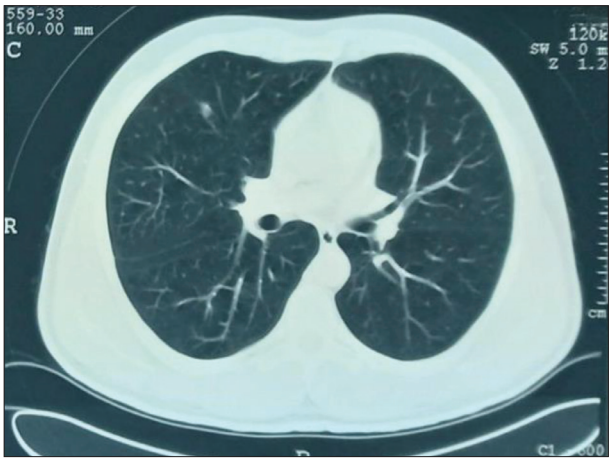

Figure 2. Computed tomography scan of the lung showing parenchymal nodule

effusion. A follow-up CT scan two months after discharge from the hospital revealed the regression of pulmonary changes. Several subpleural and parenchymal micronodules were present, of which the larger ones were up to 4 mm and 3 mm. No signs of enlarged lymph nodes in the mediastinum were observed. (Figure 2). Due to the reduction in the size of the lung nodules, bronchoscopy was not performed. Simultaneously, in March 2015, he was examined by a rheumatologist for the first time due to pain and swelling of the right wrist. These symptoms were not accompanied by morning stiffness. Upon medical examination, there was evidence of active arthritis of the right wrist. Results of a laboratory analysis indicated on the high ESR, CRP, slightly low levels of hemoglobin, and RBC indices as well as thrombocytosis. Immunoserological tests for systemic connective tissue diseases were positive for anti-cyclic citrullinated peptide (anti-CCP) antibody and anti-citrullinated protein antibody (ACPA) with a titer of 59.8 U/mL and 146.3 U/mL, respectively, while rheumatoid factor (RF), p antineutrophil cytoplasmic antibody (p ANCA) and c ANCA were within normal range. Plain radiography of both hands, wrists, and feet did not reveal any of the radiographic hallmarks of RA. Ultrasound of the soft tissues of the right wrist showed moderate synovial proliferation with a positive Doppler signal suggestive of acute arthritis accompanied with bone erosion at the distal ulna. Considering synovitis lasting more than six weeks, abnormal CRP and ESR, positive immunoserology, patient had a score of six points which met the American College of Rheumatology / European Alliance of Associations for Rheumatology 2010 diagnostic criteria for RA [2]. Treatment was initially started with hydroxychloroquine with a daily dose of 400 mg. Three months later, concomitant Methotrexate was added at a weekly dose of 15 mg and then increased to 20 mg (Disease Activity Score-28 (DAS28) – 3.86). Also, low doses of glucocorticoids were prescribed depending on disease activity. In a period from 2015 to 2020 disease activity estimated with DAS28 index was within the range of low disease activity. In July 2020, the patient had COVID-19 pneumonia presented with mild symptoms. Three months after this viral infection, he suffered from arthritis flare up (DAS28 – 5.74). Regarding the loss of efficiency of combination therapy with Methotrexate and glucocorticosteroid, an inhibitor of Janus kinase (JAK) – baricitinib was added in a daily dose of 4 mg in August 2021. Low disease activity was achieved after three months (DAS28 – 2.18). During the most recent visit, the patient did not have any signs of active synovitis and inflammatory markers were in the reference range (DAS28 – 2.52). Additionally, no adverse events were reported during a 20-month period of baricitinib administration.

The paper was approved by the Ethics Board of the Special hospital for rheumatic diseases Novi Sad and the patient gave written consent to publish all shown materials.

DISCUSSION

RA is a systemic autoimmune disease that usually presents in the form of a symmetric polyarthritis. However, about half of patients with RA also have extra-articular manifestations that may occur at the very beginning or later in the course of the disease, but are rarely the presenting symptom of the disease [3]. In the group of cardiac involvement, pericarditis was observed to be the most common. Depending

on the method used for diagnostic assessment (ECHO or autopsy), pericarditis was found in about 30–50% of patients [4]. On the other hand, less than 10% of patients experience any symptoms during a lifetime. Symptomatic pericarditis is more frequent in male patients, in patients with high concentrations of RF, and rheumatoid nodules [5]. Bearing in mind the results of the previously mentioned study, it can be concluded that this manifestation of RA is not rare. On the other hand, after reviewing the literature, there were not many reports of pericarditis as the initial sign of RA as in the case of our patient.

The prevalence of PNs varies between 1% to 30% in patients with RA depending on the sophistication of the diagnostic method used. Therefore, the prevalence of PN detected by radiogram is less than 1%, CT scan between 10% and 22% and pathohistological analysis about 30% [6]. Risk factors for nodule development as well as its progression are older age, male sex, seropositivity, smoking, longer duration of the disease, certain drugs for the treatment of RA, and comorbidities [7]. PNs can be radiographically presented as single or multiple, with solid or cavitary structure, they are most often localized in the periphery in the subpleural region and they vary in diameter, which can range from a few millimeters to several centimeters [6]. Patients with PN are generally without symptoms and do not require treatment, however, due to the localization of these changes there is a risk of sustaining a pneumothorax, hydropneumothorax and bronchopleural fistula which are conditions seeking medical intervention [7]. In our patient presence of PN which preceded the articular symptoms was revealed incidentally on CT scan performed because of persistent pericarditis and it is a rare presenting feature of RA.

RA is characterized by a symmetrical polyarthritis, but in a small percentage of patients it is initially presented as monoarthritis, usually affecting the large joints such as hip and knee. Although monoarticular RA is uncommon, it usually progresses to a polyarticular form in a period of time, which was shown to be between three and five years [8]. In a cross-sectional study with a total of 400 patients included, only one patient had a monoarticular manifestation of disease [9]. Anti-CCP are a type of autoantibody with high diagnostic specificity for RA. Anti-CCP antibodies can be present in the blood years before the manifestation of disease [3]. The main difference between anti-CCP and ACPA is that anti-CCP is more specific to RA, while ACPA is a bit more sensitive and can be used to detect RA earlier. Anti-CCP is typically associated with more active cases of the disease, while ACPA could sometimes be found in milder cases. Our patient was tested positive for this type of antibodies which subsequently directed the diagnostic evaluation towards RA.

Infections are a risk factor for disease exacerbation in patients with inflammatory arthritis [10]. The panel of proinflammatory cytokines that lead to severe forms of lung damage is comparable to cytokine profile responsible for the pathogenesis of the inflammation of the synovium in RA. Therefore, it could be presumed that COVID-19 infection could provoke a disease flare in RA patients [11]. In our patient, the disease presented mainly in the form of oligoarthritis until the patient had pneumonia caused by severe acute respiratory syndrome coronavirus 2. After the infection recovery, he suffered from exacerbation of joint ailments which manifested as polyarthritis. Baricitinib modulates signaling pathway of various cytokines involved in inflammatory processes throughout inhibition of JAK type 1 and type 2. Yang et al. [12] showed that in a group of patients treated with baricitinib, at week 12, a statistically significant improvement in American College of Rheumatology 20% (ACR20) response was achieved compared to patients randomized to a placebo group. Furthermore, they reported that treatment benefit was noticed even after one week of treatment and was kept during the 52 weeks. Study assessing a short-term effectiveness and safety of baricitinib in patients with RA, demonstrated that the effectiveness of baricitinib was significantly superior in targeted disease-modifying antirheumatic drug (DMARD) naïve patients compared to patients who were previously treated with targeted DMARD. Although the period of 24 weeks is short for evaluation of long-term adverse events, in this study six patients out of 113 involved in the trial discontinued baricitinib because of adverse events [13]. Treatment of RA patients usually considers prolonged use of DMARDs, thus it is very important to have an insight on the long-term safety profile of the prescribed drug. Group of authors conducted the largest integrated safety analysis of baricitinib with mean duration of the treatment lasting 4.6 years and up to 9.3 years. Results showed that the safety profile of baricitinib was comparable with other JAK inhibitors and biological DMARDs [14]. Furthermore, this JAK inhibitor can be used for a long period of time without concern of an increased risk of side effects in patients with RA. Our patient achieved low disease activity after three months of administering baricitinib. During 20 months of using combination therapy no side effects occurred.

In conclusion, every patient with pericarditis of unknown etiology should be diagnostically evaluated in term of connective tissue disease including RA, because initial clinical presentation in some group of patients could lack characteristic joint inflammation.

Conflict of interest: None declared.

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Атипична клиничка слика реуматоидног артритиса

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САЖЕТАК

Увод Реуматоидни артритис је системска аутоимуна болест са запаљењем зглобова као главним обележјем. Екстраартикуларне манифестације се јављају код скоро половине болесника и то или на почетку или у каснијем току болести. **Приказ болесника** Мушкарац стар 43 године жалио се на бол у грудима, сув кашаљ и умор. На основу ехокардиографског налаза постављена је дијагноза перикардитиса. Због погоршања респираторних симптома примљен је у болницу. Иницијалном дијагностичком обрадом верификоване су повишене концентрације реактаната акутне фазе, перикардни излив и билатерални нодуси плућа. Патохистолошком анализом пулмонарних нодуса искључени су малигнитет и туберкулоза. Болесник је лечен колхицином, чиме је постигнута регресија перикардног излива. Потом му је због артритиса десног ручног зглоба, високе седиментације еритроцита и Ц-реактивног протеина, позитивне имуносерологије и коштане ерозије на дисталном окрајку улне постављена дијагноза серопозитивног реуматоидног артритиса. Лечен је антималаријком, метотрексатом и глукокортикоидима све док није оболео од пнеумоније ковида 19, након чега долази до погоршања артритиса. Због секундарног губитка ефикасности комбиноване терапије метотрексатом и глукокортикоидом, додат је барицитиниб. Ниска активност болести је постигнута после три месеца, а током 20-месечне примене овог лека нису се јавила нежељена дејства.

Закључак Сваки болесник са перикардитисом непознате етиологије треба да буде дијагностички евалуиран у правцу болести везивног ткива укључујући реуматоидни артритис, зато што иницијална клиничка слика код одређене групе болесника може да буде без карактеристичног синовитиса.

Кључне речи: перикардитис; плућни нодус; реуматоидни артритис; пнеумонија ковида 19; акутизација; барицитиниб

DOI: https://doi.org/10.2298/SARH230206069K
UDC: 616.146-006.36-089

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Resection of inferior vena cava leiomyosarcoma and reconstruction using ProxiCor patch

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SUMMARY

Introduction Leiomyosarcoma of the inferior vena cava (IVC) is a rare mesenchymal tumor originating from the endothelial smooth muscle of the intima and account for about 1–2% of all the sarcomas of the soft tissue.

The objective of this article is to show a case of IVC leiomyosarcoma, it's resection and reconstruction using a ProxiCor patch.

Case outlines We showed a case of a 65-year-old woman presented with abdominal pain and mass in subhepatic space, who underwent surgery and resection of a leiomyosarcoma of IVC. IVC was reconstructed with ProxiCor patch, and histopathologically confirmed that it was leiomyosarcoma.

Conclusion Our experience has shown that the application of extracellular matrix is safe and has given a satisfactory treatment result. A comparison with a larger patient sample should give a true representation of the advantages and disadvantages of this type of material in vascular reconstructive procedures.

Keywords: inferior vena cava; leiomyosarcoma; ProxiCor

INTRODUCTION

Leiomyosarcoma (LMS) of the inferior vena cava (IVC) is a rare mesenchymal tumor originating from the endothelial smooth muscle of the intima and account for about 1–2% of all the soft tissue sarcomas [1]. From Perl and Virchow's first description in 1871 until today, less than 450 cases have been reported in literature [2]. Women in the fifth to sixth decade of life are dominantly affected [3]. Radical tumor resection was associated with better five- and 10-year survival rates 49.4% and 29.5%, respectively [3].

Because this disease is not common, data for management of this tumor are scarce and radical removal with grossly negative margins is considered the main treatment option [4]. Reconstruction techniques of IVC vary greatly in the published literature so far, which makes it difficult to form a consensus on the most appropriate reconstruction strategies, especially when achieving negative margins requires reconstruction in the form of interposition of different grafts [5, 6].

The purpose of this case report is to document our center's experience with IVC reconstruction using ProxiCor (Elutia, Silver Spring, MD, USA) patch after "en block" resection of LMS and the belonging segment of the IVC in order to achieve negative resection margins.

CASE REPORT

A 65-year-old female with a recent history of chronic abdominal pain was referred to our clinic. An abdominal computed tomography scan showed a mass of 73 × 56 × 54 mm in the subhepatic space, just below the right adrenal gland in close relationship with the IVC (Figures 1a and 1b). Esophago-gastroduodenoscopy and colonoscopy showed normal findings.

After multidisciplinary evaluation of the case, the patient was offered surgical treatment. Through midline incision, and after Cattell-Braasch and a Kocher maneuver, the infrahepatic IVC and renal veins were exposed. Intraoperative finding showed that previously described mass originated from the anterior aspect of the upper segment of the IVC, and it did not infiltrate the adjacent structures. Both renal veins and the right gonadal vein were prepared and reined in (Figure 1). A cranial and caudal clamping of the IVC was applied and the tumor was resected (Figure 2).

The vena cava defect of approximately 7 cm in size was reconstructed using a ProxiCor patch (Elutia).

The patch was sutured with two 5/0 polypropilene running sutures (Figure 3.). A heparinized solution was injected into the vessel and vascular clamp was then removed with good results.

The patient tolerated the procedure well and had no complications during her stay in the hospital. The patient was discharged on the ninth postoperative day with oral anticoagulant therapy.

No symptoms, nor complications were observed during the postoperative period and checkups.

Received • Примљено: February 6, 2023
Revised • Ревизија: June 4, 2023
Accepted • Прихваћено: June 22, 2023
Online first: July 10, 2023

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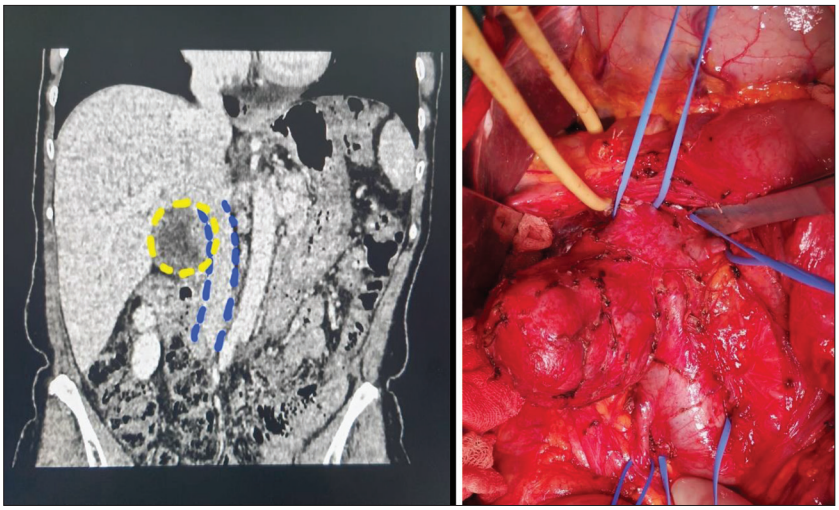

Figure 1. Multidetector computed tomography of the abdomen, coronal section; the yellow dashed lines mark the tumor; the blue dashed lines mark the border of the inferior vena cava (left); intraoperative finding (right); yellow tape is on the hepatoduodenal ligament, the uppermost blue tape on the inferior vena cava, left blue tape is on the left renal veins, two lower blue tapes are on the right gonadal vein and lower portion of the inferior vena cava

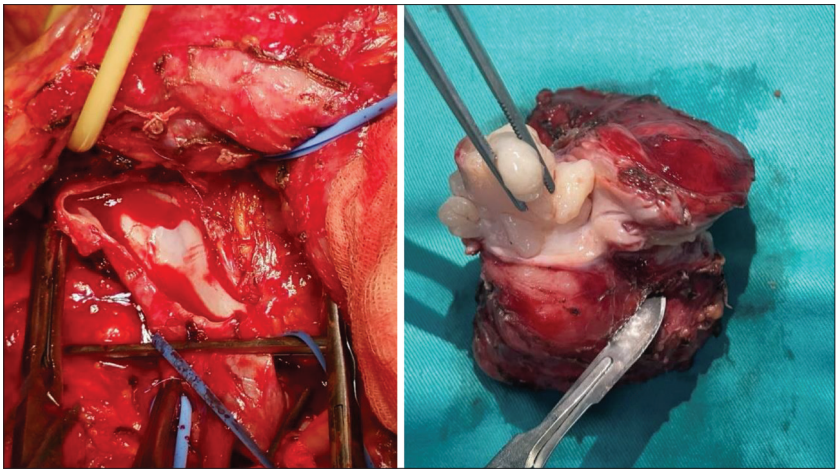

Figure 2. Resected inferior vena cava (left); resected tumor protruding into the lumen of the inferior vena cava (right)

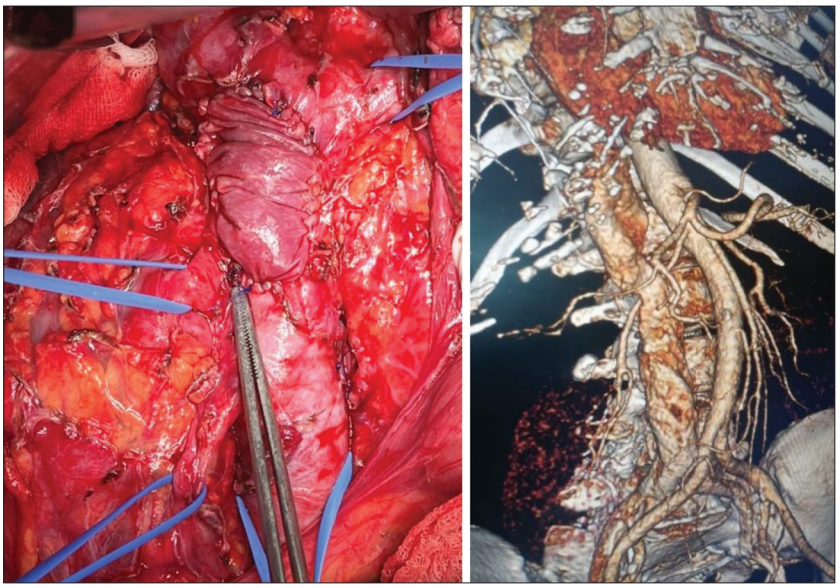

Figure 3. Inferior vena cava reconstruction using ProxiCor patch (Elutia), intraoperative appearance (left); a three-dimensional multidetector computed tomography reconstruction during the postoperative period (right)

The histomorphological and immunohistochemical characteristics of the tumor correspond to a high-grade primary malignant mesenchymal tumor of smooth muscle differentiation of the LMS type, with the largest diameter of 67 mm.

No evidence of the disease at the time of this report, six months after the surgery.

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

DISCUSSION

LMS of the IVC are exceedingly rare and with an incidence < 1/100,000 of all adult malignancies [7]. Because of the rarity of the disease, case studies and case reports are making the majority of available literature, thus are clinical decisions in everyday practice so difficult and no consensus on ideal management of these tumors exist. To our knowledge, surgical resection with negative margins is currently the only curative treatment and the best predictor of long-term survivals for LMS of the IVC [8]. In study conducted by Hines et al. [9], which included 14 patients with IVC LMSs, a five-year survival rate in patients who had positive margins was 0%, while on the other hand, patients with negative margins had significantly higher five-year survival rate of 68%. Similar results were shown in a study by Hollenbeck et al. [10] that included 25 patients, which showed a three-year survival of 76% in patients with negative margins and 0% in group of patients with positive margins. On the other hand, a recent study has shown that neither disease-free survival rate, nor overall survival was not influenced by microscopic margin status [2].

In rare cases, the slow growth of the tumor causes complete obstruction of the IVC and promotes the development of numerous collaterals, and allows radical surgery without vascular reconstruction of IVC; however, low extremity edema is a frequent complication [11].

In the majority of cases, after resection of the IVC due to LMS, vascular reconstruction is often required. In the previous literature, the highest percentage of reconstruction involves the use of polytetrafluoroethylene graft [12]. In a study by Pan et al. [12] among the 315 cases (83.6%) with provided operative details, the IVC was ligated

in 20.3%, primarily repaired in 21.9%, and replaced by prosthetic graft in 49.2%. Other types of materials that were used in reconstruction of IVC included: cadaveric graft (3.2%), bovine pericardium (1.6%), autologous vein (3.5%), and autologous peritoneum (0.3%) [12].

The use of biological material in IVC reconstruction is extremely rare [12, 13]. Therefore, the main indication for the application of biological material remains after the removal of the infected prosthetic graft [13]. In our case, we used ProxiCor (Elutia) to reconstruct the IVC defect after resection. ProxiCor (Elutia) is an extracellular matrix (ECM) derived from submucosa of porcine small intestine.

The previous experience of this material is dominant in cardiac surgery in pericardial reconstruction and in cases such as repair of atrial or ventricular septal defect [14]. Unlike the synthetic alternative, this material has shown reduced foreign body reaction and postoperative inflammation [14]. Compared to other materials used in reconstructive procedures, ECM is significantly more expensive. To the best of our knowledge this is the first case of vascular reconstruction by ECM after IVC resection due to LMS. In our case, after the application of this material, there were no postoperative complications in the form of IVC thrombosis, thromboembolic complications, or infections.

Intraoperative bleeding control with caudal and proximal IVC clamping has been shown to lead to stasis and increase the risk of thrombosis, and therefore intraoperative systemic heparinization prevents this complication [15]. In contrast, the use of postoperative systemic anticoagulants after IVC resection and reconstruction is still debated and there are no clear guidelines on this topic. During the hospitalization, our patient was prescribed low-molecular-weight heparin (0.4 ml twice a day), while in the postoperative period, novel anticoagulant drug was prescribed. Until the publication of the case report, the patency of the reconstructed segment of the vena cava was preserved.

Our experience has shown that the application of ECM is safe and has given a satisfactory treatment result. A comparison with a much larger number of patients will give a true presentation of the advantages and disadvantages of this type of material in vascular reconstructive procedures.

Conflict of interest: None declared.

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Ресекција лејомиосаркома доње шупље вене и реконструкција *ProxiCor*-ом

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САЖЕТАК

Увод Лејомиосарком доње шупље вене је редак мезенхимални тумор порекла ендотелијалних глатких мишићних ћелија интиме и чини око 1–2% свих саркома меких ткива. Циљ овог рада је да прикаже случај болеснице са лејомиосаркомом доње шупље вене, ресекцију тог тумора и реконструкцију закрпом *ProxiCor*.

Приказ болесника Приказан је случај болеснице старе 65 година, са боловима у трбуху и масом у субхепатичном простору, код које је урађена хируршка ресекција тумора, са реконструкцијом доње шупље вене закрпом *ProxiCor*. Хистопатолошка анализа је потврдила да се ради и лејомиосакрому.

Закључак Наше искуство је показало да је употреба екстрацелуларног матрикса сигурна и да даје задовољавајуће резултате у лечењу. Поређење са знатно већим бројем болесника пружиће бољи увид у предности и мане овог материјала у васкуларним реконструктивним процедурама.

Кључне речи: доња шупља вена; лејомиосарком; *ProxiCor*

DOI: https://doi.org/10.2298/SARH220920063P
UDC: 616.341-006.44-073

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Ileal leiomyosarcoma as a cause of small bowel obstruction

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SUMMARY

Introduction Ileal leiomyosarcoma is unusual form of malignant gastrointestinal tumor. Often insidious in clinical presentation, it frequently presents a diagnostic challenge. Occasionally, a correct diagnosis is finally established due to an emergency situation.

The aim of this study was to present the role of magnetic enterography in determining the precise cause of small bowel dilation.

Case outline A 59-year-old female patient presented with small bowel obstruction. Erect abdominal radiograph identified the presence of small bowel obstruction and excluded pneumoperitoneum. A non-contrast computed tomography of the abdomen and pelvis noted transitional zone in the region of terminal ileum with collapsed bowel lumen distal to the transitional point, without determined underlying cause. Magnetic resonance enterography observed obstructive intraluminal soft-tissue mass with fatty component sized up to 4 cm in the terminal ileum, with mesenteric involvement. The abdominal surgeon revealed ileal intraluminal tumor which affected the locoregional mesentery and serosa of the adjacent bowel. Histological and immunohistochemical analysis confirmed the diagnosis of ileal leiomyosarcoma with involvement of wall serosa and mesenteric fat tissue.

Conclusion Magnetic resonance enterography is a reliable diagnostic tool for detection and diagnosis of malignant small bowel tumors. Sometimes, tumors manifest clinically as bowel obstruction. Surgical treatment is necessary, while histology and immunohistochemistry are crucial to confirm the diagnosis of small bowel leiomyosarcoma.

Keywords: leiomyosarcoma; small bowel malignant tumor; magnetic resonance enterography

INTRODUCTION

Malignant tumors of the small bowel account for less than 5% of all gastrointestinal malignancies. Sarcomas account for only 1.2% of small bowel malignancies, with leiomyosarcoma as the most common subtype [1, 2]. Primary leiomyosarcomas of the gastrointestinal tract are uncommon. Thus, the World Health Organization cannot provide their current demographic or clinical features [1, 3]. They are often diagnosed incidentally during abdominal pain investigation. Magnetic resonance enterography (MRE) is a non-invasive cross-sectional technique with higher spatial resolution than computed tomography and thus, it enables better visualization of the intestinal wall and accurate characterization of the small bowel neoplasms and extraenteric extent of the disease [4].

CASE REPORT

A 59-year-old female patient presented to the Emergency Department with complaints of acute supraumbilical abdominal pain, nausea and vomiting. She also noticed loss of appetite and abdominal bloating. The symptoms had lasted for four days. She had had occasional vague abdominal pain with diarrhea for two months. She underwent pelvic surgery due to endometrial cancer and received complete pelvic radiation therapy 30-years ago. Tumor markers for ovarian cancer were elevated for four years.

The patient underwent ultrasonographic evaluation, which revealed dilated lumen of the small bowel. There were no signs of abdominal mass on palpation. Erect native abdominal radiography showed features of small bowel obstruction, without pneumoperitoneum. The hemogram was normal. Abdominal and pelvic computed tomography was performed without contrast administration due to an allergy to iodine. Dilatation of the ileum and jejunum was noted, with transitional zone in the region of terminal ileum, but without identification of the cause of obstruction. Lumen of the dilatated small bowel was approximately 35 mm. Lumen of the ileum distal to the transitional point was collapsed. The patient was administered to Clinic for Abdominal and Endocrine Surgery. After admission, the conservative treatment was attempted by placing a nasogastric tube, parenteral administration of antispasmodics

Received • Примљено: September 20, 2022
Revised • Ревизија: May 28, 2023
Accepted • Прихваћено: June 2, 2023
Online first: July 3, 2023

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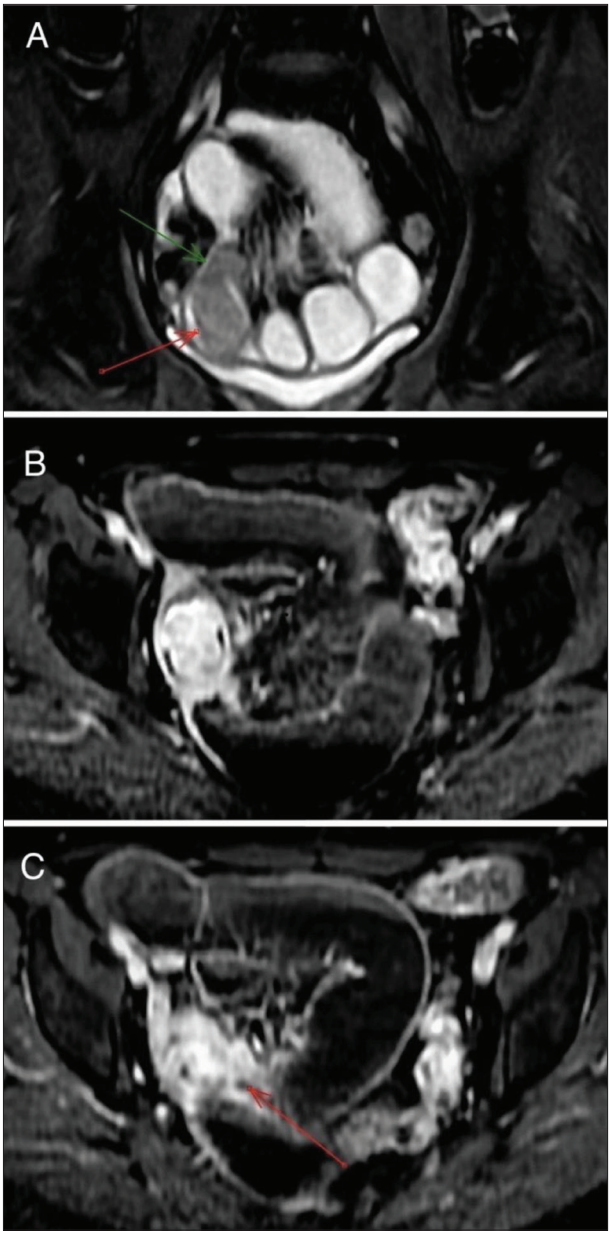

Figure 1. Magnetic resonance enterography demonstrates intraluminal ileal leiomyosarcoma presenting as moderate T2W hyperintensity (A – coronal image, red and green arrow) with intense heterogeneous enhancement (B – axial image) and mesenteric involvement (C – axial image, red arrow)

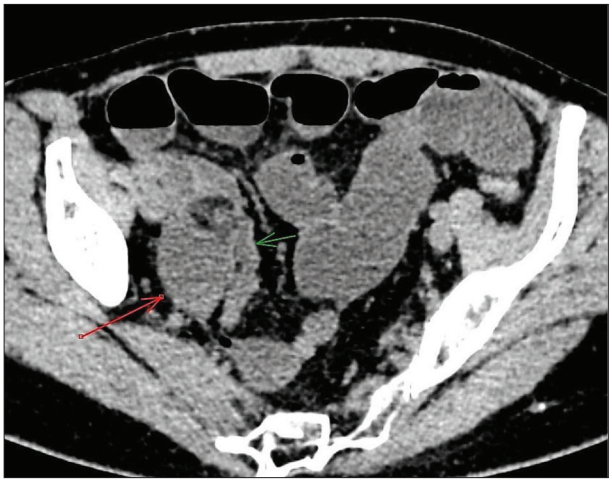

Figure 2. Native computed tomography scan in axial plane showing dilatated bowel lumen proximal to the transitional point (red arrow), collapsed bowel lumen distal to the transitional point (green arrow) and intraluminal fat-containing component in the ileum in the transitional zone

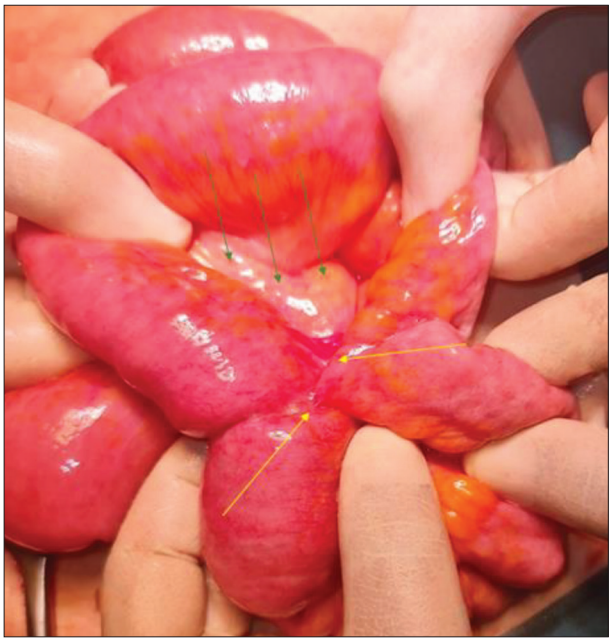

Figure 3. Intraoperative view of locally advanced stenotic tumor of the ileum (green arrows) with involvement of the adjacent small bowel (yellow arrows)

and analgesics, but without clinical improvement. The next day, after revision of the entire medical documentation, with the consent of the attending abdominal surgeon, radiologist decided to perform an MRE examination with reduced volume of luminal contrast agent. MRE with diffusion weighted imaging and application of intravenous contrast agent was performed. Mechanical obstruction of the small bowel was confirmed. Also, oval polypoid obstructive intraluminal soft mass in terminal ileum, diameter up to 4 cm, with partially indistinct contours and eccentric thickening of the intestinal wall was observed. The lesion had moderate T2W signal hyperintensity, with internal fat component depicted on dual sequence and restriction of diffusion. After administration of intravenous contrast agent, the lesion showed intense heterogeneous enhancement. Mesenteric involvement was present, with pronounced vascular structures and altered morphology of lymph nodes, without metastases in other organs (Figure 1). Initial non-contrast computed tomography images were reviewed, revealing intraluminal fat-containing component in the ileum in the transitional zone, which was initially thought to be the intraluminal content (Figure 2).

After surgical board, the patient was scheduled for open laparotomy. The surgery revealed the presence of a locally advanced stenotic tumor of the ileum with involvement of the adjacent small bowel (Figure 3). Partial small bowel resection with latero-lateral ileo-ileal anastomosis was performed.

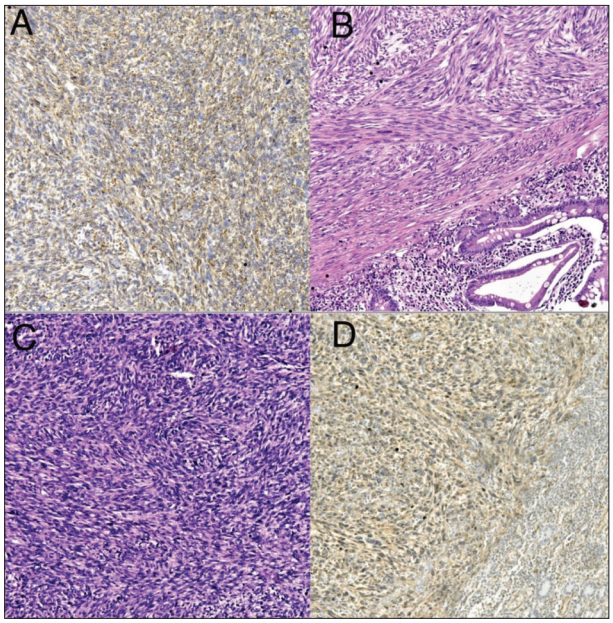

Figure 4. Microscopic photographs of the ileal leiomyosarcoma; A – Desmin immunostain, 10 × 10; B – HE, 10 × 10; C – HE, 10 × 10; D – SMA, 10 × 10

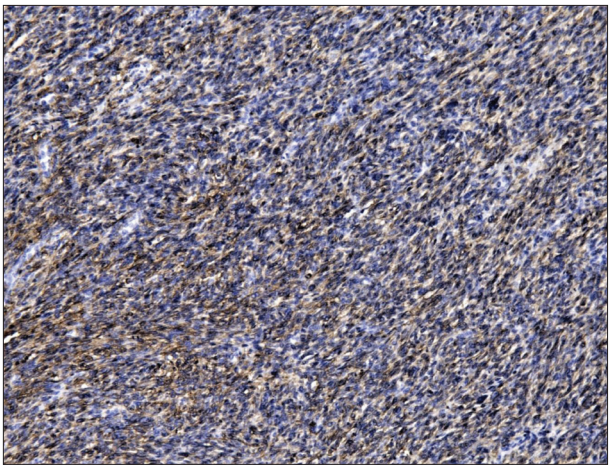

Figure 5. Microscopic photography of the ileal leiomyosarcoma. H caldesmon, 10 × 10

The tumor nodule was 5 × 3 cm in size. Histopathological examination showed that tissue of tumor was made up of spindle cells partly in a palisade arrangement, elongated vascular hyperchromic nuclei, and medium abundant acidophilic cytoplasm. Multinucleated tumor cells were focally present. Immunohistochemical analyses showed actin and desmin positive reactivity, CD117, CD34, DOG 1, and S100 negativity. Histological and immunohistochemical analysis were consisted with definitive diagnosis of leiomyosarcoma of ileum with involvement of intestinal serosa and locoregional fat tissue (Figures 4 and 5).

Decision of the Ethics Committee of the University Clinical Center of Vojvodina is as follows: Consent is given to carry out research in order to produce a scientific paper entitled "Ileoal leiomyiosarcoma as a cause of small bowel obstruction", at the request of Dr Jelena Pilipović-Grubor.

DISCUSSION

Leiomyosarcomas are aggressive mesenchymal malignant tumors. The median overall survival for intestinal leiomyosarcoma is about one year, while a five-year survival rate ranges from 5% to 27%, in patients with tumors over 5 cm in diameter [5]. The fact that only 26 cases of leiomyosarcoma have been published to date shows how uncommon these tumors are [2]. Most commonly they occur in the retroperitoneal space, uterus, vascular wall, and soft tissue. Within the gastrointestinal tract, the small bowel is the most common site of presentation, of which 32% of cases occurs in the jejunum and 25% in the ileum [6].

Clinically, the small bowel malignant neoplasms are often asymptomatic in the early stages. This may delay the final diagnosis of this disease, which already has poor prognosis [3]. It typically affects middle-aged patients, with a mean age of 50 years [7]. As in our case, most patients have non-specific clinical symptoms, such as recurrent vague abdominal pain (usually treated with a muscle relaxant and a probiotic for a period of time) [2, 8]. These are the main complaints when the small bowel tumors are small in size. Respectively, while intraluminal small bowel neoplasms are smaller than 5 cm, they are usually detected incidentally, during a clinical and radiological examination or follow-up of other diseases and conditions associated with the abdomen and pelvis. However, when they are large, they can manifest with anemia, hemorrhage and acute abdominal pain, but often with metastases [9].

Leiomyosarcomas of the small bowel grow slowly, predominantly extraluminally. Conversely, in our patient it grew primarily intraluminally, which makes our case even more rare. At a certain moment, along with other clinical symptoms and signs, they develop bowel subocclusion. What further complicates and delays the diagnosis are recurrent subocclusions, which are manifested by acute abdominal pain. Subocclusions occur and resolve spontaneously many times. It is highly likely that this is exactly what was happening to our patient for two months. Recurrent subocclusions are clinically manifested by chronic cramping abdominal pain that often disappears after application of conservative therapy, but should always raise suspicion of an intestinal tumor, especially in elderly patients [10].

Conventional computed tomography is the imaging modality routinely used in bowel obstruction, as initial test (after ultrasonographic evaluation and abdominal radiography), but it has limited specificity. Although it has high diagnostic accuracy in the identification of high-grade small bowel obstructions, it is unreliable in the identification of low-grade small bowel obstructions [11]. However, the conventional computed tomography examination provides significant information about the location where small bowel caliber changes from normal to abnormal (collapsed). Computed tomography can evaluate associated complications, locoregional changes, as well as other organs. In the presented case, intravenous contrast medium was not administered due to an allergy

to iodine. This precluded the detection of an intraluminal small bowel neoplasm.

The ability of radiological cross-sectional techniques (computed tomography and magnetic resonance) in detection and evaluating the small bowel neoplasm has significantly increased with introduction of luminal contrast agents [11]. The most commonly used enteral contrast agent in MRE is biphasic contrast, which cause high signal intensity on T2 weighted images and low signal intensity on T1 weighted images [4]. To achieve optimal small bowel distension, which is crucial for the correct evaluation of the bowel wall, a volume of 1350–1500 ml is adequate in most cases [12]. In patients who have had a small bowel resection or have subacute and low-grade small bowel obstruction, as our patient, a volume of enteral contrast is reduced [13]. MRE imaging provides more detailed morphologic information compared to a computed tomography scan. Additionally, dynamic CINE magnetic resonance imaging provides functional data about motility of the small bowel [4].

Magnetic resonance finding of intestinal leiomyosarcoma can be extraluminal or rarely intraluminal heterogeneous signal intensity mass on T2 weighted images with partially indistinct contours and eccentric thickening of the intestinal wall. On fat suppressed T2 weighted images, there is usually an irregular zone of low signal intensity within the leiomyosarcomas duo to the presence of a lipid component in the tumor. On postcontrast images, after injection of gadolinium-based contrast agent, leiomyosarcomas show heterogeneous moderate enhancement. Often, as in other malignant tumors of the small bowel, there are already changes in locoregional fat tissue, with pronounced vascular structures and altered morphology of lymph nodes. The addition of diffusion weighted sequence to MRE improves sensitivity for small bowel disease, especially in the detection of malignant tumors which have diffusion weighted imaging hyperintense signal, as a consequence of hypercellularity. In addition to allowing the identification of a malignant tumor of the small bowel, MRE provides enough data to accurately determine the stage of the disease [4, 13].

Ileal leiomyosarcoma is an unusual cause of small bowel obstruction in adults. MRE is a highly sensitive diagnostic procedures for detection and assessment the mesenchymal malignant tumors of small bowel, their involvement of local invasion and extraintestinal structures.

Conflict of interest: None declared.

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Леомиосарком илеума као узрок опструкције танког црева

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САЖЕТАК

Увод Леомиосарком илеума није чест облик малигног тумора гастроинтестиналног тракта. Због подмукле клиничке слике неретко представља дијагностички проблем. Понекад се права дијагноза постави тек када дође до ургентног стања.

Циљ овог рада је да се представи улога магнетнорезонантне ентерографије у одређивању тачног узрока настанка проширења лумена танког црева.

Приказ болесника Приказујемо случај болеснице старости 59 година са клиничком сликом опструкције танког црева. Нативни рендгенски снимак абдомена у стајању утврдио је постојање опструкције танког црева, без пнеумоперитонеума. Нативни преглед абдомена и мале карлице на компјутеризованој томографији без контраста приказао је транзиторну зону у регији терминалног илеума са колабираним луменом илеума дистално од места транзиторне тачке, без детерминисања правог узрока. Магнетнорезонантна ентерографија је открила постојање опструктивне интралуминалне мекоткивне промене у терминалном илеуму, величине око 4 *cm*, која садржи липидну компоненту и захвата околни мезентеријум. Абдоминални хирург је установио постојање тумора дисталног илеума са захватањем локорегионалног мезентеријума и серозе околних црева. Хистолошком и имунохистохемијском анализом потврђена је дијагноза леомиосаркома илеума уз инфилтрацију серозе зида и мезентеријалног масног ткива.

Закључак Магнетнорезонантна ентерографија је поуздана дијагностичка метода за откривање и карактеризацију малигних тумора танког црева. Понекад се тумори приказују клиничком сликом опструкције црева. Хируршко лечење је неопходно, док су хистологија и имунохистохемија пресудни за постављање дијагнозе леомиосаркома танког црева.

Кључне речи: леомиосарком; малигни тумори танког црева; магнетнорезонантна ентерографија

DOI: https://doi.org/10.2298/SARH221227086B
UDC: 618.31

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Spontaneous bilateral tubal pregnancy – case report and review of diagnostic and treatment difficulties

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SUMMARY
Introduction Spontaneous bilateral ectopic pregnancy is a rare condition easily overlooked or misdiagnosed. We present a case of spontaneous bilateral tubal ectopic pregnancy and discuss the difficulties in diagnosing and treating such patients.
Case outline A 39-years-old patient with a history of irregular and abundant menstrual cycles complained of pelvic pain and light bleeding after 55 days of amenorrhea. Ultrasound revealed enlarged uterus with a myoma and a heterogenic formation with echogenic ring sign beside the left ovary. Free fluid with clots was present in the pelvis. As the patient was hemodynamically unstable and ectopic pregnancy was suspected, emergency laparotomy was performed. During the surgery we found that both tubes were significantly edematous, dilated, and livid in their ampullary regions. On the left tube anterior wall rupture 15 × 8 mm was noticeable, while right tube was intact with bleeding from its abdominal ostium. Even though the patient was not informed about the possibility of bilateral salpingectomy, after thorough consideration and due to the extent of tubal damage bilateral salpingectomy was eventually performed. Histopathological analysis confirmed the presence of decidua, partially viable and partially necrotic chorionic villi, and trophoblastic tissue in both right and left tubes.
Conclusions Careful preoperative and intraoperative examination of both Fallopian tubes as well as the whole abdominal and pelvic cavity should be mandatory during every assessment of patients with ectopic pregnancy.
Keywords: ectopic pregnancy; bilateral; spontaneous; diagnosis; treatment

INTRODUCTION

Ectopic pregnancy occurs in 1.5–2% of all pregnancies. Even with modern diagnostic and therapeutic tools ectopic pregnancy remains the most common life-threatening emergency in early pregnancy, causing significant maternal morbidity and mortality [1, 2, 3].

The ectopic trophoblast implantation mostly occurs in the ampullar region of one of the Fallopian tubes. However, two or more simultaneous gestations can occur in both of the tubes in the same patient [1, 2]. This condition is called bilateral ectopic pregnancy and is a rare clinical entity (1 in 200,000 pregnancies) usually associated with assisted reproduction. Contrary, primary i.e., spontaneous bilateral ectopic pregnancy is even more infrequent (1/725-1580 of the ectopic pregnancies) [1–4].

We present an incidental finding of spontaneous bilateral tubal ectopic pregnancy during urgent laparotomy and discuss the difficulties in diagnosing and treatment of such patients.

CASE REPORT

A 39-years-old patient was admitted to our hospital due to diffuse moderate blunt intermittent pelvic pain during the previous three days. Moreover, she had just started bleeding after the period of amenorrhea, what was accompanied by general weakness and coldish sweating.

The patient complained that her menstrual cycles were irregular (25–45 days), profuse and lasting 10–15 days since her last delivery. At the time of examination, amenorrhea lasted for 55 days. Still, patient stated that during this period of amenorrhea she noticed occasional spotting. There was no past history of any risk factor that might be linked to ectopic pregnancy (sexually transmitted diseases, pelvic inflammatory diseases, pregnancy termination, previous operations, intrauterine devices, fertility enhancing drugs or assisted reproduction). She had two spontaneous pregnancies followed by term vaginal deliveries of healthy children five and two years prior.

On examination she was pale, sweaty, and hypotensive with a blood pressure of 90/60 mmHg and a pulse of 92 beats per minute. The abdomen showed signs of peritoneal irritation (tension and painfulness). Her vulva was blood-stained and light fresh bleeding from the uterus was visible. Gynecologic examination revealed enlarged, softened uterus with uneven surface and bilateral thickening of adnexal regions. The uterus, adnexa, and the pouch of Douglas were

Received • Примљено: December 27, 2022
Revised • Ревизија: September 13, 2023
Accepted • Прихваћено: September 21, 2023
Online first: September 29, 2023

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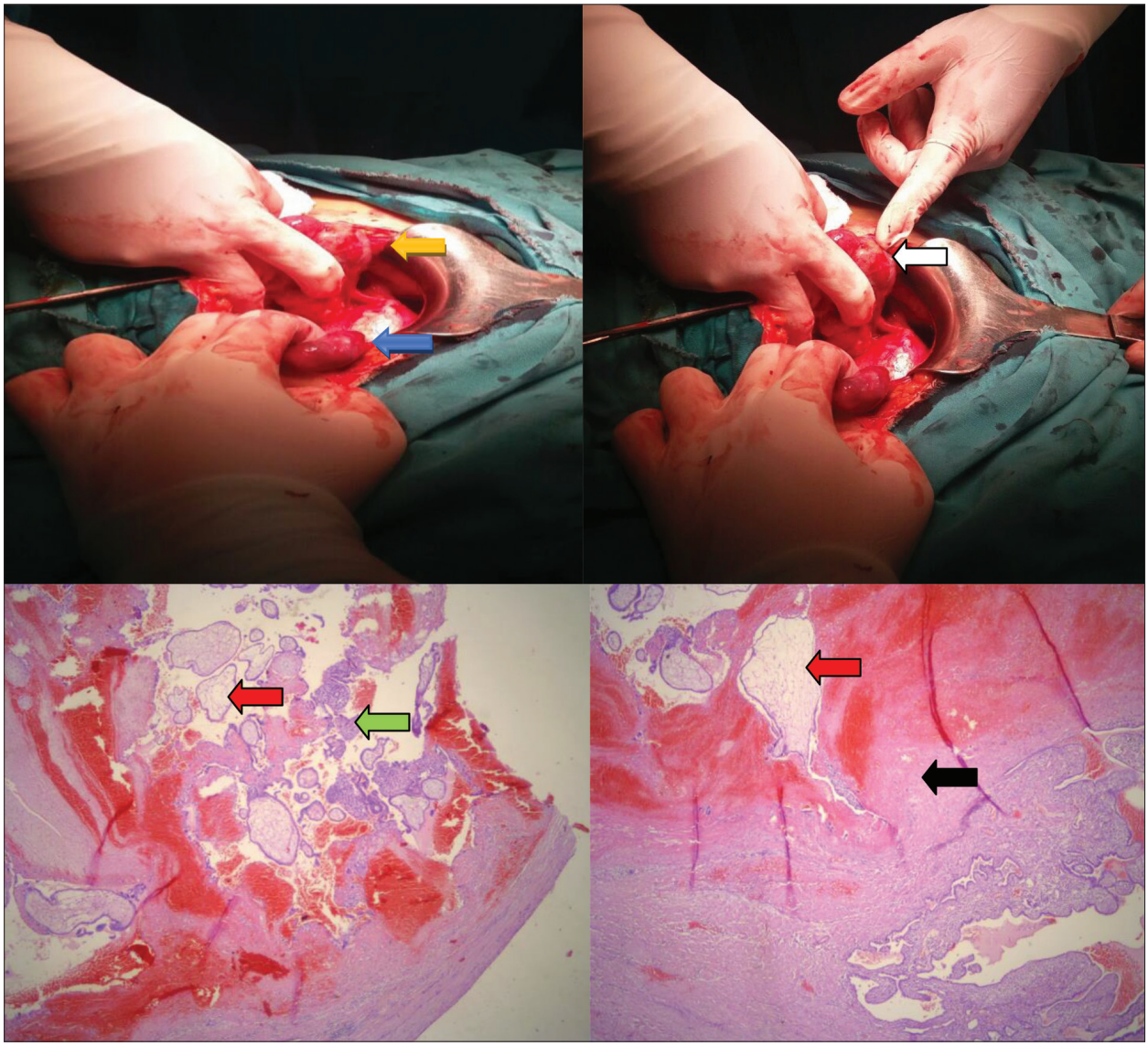

Figure 1. Intraoperative and histopathological findings of bilateral ectopic pregnancy: yellow arrow points to the left Fallopian tube with tubal pregnancy; blue arrow points to the right Fallopian tube with tubal pregnancy; white arrow points to the rupture of the anterior wall of the left Fallopian tube; red arrows point to extrauterine chorionic villi in both tubes; green arrow points to trophoblast; black arrow points to ectopic decidua attached to tubal wall

painful on palpation. There were no other pathological findings. Hemoglobin and hematocrit levels were significantly decreased (92 g/l and 30% respectively), but all other laboratory tests were in referral range. Serum Beta human chorionic gonadotropin (HCG) was 14,750 IU/l.

Ultrasound scan showed enlarged uterus 98 × 65 × 80 mm, with a myoma 43 × 35 mm on the right lateral and posterior wall. The endometrium was 14 mm thick with no signs of intrauterine gravidity. The left ovary was 36 × 23 mm in diameter with a follicle sized 19 mm. Next to the left ovary a heterogenic formation sized 39 × 35 mm with echogenic ring sign, suspected of ectopic gestational sack was seen. The right ovary was 34 × 32 mm in diameter with the largest follicle of 13 mm. Free fluid with blood cloths was presented in the Douglas pouch.

Considering the patient's condition, clinical, and ultrasound signs of ectopic pregnancy accompanied by abdominal hemorrhage, we performed an emergency laparotomy. The patient was informed about her condition and findings, the need for urgent surgery and the possibility of removing the left Fallopian tube. During surgery, we astonishingly found that both tubes were significantly edematous, dilated (right 37 × 32 mm and left 35 × 44 mm) and livid in their ampullar segments (Figure 1). Both tubes fell into the Douglas pouch and blood was dripping from the ruptured anterior wall (15 × 8 mm in diameter) of the left Fallopian tube. The right tube was intact but still small amount of blood was observed on the fimbrial end.

Because of the extent of tubal damage left salpingectomy had to be performed using Covidien LigaSure 5 mm Sealer/Divider® (Medtronic, Dublin, Ireland) coagulation. Right salpingotomy just above the dilated part of the tube and evacuation of ovular tissue from the Fallopian tube was attempted, but it was followed by abundant bleeding from the site of the salpingotomy. Consequently, after considering patients' hemodynamic instability and that she already

had two normal childbirths, it was decided to perform the right salpingectomy as well. Upon this, hemodynamic stability was achieved.

Histopathological analysis confirmed the presence of decidua, partially viable and partially necrotic chorionic villi, and trophoblastic tissue in both right and left tubes (Figure 1). The postoperative course was uneventful, and the patient fully recovered. The patient was informed about an unexpected finding and the course of the operation as this life-threatening condition required to extend the procedure, with which she consented.

The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved. No personal data of the patient were presented in the manuscript.

The patient's written consent was obtained for the writing of this case report.

DISCUSSION

The typical risk factors for ectopic pregnancy include sexually transmitted diseases, endometriosis, and surgical intervention in the pelvis and abdomen that all can cause damage of the endosalpinx or adhesions that incorporate the Fallopian tubes. Also, Müllerian malformations, hormonal imbalances, late and multiple ovulations, endometrial tissue movements, tubal transmigration of the fertilized ovum, history of previous ectopic pregnancy, tobacco smoking, etc. [5, 6, 7]. In recent decades, one of the most common causes of ectopic pregnancy is assisted reproduction techniques especially those with ovulation induction. On the other hand, in the case of spontaneous bilateral tubal pregnancy, a spontaneous ovulation of two or more oocytes or the early embryo division must occur which is quite rare [4, 6]. Therefore, a personal or family history of twinning and the use of fertility drugs are considered to increase the risk of spontaneous ectopic pregnancy. Still, approximately half of women with ectopic pregnancies do not have any known risk factors [1, 2]. Our patient also had no major risk factors. Her only complaints were irregular cycles in past two years that implied hormonal disturbance. Her endocrinological status was still under the evaluation at the time of bilateral ectopic pregnancy occurrence. Moreover, abundant bleeding and anemia could imply on the cycle disturbances due to uterine myoma.

The majority of all ectopic pregnancies (up to 97%) are localized in the Fallopian tubes especially in their ampullar region (80%) [5]. The same is for bilateral tubal ectopic pregnancy that is ampullar in 73% of cases, and around 70% are unruptured at the time of diagnosis [1, 2, 8]. The gestational age of bilateral ectopic pregnancy at the time of diagnosis is usually 5–13 gestational weeks [1, 2, 8]. Our patient was in the sixth gestational week and had a typical, ampullar localization of ectopic pregnancy in both Fallopian tubes. Moreover, while one tube was intact, the other had already ruptured causing hematoperitoneum.

The most common symptoms/signs of ectopic pregnancy incorporate the triad of amenorrhea, vaginal bleeding, and pelvic pain. As the condition progresses with the rupture of the tubes, patients develop abdominal bleeding, acute abdomen, and finally hemorrhagic shock [6, 9]. The majority of patients with bilateral ectopic pregnancy have similar presentation and findings to those with a unilateral ectopic pregnancy, which makes the early diagnosing of bilateral tubal pregnancy particularly challenging [10–13]. Clinical analysis of our patient confirmed classical signs and symptoms of ectopic pregnancy. However, at that moment there were no indications for bilateral tubal affection. Moreover, due to irregular menstrual cycles the patient did not suspect pregnancy at all, which delayed the diagnosis.

Thorough gynecological examination with detailed transvaginal ultrasound scan can usually detect ectopic pregnancy in around 90% of cases [1, 2]. Color Doppler increases the ultrasound diagnostic accuracy even more [7, 8]. However, bilateral ectopic pregnancy is easily overlooked even when unilateral one is diagnosed due to the fact that ultrasound finding explains all of the clinical symptoms [4, 7]. Furthermore, different uterine and adnexal pathologies could mislead the interpretation of the ultrasonographic findings [12].

Moreover, the Beta HCG serum levels are not reliable in these cases. Generally, in case of ectopic pregnancy Beta HCG levels are increased, but their amplification progresses slower than in the healthy intrauterine pregnancy. Studies have also shown that in patients with bilateral ectopic pregnancy Beta HCG levels could be either significantly higher, or in the referral range for the gestational week, just like in our case [7, 8, 9].

Consequently, bilateral tubal ectopic pregnancy is usually confirmed only intraoperatively upon careful inspection of both tubes. Missed diagnosis could delay the treatment and worsen prognosis, making it a life-threatening condition [6, 7, 14]. In this case, we missed the ectopic pregnancy in the right tube by the transvaginal ultrasound as it was superposed by the myoma of the right uterine wall.

The treatment of ectopic pregnancy includes medications or surgical approaches that are selected according to patients' general condition, extent of tubal damage, and need for fertility preservation [6, 14, 15]. However, due to its rarity, currently there are no adequate protocols for bilateral tubal ectopic pregnancy management [6]. Although there were patients efficiently treated with Methotrexate, the success rate was not satisfactory because the levels of Beta HCG were higher than the permissible for Methotrexate application at the time of diagnosis [1, 5, 6]. It is still unclear whether the usual dose of Methotrexate used for unilateral tubal ectopic pregnancy should or should not be increased in the case of bilateral one [1, 5, 6].

According to current guidelines, surgical treatment of ectopic pregnancy should be performed in case of significant abdominal pain, adnexal mass of 35 mm or larger, positive fetal heartbeat, and/or Beta HCG levels over 5000 mIU/ml [4]. It includes salpingectomy (removal of the affected tube if it is ruptured and significantly damaged) or salpingotomy (conservative method of pregnancy removal with

tubal preservation when the tubes have remained intact and in patients who wish to preserve fertility). Laparoscopy is method of choice for majority of these patients [1, 4, 5, 6].

The choice of treatment for patients with bilateral tubal ectopic pregnancy in which both tubes are damaged is never easy, especially in nulliparous young women when diagnosis is intraoperatively established [11, 12, 13]. Thus, it is advisable that in all cases of ectopic pregnancies patients should be informed of all potential treatment options and complications, and their consent is obtained before surgery [1]. In patients with bilateral tubal ectopic pregnancy bilateral salpingostomy is performed in 42%, bilateral salpingectomy in 33%, and combination of salpingostomy and salpingectomy in 25% of cases, mostly by laparotomy in more urgent and complex situations [6, 14, 15]. We had to perform bilateral salpingectomy as the patient was hemodynamically unstable during the operation, and taking into account that she had already had two healthy children.

In conclusion, the presented case highlights the fact that careful preoperative and intraoperative examination of genital organs, both Fallopian tubes, as well as the whole abdominal and pelvic cavity should be routine and mandatory during assessment of all patients with ectopic pregnancy.

Conflict of interest: None declared.

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Спонтана билатерална тубарна трудноћа – приказ случаја и тешкоће у дијагностици и лечењу

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САЖЕТАК

Увод Спонтана билатерална ектопична трудноћа је ретко стање које се лако превиди или погрешно дијагностикује. Представљамо случај спонтане билатералне тубарне ектопичне трудноће и разматрамо потешкоће у дијагностици и лечењу таквих пацијенткиња.

Приказ случаја Пацијенткиња стара 39 година са историјом неправилних и обилних менструалних циклуса жалила се на бол у карлици и оскудно вагинално крварење након 55 дана аменореје. Ултразвуком је утврђена увећана материца са миомом и хетерогена формација са ехогеним прстенастим одјеком поред левог јајника. У карлици је била присутна слободна течност са коагулумима. Пошто је пацијенткиња била хемодинамски нестабилна и сумњало се на ектопичну трудноћу, урађена је хитна лапаротомија. Током операције уочено је да су оба јајовода била едематозна, проширена и ливидна у својим ампуларним сегментима. На левом јајоводу је примећена руптура предњег зида 15 × 8 *mm*, док је десни јајовод био интактан, са крварењем из абдоминалног отвора. Иако пацијенткиња није била обавештена о могућности билатералне салпингектомије, због степена оштећења јајовода, после детаљног разматрања урађена је билатерална салпингектомија. Хистопатолошком анализом потврђено је присуство децидуе, делимично вијабилних и делимично некротичних хорионских ресица, као и трофобластног ткива у левом и десном јајоводу.

Закључак Код пацијенткиња са ектопичном трудноћом неопходна је пажљива преоперативна и интраоперативна евалуација како унутрашњих гениталних органа, тако и целе мале карлице и трбушне дупље.

Кључне речи: ектопична трудноћа; билатерална; спонтана; дијагноза; лечење

DOI: https://doi.org/10.2298/SARH230510065V
UDC: 616.22-005.98

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Edema of the larynx – an emergency caused by angina Ludovici

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SUMMARY

Introduction Laryngeal edema is a rare complication of angina Ludovici. Infections of this region are mostly of dentogenic origin, less often caused by tonsillitis or other infections in the pharynx. We present a case of a patient with laryngeal edema and dyspnea caused by a lower jaw tooth infection and an ipsilateral submandibular abscess.

Case outline The clinical picture of our patient progressed rapidly – from toothache, painful swelling of the floor of the oral cavity, submandibular and submental regions, bilaterally, all the way to life-threatening dyspnea. A flexible nasopharyngolaryngoscopy was performed. Swelling of the base of the tongue on the left side was observed, along with pronounced edema of the aryepiglottic fold on the same side, which narrowed the breathing space. Since the breathing space was significantly reduced, the patient was urgently hospitalized. The surgical treatment was carried out in the form of an external incision and drainage of the abscess collection of the left submandibular region, with the use of oxygen support and parenteral therapy, in accordance with the recommendations from the available medical literature. Constant monitoring of saturation levels indicated a significant improvement after just a few hours of medicamentous therapy.

Conclusion The goal of our work is to point out a very rare but serious complication, laryngeal edema, which can lead to airway obstruction even in the first few days of the development of the infection, and endanger the life of the patient.

Keywords: edema of the larynx; stridor; submandibular abscess

INTRODUCTION

Edema of the larynx, as a result of an infection of the submandibular region, is a rare condition, but nonetheless life-threatening. Infections of this region are most often of dentogenic origin. Wide communication with other deep spaces of the head and neck, as well as the mediastinum, represents an ideal route for the spread of the infection that can lead to sepsis and a fatal outcome [1]. In this paper, we will present a case of a 45-year-old man with laryngeal edema and difficulty breathing, caused by lower-jaw tooth infection and an ipsilateral submandibular abscess.

CASE REPORT

A 45-year-old man was urgently hospitalized at the Department of Otorhinolaryngology with Maxillofacial Surgery due to painful neck swelling and stridorous breathing. As the patient stated, the first symptom was a toothache in the left side area of the lower jaw, which intensified significantly by the time of hospitalization. Progressive dyspnea lasted for three days. The clinical examination revealed palpable, painful swelling of the submandibular region on both sides as well as submentally; it was of a harder consistency, without the phenomenon of fluctuation, followed by hyperemia and tightness of the skin of the above-mentioned regions. Oropharyngoscopy was difficult to perform due to the presence of trismus, edema of the tongue and the tissues of the sublingual region. Since it was impossible to view the distal structures, a flexible nasopharyngolaryngoscopy was performed. During this procedure, several findings were noted: a swelling of the base of the tongue on the left side together with omega epiglottis, as well as a massive edema of the aryepiglottic fold on the same side, which narrowed the breathing space and suppressed the ipsilateral pyriform sinus (which did not open during the examination). The partially visible structures of the glottis were in order, both halves of the larynx were mobile (Figure 1). The breathing space was reduced yet sufficient at the time of the examination, while the measured oxygen saturation was around 92%.

Laboratory analysis revealed elevated parameters of inflammation, C-reactive protein 234 mg/L, Le 20 × 10^9/L, Ly 5.1%, Gr 93.8%, while other values were within the reference limits. Upon admission to the department, parenteral therapy was administered (ceftriaxone, metronidazole, and levofloxacin, along with corticosteroid and rehydration therapy), as well as oxygen support through a nasal cannula,

Received • Примљено: May 10, 2023
Accepted • Прихваћено: June 16, 2023
Online first: July 3, 2023

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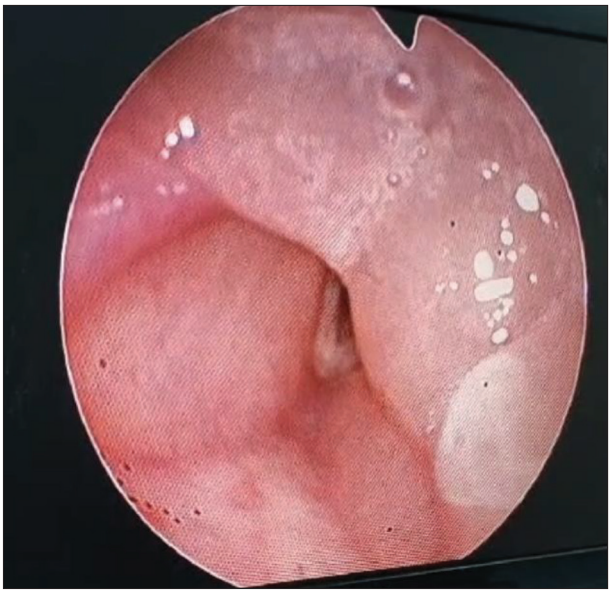

Figure 1. Massive edema of the left aryepiglottic fold with narrowing of the breathing space and suppressing the ipsilateral pyriform sinus

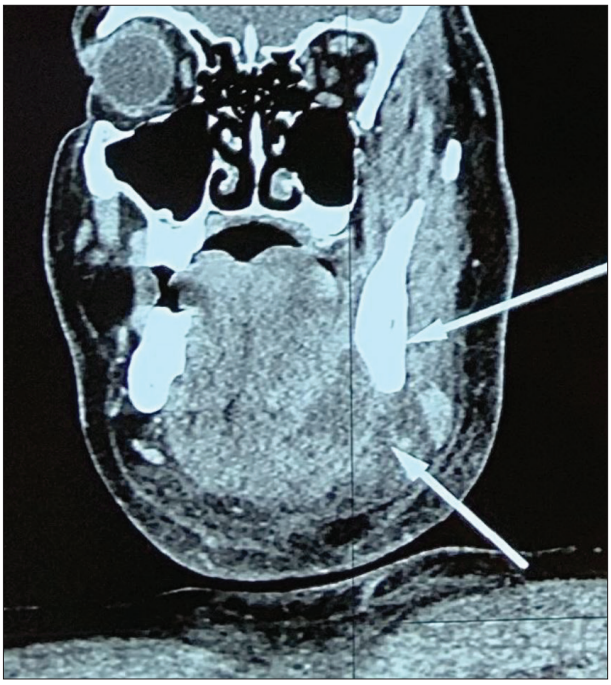

Figure 2. The finding corresponds to a dental abscess with parapharyngeal propagation to the left

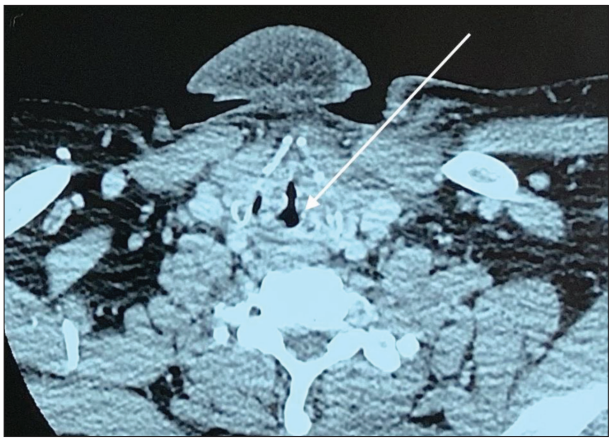

Figure 3. CT image of the massive edema of the left aryepiglottic fold with reduced breathing space

with oxygen flow values of about 5 L/minute. During hospitalization, a computed tomography (CT) scan of the neck was performed, the findings of which indicated the existence of a liquid collection of dense content, about 15 mm in diameter, at the level of the tooth root in the left ramus of the mandible. The submandibular left abscess formation with a transverse diameter of 55 × 35 mm propagated posteriorly towards the parapharyngeal and paraglottic space with a mass effect on the oropharynx and supraglottis, obliterating the left pyriform sinus (Figures 2 and 3).

Other findings, such as chest X-ray and abdominal ultrasound, did not show any pathological changes. Upon arrival of the diagnostic imaging findings (CT of the neck), an incision of the abscess collection of the left submandibular region was made externally, during which a large amount of purulent-hemorrhagic content was obtained, after which passive drainage was placed. The patient was observed carefully, with regular monitoring of the saturation levels. After four hours of applied corticosteroid therapy, the patient reported a subjective improvement in breathing, while after 24 hours of applied therapy, a significant reduction of laryngeal edema was observed by fiberoptic examination. After the stabilization of the general condition, a maxillofacial surgeon was consulted, who performed the extraction of tooth 36 under local anesthesia, which had caused the dentogenic infection.

Appropriate surgical therapy (timely incision and drainage of the abscess) as well as medical therapy, regular bandaging and removal of the cause of the infection (tooth extraction) resulted in regression of the laryngeal edema and healing of the infection, along with stabilization of laboratory parameters of inflammation, which were within reference values at discharge.

All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments and comparable ethical standards. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

Obstruction of the respiratory tract caused by edema of the mucous membrane of the larynx, although an uncommon symptom, is one of the numerous complications that can occur as a result of a submandibular abscess. Depending on the location and the size of the edema, as well as the patient's age, it can manifest itself in the form of minor breathing difficulties, up to a potentially life-threatening condition. Etiological factors for the development of laryngeal edema can be various. To start with, they can be infectious, caused by viruses, bacteria, or fungi. Additionally, there are

allergic ones in the form of angioedema, or as part of an anaphylactic reaction to the use of certain medications or food. Other potential causes of airway obstructions should also be noted, such as trauma to the larynx, foreign bodies, autoimmune diseases, and tumors of the larynx [1, 2, 3].

Cellulitis of the floor of the oral cavity was first described in literature in 1836 by a German military doctor Wilhelm Frederick von Ludwig, after whom this condition was named. It involves inflammation of the submandibular, sublingual, and submental regions, with a tendency to spread rapidly along the fascia to adjacent regions [4]. The infection usually starts from the infection of the roots of the lower premolars and molars, in cases where the purulent exudate spreads through the inflamed pulp to the periodontium and bone breaks through the cortical part of the lower jaw below the attachment of the mylohyoid muscle [1]. The swelling increases rapidly and tends to spread, generally does not fluctuate, and is extremely painful on palpation. The patient has elevated body temperature, a headache, difficulty in opening the mouth, hypersalivation is present, and saliva can be seen leaking from the mouth due to difficult and painful swallowing. The tongue and the floor of the oral cavity are raised, which makes breathing difficult, and larynx edema can also occur. Subjective disturbances and clinical findings worsen rapidly. This condition can lead to asphyxia within 24 hours [1, 5, 6, 7].

In about 70% of cases before the "antibiotic era," tonsillitis was the most common cause of Ludwig's angina. However, the work of İsmi et al. [8] indicates that there are more and more cases where the spread of infection has dentogenic causes. In developing countries, given the economic conditions and insufficient education of the population, dentogenic infections are the primary cause of these conditions in more than 80% of examined patients, while it is less often the result of inflammation of the tongue (e.g., piercing), submandibular gland, tonsils or pharynx. Publications available on Medline support the fact that laryngeal edema as a complication of Ludwig's angina is a rare occurrence [5, 9].

Other possible factors are obesity, tobacco and alcohol abuse, as well as malnutrition [10]. Furthermore, chronic diseases such as diabetes mellitus, hypertension or immunocompromised conditions can additionally contribute to the development of a more severe clinical picture and complications. This anatomically significant region of the neck is bounded medially by the hyoglossus muscle, anteriorly and posteriorly by the digastric muscles, and externally by the platysma and skin. Since the submandibular gland and neck lymph nodes are also located in this area, this should also be taken into account in the differential diagnosis of inflammation and swelling of this area [5, 6].

The spread of infection through the so-called "dangerous" areas of the neck along the fascia can lead to the development of numerous complications, the most common of all is mediastinitis, which can further lead to the development of empyema, pneumonia, and pericarditis, as well as Lemierre syndrome if there is involvement of the carotid artery and the occurrence of septic thrombophlebitis, and finally sepsis. Rupture of the carotid artery is not a rare occurrence either. Death occurs due to suffocation, sepsis, mediastinitis, or aspiration pneumonia [1, 11].

From the study by Almutairi et al. [12], published in 2020, we see that the majority of patients complained of neck pain (59.6%), followed by dysphagia (43.7%), and toothache (42.6%). Also, a study by Bottin et al. [13] showed similar results. Namely, 71.1% of patients complained of neck pain, odynophagia was present in 54.2% of cases, and dysphagia in 51.8%. Our patient was no exception. Neck swelling was preceded by a toothache, followed by tongue swelling, trismus, and difficulty breathing, which is not a common symptom and can be considered a complication. In the aforementioned studies, swelling of the neck as the main symptom was accompanied by fever in almost 50% of the cases, and trismus in about a quarter of the monitored patients [12]. In our case, the patient did not have fever.

These dentogenic infections are basically polymicrobial, with the unwritten rule being that the deeper the infection is localized, the more dominant the anaerobic agent is [1]. In the case of our patient, the causative agent of the infection was not isolated.

Immediate hospitalization of such patients is mandatory. Hospital treatment recommends continuous use of broad-spectrum antibiotics and corticosteroids, securing the airway (diagnostic endoscopy, intubation, or tracheotomy in case of stridor), as well as immediate surgical treatment of the abscess, in terms of incision and drainage. Prevention of the spread of infection, as well as prevention of its recurrence, will be best ensured by timely and energetic therapy that includes the extraction of the tooth causing the infection [12]. In the case of our patient, we were guided by the principles of good medical practice, which resulted in a positive outcome.

Infections of dentogenic origin are unfairly underestimated, even though in a certain number of cases they represent potentially life-threatening conditions. Although in most cases they are resolved during routine dental interventions, insufficient experience of the doctor, noncooperation of the patient, along with the other listed risk factors can lead to serious complications.

The first association of every doctor is that this condition can cause severe complications, such as mediastinitis and sepsis. However, what we wish to emphasize is that the respiratory tract should be considered even at the very beginning, since it can become compromised already in the first days of the development of the infection. Quick reaction of the doctor, immediate hospitalization, and observation, even in situations where the airway obstruction still has not developed as much, are the key steps in the treatment of such conditions. If some of the recommended steps are skipped, a seemingly insignificant dentogenic infection can lead to a fatal outcome. Finally, we would like to emphasize that health education, care for physical and mental health, and especially oral hygiene, are not only a matter of individual culture, but also of modern society to which we strive.

Conflict of interest: None declared.

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Едем ларинкса – хитно стање узроковано Лудвиговом ангином

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САЖЕТАК

Увод Едем ларинкса је ретка компликација Лудвигове ангине. Инфекције ове регије најчешће су дентогеног порекла, ређе узроковане тонзилитисом или другим инфекцијама у фаринксу. Приказујемо случај болесника са едемом ларинкса и отежаним дисањем, насталим као последица инфекције зуба доње вилице и ипсилатералног субмандибуларног апсцеса.

Приказ болесника Клиничка слика болесника је брзо напредовала. Од зубобоље, болног отока пода усне дупље, субмандибуларне и субменталне регије обострано, све до прогресивне и потенцијално животно угрожавајуће диспнеје. У току дијагностике учињена је флексибилна назофаринголаринготоскопија. Уочени су оток базе језика лево, омега епиглотис, као и изразит едем ариепиглотисног набора са исте стране који је сужавао дисајни простор и потискивао ипсилатерални пириформни синус. Дисајни простор у моменту прегледа је био редукован те је болесник хитно хоспитализован. По хоспитализацији болесника, спроведен је хируршки третман, у виду спољашње инцизије и дренаже апсцесне колекције субмандибуларне регије са леве стране, уз примену кисеоничне потпоре и паренетралне терапије, а у складу са препорукама из доступне медицинске литературе. Стални мониторинг и редовно праћење сатурације указали су на значајно побољшање већ након неколико сати од примене медикаментозне терапије.

Закључак Циљ нашег рада је да укаже на веома ретку али озбиљну компликацију, едем ларинкса, која може довести до опструкције дисајног пута већ у првим данима развоја инфекције, и животно угрозити болесника.

Кључне речи: едем ларинкса; стридор; субмандибуларни апсцес

DOI: https://doi.org/10.2298/SARH230218083I
UDC: 617-089.5

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Cervical plexus block – safe anesthesia for the patients with massive mediastinal lymphadenopathy

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SUMMARY

Introduction General anesthesia is frequently employed in neck surgery procedures. However, in patients at high risk for general anesthesia, regional anesthesia options, such as the superficial cervical plexus block, warrant careful consideration. Patients with mediastinal lymph node enlargement face an elevated risk of airway obstruction and hemodynamic mediastinal instability during anesthesia induction. In selected neck surgeries, including thyroglossal cyst excision, thyroglossal fistula repair, bronchial cyst removal, thyroidectomy, and lymph node excision, the superficial cervical plexus block presents a viable and secure alternative to general anesthesia.

Case report This report details the case of a patient with mediastinal lymphadenopathy and multiple brain metastases who underwent cervical lymph node excision. Given the patient's severe comorbidities, pronounced risk of complete distal airway obstruction, hemodynamic instability, and the potential for compression effects from mediastinal mass, a superficial cervical block was administered. This block facilitated effective perioperative analgesia without inducing respiratory or cardiovascular instability.

Conclusion The superficial cervical plexus block emerges as a prudent alternative to general anesthesia in high-risk patients requiring cervical lymph node excision procedures. Its utilization should be considered in such cases to enhance patient safety and perioperative management.

Keywords: cervical plexus; excision lymph node; airway obstruction; anesthesia; analgesia

INTRODUCTION

General anesthesia is the prevailing choice for neck surgeries; however, in patients with elevated anesthesia-related risks, regional anesthesia options such as the superficial cervical plexus block (SCPB) emerge as a potentially safer alternative [1]. Notably, patients presenting with mediastinal lymph node enlargement face an increased susceptibility to airway obstruction, and hemodynamic instability during the induction of general anesthesia. This susceptibility arises from the potential compressive effect of mediastinal masses on structures distal to the tracheal tube tip, including the inferior and superior vena cava, ascending and descending aorta [2]. For specific neck and maxillofacial surgical procedures (e.g., thyroglossal cyst excision, thyroglossal fistula repair, branchial cyst removal, thyroidectomy, lymph node excision, lipoma removal, mandibular fracture repair), SCPB represents a viable and safe alternative to conventional general anesthesia [3]. The SCPB encompasses the sensory innervation of the anterolateral neck, originating from the anterior primary rami of the second to fourth cervical nerves [2, 3].

CASE REPORT

A 67-year-old male with bilateral neck lymphadenopathy was admitted to the Clinic for Ear, Nose, Throat, and Maxillofacial Surgery at the University Clinical Centre of Serbia for the excision of a left cervical lymph node. The patient had noticed a visible neck mass on the left side four months prior, and had been experiencing hoarseness. His medical history only revealed hypertension. Physical examination upon admission revealed normal ear, nose, and throat findings, along with the palpable, a 30 mm-sized neck tumor in the left IIa region. A computed tomography (CT) of the brain revealed multiple metastases of unknown primary origin. Neck and chest CT scans revealed a left-sided neck lymph node measuring 25 × 16 × 25 mm, a right-sided neck lymph node measuring 12 × 6 mm, and an 86 × 77 mm conglomerate of mediastinal lymph nodes situated in front of the trachea, among the ascending and descending aorta, and the inferior vena cava (Figure 1). Other routine investigations yielded normal results. The patient received midazolam as premedication. A landmark based SCPB was performed for the patient undergoing lymph node excision in the upper third of the left neck area. A 20 ml solution of local anesthetics (0.5% bupivacaine 10 ml + 2% lidocaine 6 ml + 0.9% NaCl 4 ml) was employed. The procedure involved placing a 22G needle subcutaneously at the mid-portion of the posterior border of the sternocleidomastoid muscle, while targeting the origin of all superficial branches of the cervical plexus.

Received • Примљено: February 18, 2023
Revised • Ревизија: September 3, 2023
Accepted • Прихваћено: September 6, 2023
Online first: September 8, 2023

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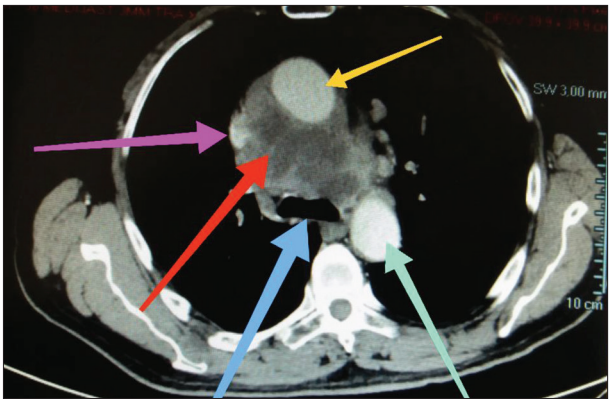

Figure 1. Computed tomography scan of mediastinal lymphadenopathy at the level of tracheal carina; pink arrow – inferior vena cava; red arrow – lymph node conglomerate; blue arrow – tracheal carina; green arrow – descending aorta; yellow arrow – ascending aorta

Subsequently, 10 ml of the local anesthetic solution was injected subcutaneously at this point, following aspiration. The needle's depth of insertion was maintained at 0.5 cm to minimize the risk of deeper block or inadvertent injection.

Given the lymph node's positioning between the innervation areas of the great auricular nerve and transverse cervical nerve, the needle was redirected towards these nerves, and each was blocked by the administration of 5 ml of local anesthetic solution. The block's efficacy was assessed after a 10/minute interval, with the patient receiving oxygen via a simple face mask. Throughout the intraoperative period, monitoring included blood pressure, heart rate, echocardiography, and pulse oximetry. The surgical procedure was finished after 25 minutes, with the perioperative period proceeding without complications such as pain, respiratory issues, or hemodynamic instability. The patient was discharged from the hospital on the second postoperative day.

This case report has received approval from the Ethics Committee of the University Clinical Centre of Serbia (Reference No: 1100/6).

DISCUSSION

Mediastinal lymph node enlargement can result from various etiologies, including neoplasms (e.g., Hodgkin's disease, non-Hodgkin lymphoma, leukemia, metastasis), granulomatous diseases (e.g., sarcoidosis, amyloidosis, Wegener's disease), or reactivity to infectious diseases (e.g., tuberculosis, fungal infections, viral and mycoplasma pneumonias) [4]. Depending on their location, mediastinal masses may lead to airway obstruction, producing symptoms such as dyspnea in cases of proximal obstruction or a non-productive cough with distal obstruction. In our patient's case, hoarseness likely resulted from the compressive effect of the mediastinal mass on the left recurrent laryngeal nerve, as part of the mass extended beneath the aortic arch, where the nerve typically courses. Severe airway obstruction can unexpectedly occur upon the induction of general anesthesia in patients, even in the absence of preoperative symptoms, emphasizing the need for a careful review of chest radiographs and CT scans for signs of asymptomatic airway obstruction. Typically, the point of obstruction is distal to the tracheal tube tip. Furthermore, the loss of spontaneous ventilation can lead to complete airway obstruction. [5]. Previous literature has documented severe respiratory complications during general anesthesia in children with mediastinal masses [6]. While our patient did not exhibit clinical signs of airway obstruction, the position of the mass posed a significant risk of distal airway obstruction during anesthesia induction and a loss of spontaneous breathing. Although an option would have been to opt for general anesthesia while maintaining spontaneous breathing, this approach could have led to coughing and increased intracranial pressure. Given the presence of diffuse brain metastases, such outcomes were strongly discouraged.

Cervical plexus block (CPB) is widely utilized in neck vascular surgery, but its application in non-vascular neck surgery has been increasing. Regional anesthesia techniques, such as CPB, offer numerous advantages over general anesthesia for surgeries involving the neck region. CPB does not compromise the airway, breathing, or hemodynamics. The contemporary popularity of CPB has surged as it offers opioid-free anesthesia, sparing patients from the various side effects associated with opioid usage. This concept aligns with the principles of opioid-free analgesia, rendering CPB a favored method of anesthesia, particularly in thyroid surgery [7, 8]. In case of surgery of posterior neck region, general anesthesia is the method of choice, because CPB encompasses the sensory innervation of the anterolateral neck. CPB can be performed at superficial, intermediate, or deep levels. Deep CPB, described as a paravertebral block targeting the C2–C4 spinal nerves, not only affects superficial branches but also deep branches of the cervical plexus, resulting in neck muscle relaxation. Local anesthetics are injected into the space between the paravertebral fascia and the cervical transverse process. Superficial CPB, on the other hand, is conventionally characterized as a subcutaneous injection technique administered at the mid-portion of the posterior border of the sternocleidomastoid muscle, targeting the superficial branches of the cervical plexus. Both ultrasound-guided and landmark-based techniques are available for performing CPB. In the case of SCPB, there is currently insufficient clinical data to definitively establish the superiority of ultrasound-guided techniques over landmark-based methods. Hence, we elected to employ a landmark-based approach, which is readily accessible and does not necessitate specialized equipment such as an ultrasound machine. Intermediate CPB, in which the needle pierces the investing fascia of the neck, deep to the subcutaneous layer but superficial to the prevertebral fascia, represents another variation [9].

The literature indicates that SCPB yields results comparable to combined cervical block but with fewer complications [10]. In a study conducted by Mukhopadhyay et al. [1], which involved bilateral SCPB, no major complications (e.g., central nervous system toxicity, spinal anesthesia) were observed, with only minor hematomas reported. Severe complications, such as phrenic nerve blockade, are uncommon following superficial block but are more frequently

encountered with deep CPB. SCPB serves as a valuable anesthesia method for patients with severe comorbidities or specific conditions, including asthma, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, difficult airway, urgent tracheostomy, active COVID-19 infection, hypertension, previous cerebral embolism, all of which are considered high-risk factors for general anesthesia. In such patients, SCPB offers a simple and secure alternative to general anesthesia, with established efficacy and safety, especially in high-risk scenarios [11–17]. Our patient experienced no pain during or after the procedure, aligning with data from the literature indicating effective perioperative analgesia in neck surgery achieved through SCPB [13, 18, 19]. A recent study by Patel et al. [20] found that SCPB, in conjunction with general anesthesia, resulted in reduced intraoperative fentanyl requirements and postoperative paracetamol use compared to general anesthesia alone in various head and neck surgeries. These findings corroborate the efficacy of SCPB in providing effective analgesia in head and neck surgery [20].

To conclude, we presented a case of SCPB that provided effective perioperative analgesia without inducing respiratory or cardiovascular instability in a patient with diffuse brain metastases and significant mediastinal lymphadenopathy undergoing neck lymph node excision. SCPB should be considered as a safe alternative to general anesthesia for high-risk patients requiring cervical lymph node excision.

Conflict of interest: None declared.

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Блок цервикалног плексуса – безбедна анестезија за болеснике са масивном медијастиналном лимфаденопатијом

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САЖЕТАК

Увод Општа анестезија се често користи у операцијама на врату. Међутим, код болесника са високим ризиком за општу анестезију, могућности регионалне анестезије, као што је блок површинског цервикалног плексуса, захтевају пажљиво разматрање. Болесници са увећањем медијастиналних лимфних чворова суочавају се са повећаним ризиком од опструкције дисајних путева и хемодинамске нестабилности током индукције у анестезију. У одабраним операцијама на врату, укључујући ексцизију тироглосалне цисте и фистуле, уклањање бронхијалне цисте, тироидектомију и ексцизију лимфних чворова, површински блок цервикалног плексуса представља одрживу и сигурну алтернативу општој анестезији.

Приказ болесника Овај приказ описује случај болесника са медијастиналном лимфаденопатијом и вишеструким метастазама на мозгу који је подвргнут ексцизији цервикалних лимфних чворова. С обзиром на тешке коморбидитете болесника, изражен ризик од потпуне опструкције дисталних дисајних путева, хемодинамску нестабилност и могућност компресивних ефеката медијастиналне масе, примењен је површински цервикални блок. Овај блок је омогућио ефикасну периоперативну аналгезију без изазивања респираторне или кардиоваскуларне нестабилности.

Закључак Блок површинског цервикалног плексуса намеће се као опрезна алтернатива општој анестезији код болесника са високим ризиком који захтевају ексцизију цервикалних лимфних чворова. У таквим случајевима треба размотрити његову употребу како би се побољшала безбедност болесника и периоперативног третмана.

Кључне речи: цервикални плексус; ексцизија лимфног чвора; опструкција дисајног пута; анестезија; аналгезија

DOI: https://doi.org/10.2298/SARH220921070R
UDC: 615.214.015.6

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Abuse and addictive potential of pregabalin

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SUMMARY
Introduction In the Republic of Serbia, pregabalin was marketed for the first time in 2006. Although the abuse of pregabalin has not been a common topic in the literature so far, it is often seen in everyday practice. Also, it seems that it is more common among addicts.
Case outline We report on a 41-year-old male patient who has a long history of multiple substance abuse and is currently undergoing buprenorphine substitution therapy. He began using pregabalin because it caused euphoria and elevated mood, in daily doses which varies between 1050–2100 mg. The highest daily dose was 4200 mg. At the time he was admitted to the hospital for pregabalin detoxification, he met the general criteria for addiction syndrome. On admission, the patient was tense, anxious, irritable, drenched in sweat, and had insomnia. With an adequate dose of buprenorphine, the patient continued to complain about the reduction of the pregabalin dose and insisted on adjusting the dose. Shortly, he was discharged from hospital at his personal request. After a month, during the check-up examination, he was diagnosed with a relapse of pregabalin use. He was readmitted to the hospital for detoxification treatment, the pregabalin dose was gradually reduced by 100 mg per week. After that the patient went to therapeutic community to continue treatment.
Conclusion This case indicates that practitioners have to be cautious when prescribing pregabalin to people prone to addiction. Further research is needed to identify risk factors for the development of pregabalin abuse syndrome, as well as to create clear guidelines for the treatment of abstinence syndrome.
Keywords: pregabalin; addiction; abuse; abstinence syndrome

INTRODUCTION

Pregabalin is an analog of gamma-amino butyric acid (GABA), and its effect is achieved by binding to an auxiliary subunit (62-д protein) of voltage-dependent calcium channels in the central nervous system [1]. There are several therapeutic indications for the use of pregabalin. In Serbia, it is used in the treatment of neuropathic pain, and epilepsy, as well as for treating generalized anxiety disorder [2]. Depending on the indication, the daily dose of pregabalin ranges from 150 to 600 mg. In the Republic of Serbia, it was first marketed in 2006. Although so far abuse and dependence on pregabalin have not been common topics in the available literature, it can be said that doctors often come across these cases in everyday practice. This has been noted both in Serbia and other countries [3, 4, 5]. Also, it seems that it is more common among addicts [6]. A study conducted in Serbia processed the results of toxicological and chemical analyses of blood and urine in postmortem cases in 2019, which recorded the potential risks of pregabalin abuse that can lead to addiction and severe poisoning with a fatal outcome [7]. For this reason, in some countries, a special warning has been added to the prescription of the drug, to increase caution when prescribing pregabalin to persons with a history of substance abuse [8]. The case report stresses out the importance of special caution when prescribing pregabalin.

This study was approved by the local ethics committee according to the Declaration of Helsinki.

CASE REPORT

We present a 41-year-old male patient who has been treated several times because of mental disorder due to psychoactive substances at the Clinic of Psychiatry, University Clinical Center of Vojvodina in Novi Sad. He is an unemployed construction technician, divorced, and has three children. Family history of mental disorders as well as his history of somatic illnesses is negative. As a patient with a long history of multiple substance abuse, he started abusing diazepam and tramadol during seventh grade of elementary school. When he was in high school his parents divorced, and he started consuming other substances such as tetrahydrocannabinol (THC), cocaine, stimulants, and finally heroin, which he used intranasally. At the age of 28, he went to the therapeutic community for detoxification treatment, where he stayed for a year. After leaving the therapeutic community, and after a short period of abstinence, he started using psychoactive substances again. In 2017, he consumed mostly opiates (buprenorphine 16–24 mg per day), which he procured illegally. In September 2018, he went to an outpatient psychiatrist when, in addition to the diagnosis of opiate addiction, he was

Received • Примљено: September 21, 2022
Revised • Ревизија: June 30, 2023
Accepted • Прихваћено: July 7, 2023
Online first: July 11, 2023

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diagnosed with generalized anxiety disorder and a mild depressive episode. Diagnoses were established according to the criteria of the International Classification of Diseases 10 Version (ICD-10) (F11.2, F41.1, F32.0) and antidepressants and pregabalin were introduced into the therapy [9]. In November of the same year, he was hospitalized for the first time at the Psychiatric Clinic to receive buprenorphine substitution therapy. The hospital discharge list included: Buprenorphine 10 mg, escitalopram 20 mg, pregabalin 150 mg, mirtazapine 15 mg. After leaving the hospital, he was non-compliant when it came to therapy and check-in examinations. The fact that he was unstable in the buprenorphine program, he was admitted to the hospital for the second time in December 2019. During the second hospitalization, buprenorphine therapy was reintroduced. This time, the hospital discharge list included: buprenorphine 16 mg, escitalopram 20 mg, and mirtazapine 15 mg. Shortly after leaving the hospital, following the recommendation of a friend, he started abusing pregabalin in the initial dose of 1575 mg. Side-effects after the initial dose manifested in the form of imbalance, dizziness, headache, and inarticulate movements. Because of this, he reduced the dose of pregabalin to 1050 mg, and sporadically took the stated dose with buprenorphine therapy on his own. The mentioned side effects did not occur during the next use. Pregabalin initially caused euphoria and elevated mood, and he described that the effects are similar to amphetamine (e.g., increased wakefulness, increased muscle strength). With pregabalin, he got the impression of an improved effect of buprenorphine therapy. Also, after the euphoria, it was easier for the patient to fall asleep and sleep peacefully for several hours. Occasional use of pregabalin gradually intensified and became more frequent, until the moment when the patient started using pregabalin every day for one year. Pregabalin was consumed orally, in the morning and the evening. Depending on the financial resources, the daily doses ranged from 1050 mg to 2100 mg. The highest daily dose consumed by the patient was 4200 mg divided into two doses (one in the morning and one in the evening). After a year, he came to see a psychiatrist wishing to start a pregabalin detoxification therapy. By that time, the patient had largely lost control of his pregabalin intake. On several occasions, he tried unsuccessfully to reduce the dose and stop using pregabalin. At that time the patient already met the general criteria for addiction syndrome according to the ICD-10 and showcased a strong desire to take the substance, had low self-control, demonstrated evidence of tolerance and physiological abstinence syndrome, and continued using the substance despite clear facts about undeniable harmful consequences [9]. Due to the impossibility of establishing abstinence in external conditions, the patient was hospitalized at the Psychiatric Clinic for the third time. Before the hospitalization, the patient took pregabalin at a daily dose of 2100 mg. Buprenorphine was taken for the last time a day prior to admission. Upon admission, the patient was tense, anxious, irritable, suffering from insomnia, and excessive sweating. According to the prescription, the maximum recommended daily dose of pregabalin is 600 mg, as well as valproate (750 mg), anxiolytic (diazepam 40 mg), and hypnotic therapy (midazolam 15 mg) to alleviate the symptoms of withdrawal syndrome. The laboratory analysis of sampled blood showed that there were no significant deviations from the reference values. Discontinuation of pregabalin therapy has been initiated. The patient was stable on the adequate dose of buprenorphine. However, the patient complained about the reduction of the pregabalin dose and still insisted on the pregabalin dose increase. In those moments, abstinence symptoms in the form of anxiety, irritability, tremor, and psychomotor restlessness were observed. There was a partial reduction of withdrawal symptoms during the 11 days of hospitalization with the contribution of the following therapy: diazepam 40 mg, pregabalin 300 mg, midazolam 15 mg, sertraline 100 mg, and valproate 1500 mg. On day 11 of hospitalization, the patient insisted on being discharged from the hospital. As there were no indications for hospitalization against his will, he was discharged. After a month, he appeared at the scheduled check-up. He was in good general condition, and stable on buprenorphine substitution therapy. However, he demonstrated low self-control and a strong craving for taking pregabalin and continued taking it despite the clear facts about the undeniable harmful consequences. One week before the control examination, he started abusing pregabalin again at a dose of 1200 mg per day. Excluding buprenorphine, the urine test tested negative for the presence of other psychoactive substances. The fourth hospitalization was initiated during which pregabalin (dose reduced by 100 mg per week) was discontinued. The patient was hospitalized for 45 days, during which the symptoms of abstinence syndrome were reduced, the day-night rhythm was established, and symptoms and signs of anxiety were reduced, with full insight and motivation for maintaining abstinence. The process of detoxification passed without major complications. The patient struggled with maintaining abstinence in the external environment which is why he continued his treatment in the therapeutic community, where, he spent the next four months. He is going to regular check-ups to this day.

DISCUSSION

In the case of our patient, the observed symptoms and signs of withdrawal syndrome are similar to those caused by the benzodiazepines (BZDs) and opiates. However, it is interesting to note that while being stable on buprenorphine substitution (i.e., using the drug in a prescribed manner), the patient did not feel the urge and abuse other substances, but still resorted to pregabalin. Even though pregabalin is most often used for the treatment of epilepsy and neuropathic pain, it is increasingly prescribed for the treatment of generalized anxiety disorder. One gets the impression that neither the doctors who prescribe this medicine nor the patients are fully aware of the risk of addiction that pregabalin carries. In Serbia and many other countries, there are no official guidelines for the treatment of pregabalin addiction and abstinence syndrome caused

by pregabalin cessation. The National Health Service in the United Kingdom has issued a detailed instruction, i.e., a scheme for reducing the dose of pregabalin when treating non-cancerous pain in primary health care [10]. Therefore, we were using BZDs and mood stabilizers in treating symptoms of the abstinence syndrome. As identified in other similar case reports, our patient also had medical history related to a behavioral disorder caused by substance use (THC, BZD, opiates) [8, 11, 12, 13]. According to the prescription, it is not recommended to combine BZD and pregabalin therapy. For this reason, we should bear in mind the importance of accurately informing patients about the potential risk of addiction when prescribing pregabalin, especially in the case of addicts. Although there are studies that indicate the risk of abuse and addiction, mental and behavioral disorders due to the use of pregabalin did not yet get the public attention they deserve [14, 15, 16]. Regarding the mechanism of pregabalin abuse at the biological level, research results are still heterogeneous and inconsistent but in the majority of cases they are in favor of pregabalin modulatory effects on the GABA and glutamate systems. One of the studies conducted on mice, investigating potential glutamatergic mechanisms, explored the involvement of glutamate in pregabalin-seeking behavior by using ceftriaxone, a potent glutamate transporter-1 up regulator. Mice that received doses of 60 and 90 mg/kg of pregabalin demonstrated drug-seeking-like behavior, which was effectively suppressed when they were pretreated with ceftriaxone [17]. The findings indicate that ceftriaxone effectively modulated the pregabalin-induced conditioned place preference, highlighting its potential as a promising candidate for developing treatments aimed at addressing pregabalin abuse. In line with this, another study states that pregabalin has the ability to influence the GABA and glutamate systems, which suggests the possibility of its potential for misuse, as well as an explanation for the development of withdrawal syndrome [18]. As we mentioned before and due to the fact that pregabalin's effect is achieved by binding to an б2-д protein of voltage-gate calcium channels, studies have shown that pregabalin and similar substances effectively inhibit the release of synaptic transmitters, particularly glutamate and norepinephrine, which are responsible for excitatory signals. They also induce a moderate increase in extracellular GABA levels in the brain, in a dose-dependent manner, resulting in mild GABA-mimetic effects such as relaxation and euphoria. These effects are commonly experienced at the start of drug therapy and after the use of higher-than-recommended doses [15]. Also, the authors of another study aimed to investigate the potential role of dopamine receptor-1 in the development of pregabalin-induced conditioned place preference [19]. Mice were assigned randomly to receive either saline or the dopamine-1 receptor antagonist SKF-83566. Among the group treated with pregabalin, a significant increase in the duration spent in the chamber associated with the drug was observed compared to the time spent in the chamber associated with the vehicle. Importantly, the administration of SKF-83566, which blocks dopamine-1 receptors, completely abolished the place preference induced by pregabalin, indicating the involvement of the dopaminergic system in pregabalin-induced reward-related behavior.

This case report stresses the importance of special caution when prescribing pregabalin. It indicates precautionary measures to keep in mind when prescribing pregabalin to individuals prone to substance abuse or dependence. It is clear that these individuals stood out as a vulnerable group, but further research is needed to identify risk factors for the development of pregabalin abuse and dependence. As in our case, the most probable reason for the abuse of pregabalin lies in its euphoric effects. The effects of pregabalin when administered correctly are not questioned. Lastly, clear guidelines are needed for the treatment of abuse and abstinence syndrome in pregabalin addiction, which seems to have pandemic potential according to our experience.

Conflict of interest: None declared.

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Злоупотреба и потенцијал прегабалина да створи зависност

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САЖЕТАК

Увод На територији Републике Србије прегабалин је први пут стављен у промет 2006. године. Иако до сада злоупотреба прегабалина није била честа тема у литератури, лекари је често могу видети у свакодневној пракси. Такође, чини се да је она чешће заступљена међу особама које су зависници.

Приказ болесника Приказујемо 41-годишњег болесника мушког пола, који има дугу историју вишеструке злоупотребе супстанци и који је тренутно подвргнут супституционој терапији бупренорфином. Прегабалин почиње да злоупотребљава због ефекта еуфорије и повишеног расположења и то у просечној дневној дози 1050–2100 *mg*. Највиша дневна доза коју је конзумирао била је 4200 *mg*. У моменту када је примљен у болницу ради детоксикације испуњавао је опште критеријуме за синдром зависности. При пријему је био напет, узнемирен, раздражљив, анксиозан, обливен знојем, имао је несаницу. По ординирању адекватне дозе бупренорфина, жалио се због смањења дозе прегабалина, те је инсистирао на њеној корекцији. Отпуштен је на лични захтев. На контролном прегледу после месец дана дијагностикован је рецидив злоупотребе прегабалина. Поново је примљен у болницу ради детоксикационог третмана. Доза прегабалина је постепено смањивана, 100 *mg* недељно. После тога је болесник упућен у терапијску заједницу да би наставио лечење.

Закључак Овај случај указује на мере опреза које лекари треба да имају приликом прописивања прегабалина особама склоним развоју зависности. Потребна су даља истраживања ради идентификовања фактора ризика за развој злоупотребе прегабалина, као и јасне смернице за третман апстиненцијалног синдрома.

Кључне речи: прегабалин; зависност; злоупотреба; апстиненцијални синдром

DOI: https://doi.org/10.2298/SARH220629084J
UDC: 614.2:[616.98:578.834

REVIEW OF LITERATURE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Insights into health sector governance in a turbulent environment – towards best-practice approach

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SUMMARY
The COVID-19 pandemic occurred at a high spreading rate with sudden pattern changes, high variability, and unpredictability. This generated uncertainty making it hard for authorities to predict, plan, and conventionally prepare preventive and suppressive actions. As a result, governments worldwide had to find new, more comprehensive, and complex solutions to manage the health sector in a turbulent environment. The paper's main objective is to analyze different organizational practices that respond to the COVID-19 crisis regarding healthcare sector resilience and describe best practices. Health sector authorities should consider applying the "new mode of governance," which refers to a policy not limited to a single approach with less hierarchy and formalism and with a flatter governance structure. Countries that have had more success in COVID-19 crisis suppression applied "dynamic resilience" with decentralization in decision-making, a more important role of front-line healthcare providers, high transparency, and flexibility enabling continuous adaptation to rapidly changing conditions.
Keywords: turbulent governance; crisis management; dynamic resilience; transformational leadership

INTRODUCTION

Before the COVID-19 pandemic, most countries had the health sector organized as a highly bureaucratic and hierarchical system with strict rules that regulated processes of providing standardized health services to their citizens. When dealing with anticipated changes and managing potential risks, governments usually apply a standard approach consisting of five phases:

1) identification of risks;
2) risk assessment;
3) risk prioritization;
4) risk response planning;
5) risk monitoring and control [1].

The phases are linear and sequential, thus making planning and preparation less demanding.

However, external conditions that influence the governance of the health sector changed radically with the pandemic. Changes occurred at a high spreading rate and severity with huge complexity and great uncertainty. The problem described in this paper can be defined as an assessment of governing authorities' capacities to predict, plan and prepare actions, to prevent and reduce adverse effects of the crisis induced by the COVID-19 pandemic.

The paper's main objective is to analyze different organizational practices that respond to the COVID-19-induced crisis regarding resilience policy and systematize/describe best practices.

TURBULENCES AS A "NEW NORMALITY" AND THEIR IMPACT ON HEALTH SECTOR POLICIES

This article is based on a literature review. We summarize current research findings and use secondary data sources to illustrate organizational changes in the system. The framework describing organizational traits is adopted chiefly from Mintzberg [2] and Goold and Campbell [3]. Our literature review of the changes in general organization in turbulent environment is applicable to healthcare sector organizations.

The conceptual framework has been grounded on the "New modes of governance" approach, introduced and applied as an alternative policy mechanism in the European Union Health Care policies [4]. At a state level, it refers to a policy not limited to a single approach with less hierarchy and formalism. The new health sector governance mode developed during the COVID-19 crisis is based on creativity and innovation supported by leadership, "communityship" and flexible organization [5]. Communityship is reached when team members work together towards a joint goal. Healthcare leaders share leadership activities with front-line workers in crisis [6]. Hospital teams had a sense of autonomy in decision-making and were flexible in connecting with other teams and the crisis command center.

During the pandemic, the issue of (de)centralization was widely discussed. Key arguments for decentralizing healthcare systems

Received • Примљено: June 29, 2022
Revised • Ревизија: May 12, 2023
Accepted • Прихваћено: August 31, 2023
Online first: September 13, 2023

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in the Organization for Economic Cooperation and Development countries were increasing efficiency and better adaptability of healthcare services to patients' needs [7]. In countries with decentralized healthcare systems, central authorities are responsible for the health policy framework as well as monitoring and coordination. In that case, lower-level authorities are taking care of the inputs and outputs of healthcare services. A conclusion of the efficiency research in responding to the COVID-19 crisis in the three Italian regions: Lombardy, Veneto, and Emilia-Romagna, was that strong vertical coordination is needed when the system is highly institutionally decentralized [7].

However, in the COVID-19 crisis, flatter organizational structures with less traditional hierarchical levels increased healthcare institutions' capabilities to adapt to new emerging requirements. Moreover, modularization refers to flexibly combining and rearranging modules such as:

a) testing, tracking, and quarantining;
b) lockdown and social/physical distancing;
c) intensive care treatment;
d) gradual re-opening of society as significantly improving the efficiency of governance response to pandemic [8].

When faced with turbulences, systems including healthcare need to demonstrate resilience, which depends on turbulent governance, as a response to "events, demands and support that interact and change in highly variable, inconsistent, unexpected or unpredictable manners is becoming a new normality" in public governance [9]. After the pandemic started more than three years ago, the new turbulence affected all major aspects of human life in Europe. Furthermore, the climate change impact on society causes the necessity to tackle the disaster and migration risks issues and calls for a new "turbulence approach" in organizational governance [9].

Turbulence has been defined as the cumulative effect of several disruptive events and crises, posing a challenge to existing decision-making and governance, so recent research suggests incorporating the "organizational turbulence" approach in public policy [10]. There are three major factors for integrating turbulence in governance:

1) speed in communications;
2) complexity due to interdependence and unpredictability;
3) potential or actual conflicts among different stakeholders.

The COVID-19 crisis proved that governance needs to evolve along with the world and that resilience becomes a sine qua non for the success of governance processes [10].

Response in low-chance, high-impact situations, such as the COVID-19 crisis, requires on-the-spot decision-making, flexibility, and informal coordination [11]. The COVID-19 pandemic required healthcare institutions to increase organizational capacities for improvisation. A good example of growing autonomy for front-line clinicians is the Pediatric Intensive Care Unit at Loma Linda University Children's Hospital, California, USA. Decision-making is migrated to the front-line staff regardless of their rank or seniority. However, improvisation requires a common frame or structure around which adjustments occur. Having structure supports collective actions through coordination [11].

NEW APPROACH IN MANAGING OF PUBLIC HEALTH ORGANIZATIONS UNDER UNCERTAINTIES

An important pandemic challenge to governance is intercurrence, where "unexpected interactions occur between otherwise independent or compartmentalized subsystems" [12]. Managers perceive intercurrence as a sudden pattern change that produces unexpected outcomes. Dynamic interactive change and uncertainty are challenging to be responded to because they are highly variable, inconsistent, unexpected, or unpredictable [11].

The first instinctive reaction of managers once they perceive turbulence is to protect the organization from it and to keep the status quo. However, the second impulse points toward organizational transformation, and Ansell and Trondal sum up "windows of opportunity" for significant policy changes and novel organizational solutions [9].

Concrete guidelines to healthcare sector managers are not to behave as rigid bureaucrats but as situation-oriented professionals who urge innovative and creative approaches in dealing with emergencies – which has to be supported by the policymakers and control officials. Hospitals should establish local incident management teams consisting of a clinical director, a managerial director, public health specialists, and a reference person to regional or state command centers [13].

As we pointed out, features of the COVID-19-induced crisis were unpredictability, and quick changes of circumstances with a high degree of surprise, resulting in a strong sense of lack of control, and high emotional disruption. In such cases, routine solutions are mainly inappropriate. However, during the two years of acute COVID-19 infection, in many cases, institutions reached for static resilience and took steps to maintain and restore equilibrium conditions. Planning aimed to find a way for the organization to resist changes.

However, over the course of the two years marked by the acute phase of the COVID-19 pandemic, it became evident that addressing turbulent challenges could not be accomplished merely by cultivating resilience in employees trained to follow established routines using emergency equipment, to be deployed in response to the next unforeseeable event with significant and widespread consequences. In other words, the proper answer to turbulent situations is not to try to restore past equilibrium but to search for new ones [14].

Some factors, such as the availability of testing capacities may lead to distortion of epidemiological situation assessment. For instance, in Italy and Spain, due to limitations in testing capacities, health institutions set more stringent criteria for testing, limiting it only to those with severe symptoms and high risks of comorbidities [15]. That could result in a flattened epidemic curve and misleading conclusions regarding epidemic status. The opposite

example provides countries like South Korea with more liberal eligibility testing policies [16].

During the pandemic, healthcare institutions were faced with limited facilities. In Italy, more than two-thirds of buildings were near the end of the life cycle, limiting their adaptability and efficiency in response to patients' demands [17]. Broader use of digital technologies by hospitals during a health crisis in monitoring the health status of patients would decrease pressure on hospital capacities. Using the Internet of Things remotely will reduce contact between infected patients and medical institution staff. A wider range of medical procedures that can be treated without physical presence based on digital systems will increase their capacities and enable more successful management, which is particularly important during turbulences [17].

As Ansell and Trondal [9] pointed out, health system institutions must demonstrate variety, modularity, and discretion to manage turbulence by adopting and applying dynamic resilience. Variety means that an organization's internal structure fits well with its environment's diversity. Modularity refers to adaptability to changing customers' requirements [18]. Discretion means that managers and employees can make decisions quickly with no significant constraints coming from complicated hierarchical procedures that require numerous levels of approval [17].

The growing role of the private sector in fulfilling citizens' health service demands led to reduced public sector capacities. Decreased public health institutions' capacities, followed by underinvesting, threatened their ability to handle pandemic emergencies.

Attempt to introduce private sector models of management in public sector health institutions in the Commonwealth nations resulted in increased inefficiency and rising costs of health services followed by deterioration of the overall quality of health care [19]. Assumed superiority of managerial over bureaucratic control in healthcare institutions did not result in improved performances as expected. In many cases, the use of managerial instruments failed to simplify hospital procedures and increased their costs [20]. Permanent monitoring and measurement of performance in the healthcare sector resulted in ambiguous responsibility and increased complexity [21].

The need for a proactive role of the state i.e., public sector in terms of emergencies has been highlighted in the International Health Regulation (IHR), a binding document adopted by the World Health Organization (WHO), and came into force in 2007, requiring coordination of efforts across states to control the effect of any health threats of international concern protecting dignity, human rights, and freedom. However, the pandemic showed that many countries failed to apply the IHR, particularly regarding the standard of "the duty to warn" i.e., early alert, notification, and response, as well as government commitment and financial support.

INTERNATIONAL EXPERIENCES IN IMPLEMENTATION OF NEW ORGANIZATIONAL MODELS – LESSONS LEARNED SO FAR

Different approaches among countries in responding to the COVID-19 pandemic-induced challenges shaped based on various theoretical models resulted in different outcomes regarding the pandemic curbing success. Experiences of more successful countries may be used for further upgrading of health sector governance. Medical institutions are not just health service providers, but significant purchasers of inputs for their operations, primarily of medicines and medical devices. During the COVID-19 crisis healthcare institutions were faced with disruptions in their supply. For that reason, the issue of purchasing should be covered in the discussion of lessons learned so far on how to improve overall medical institutions' governance.

In the United Kingdom (UK), the Government first identified risks that may endanger the UK in the future and assessed each of the risks regarding their:

1) impact;

2) likelihood to occur based on a reasonable worst-case scenario on a scale of 1–5 and plotted on a risk matrix [1].

The pandemic risk was assessed as five regarding its potential impact (maximum) and as three regarding its likelihood (medium) in the risks matrix.

In April 2020, plans for 2019 were reviewed and one of the findings was that 82% of plans failed to meet the requirements of actual incidents [1]. Similar cases of inadequate answers to pandemic challenges were evident in other countries. That was a signal that a new approach to dealing with the pandemic and other emergencies is needed.

Based on that experience, the UK Government adopted a new "bottom-up" model to dealing with turbulences. According to the new approach, "decisions should be taken at the lowest appropriate level with coordination at the highest necessary level" [1]. Since the pandemic affected the whole society, a central coordinating body (the Cabinet Office) proved necessary. Moreover, lower levels of government such as line ministries, departments, and local authorities were actively involved in planning and responding to contingencies.

The pandemic required dealing with new contingencies such as fear, anxiety, and misinformation, managing medical staff shortages, and losing suppliers of medicines and medical devices. A specialized body that would take care of potential emergencies permanently in the health sector was needed. In response to that requirement, the Health Security Agency was established in 2021. The Agency became responsible for "planning, preventing, and responding to external health threats, including pandemics" [1].

As in the UK, the "bottom-up" approach has been seen as effective enough in terms of a healthcare sector response to the pandemic in Switzerland. The empirical study has shown the importance of decentralization and decision-making participation at the micro-level i.e., level of teams and employees, which is crucial for good governance in turbulences. Although all organizational levels are essential

for enhancing the system's resilience, the workers' and team initiatives provide insights from the "battle front lines" where their collective self-regulation strategies support organizational resilience [22].

In some countries, such as Germany and South Korea, health systems responded much better to the pandemic than in other countries, owing to the significant role of state-owned health institutions and the capacities of central authorities to coordinate private health institutions efficiently. Despite Germany's developed public healthcare sector, health institutions at the lower level of public administration were neglected. Local public health authorities were underfunded and understaffed for years with shadow existence [23]. However, with the rise of the pandemic, they became one of the key strongholds in efforts to overcome the crisis. Moreover, they are expected to remain key players in potential health emergencies.

South Korea had a less centralized approach than most other Asian countries. The roles and responsibilities of local administration and local communities were significant. One of the main characteristics of the South Korean approach was a high level of transparency, including sharing all data with its citizens [24]. South Korean central coordinating body was the Korea Center for Disease Control and Prevention (KCDC) while other specific tasks were entrusted to relevant ministries and agencies. Delegation of roles and responsibilities proved to be an efficient solution when the number of infected people reached high figures. For instance, the Ministry of Interior and Safety monitored people in self-isolation, surveying those with high exposure to become contagious, primarily those who traveled to high-risk regions. That freed up the capacities of KCDC, enabling it to focus strictly on medical issues [25].

There was clear political leadership by the South Korean president, who made decisions based on expert group advice with a complete understanding of fluctuations and emerging risk factors. Decision-making was decentralized, thus enabling local authorities to manage medical institutions' capacities to meet the rapidly increasing demand for medical treatment of severe cases. Moreover, local communities were included in overcoming shortages in treatment capacities. For instance, companies like Samsung and LG offered their training centers and facilities as life treatment centers [25].

The experience of hospitals in Paris in responding to increased demands when material and human resources were highly constrained and with very strong time pressure confirms the importance of implementing flexible organizational processes [26]. Crisis teams included both physicians and nurses with complementary skills in dealing with crisis situations.

As we have already pointed out, COVID-19 crisis tested the supply function of health systems around the world. Established supply chains were broken while requirements from healthcare institutions as health service providers changed significantly. The health sector had to prioritize purchasing specific goods and services over others. Health authorities worldwide were forced to re-examine and modify purchasing arrangements due to changed needs.

Demand for health services changed towards a sharp increase in demand for pandemic-related healthcare services that include staffed hospital beds, and intensive and critical care beds [27]. Moreover, there was a surge in demand for specific pandemic-related services such were testing, tracking, and tracing. That included viral and antigen tests, tracking and tracing mobile applications that purchases were set as priorities.

The COVID-19 crisis changed health services modalities as well. For instance, in many countries, there was a surge in telehealth that required new technology, infrastructure, and training. A surge of demand for high-quality facemasks, gloves, ventilators, and other medical devices put suppliers in a favorable market and negotiating position in relation to health sector buyers. The consequences were chaotic and corrupt markets and competition among healthcare institutions to obtain needed products from monopolistic suppliers [27].

This situation led to an increased role of procurement in health policy during the crisis. In order to design a procurement system that would be able to respond to health crisis challenges, it is necessary to discuss the specifics of procurement in the health sector. Medicines and medical devices are mainly produced by monopoly providers (in particular medicines that are usually protected by intellectual property rights). The second issue is related to transaction costs of procurement [28].

If a supplier is changed frequently (once in two years, for instance), that can create disruption for patients who interact with the system, generating additional costs for medical institutions from transferring patients' records from one to the other information system, etc. [29]. In cases when suppliers count on prolonged contracts with medical institutions, they would be willing to build reliable relationships with it and to improve their service. That reduces the costs of contract execution monitoring by health institutions.

In times of crisis, speed is of utmost importance. In that situation regular (open) procedure cannot be applied, but negotiated procedure without prior notice. Numerous studies confirmed that urgent situations are related to increased risk of misuse of public funds and corruption [30–33]. Governments are faced with challenges to find a balance of interests of both sides: purchasers (health institutions) on one and suppliers (producers of medicines and medical devices) on the other that would sustain in urgent situations such as a pandemic.

In order to increase Europe's ability to respond to future crises in an adequate way and in a timely manner, the European Union (EU) set up the Health Emergency Preparedness and Response Authority (HERA). One of HERA's core goals is: "to address vulnerabilities and strategic dependencies within the Union related to the development, production, procurement, stockpiling, and distribution of medical countermeasures" [34]. Implementation of the task requires ensuring the manufacturing and procurement of key medical products and services relevant to pandemics. In order to achieve this, the EU promotes wider use of joint EU-level procurement including joint

procurement of COVID-19 therapeutics and Advance Purchase Agreements of COVID-19 vaccines [34].

The need for better procurement coordination between different levels of governance was recognized in several studies [35–39]. The COVID-19 crisis has disrupted the supply chains for medicines and medical devices globally, posing major challenges to organizations and highlighting the importance of organizational resilience [40]. As Phillips et al. [41] pointed out, national authorities in the UK failed to understand the true availability of products and local needs in medicines during the COVID-19 crisis. Broadly speaking, healthcare supply chain management (HSCM) needs to manage supply in order to be able to better adapt to changes on the demand side during turbulences. So far, HSCM in pandemics was concentrated on six domains: vaccine distribution, personal protective equipment, drug supply chain, blood supply chain, healthcare delivery strategy, and medical supply tracking methods [42]. *De lege ferenda*, the more influence of front-line employees on decision-making increases their motivation, thus having a positive impact on HSCM emphasizing workplace democracy participation in management practices [43].

CONCLUSION

The pandemic caused two kinds of answers by the governments. One was "static resilience," which aimed to maintain status quo by building various buffers. The alternative approach was "dynamic resilience" which aimed to adjust governance continuously to rapidly changing conditions. Key elements of "dynamic resilience" are decentralization in decision-making, the more important role of front-line healthcare providers, higher transparency, and flexibility.

In many countries, the pandemic resulted in calls to strengthen state capacities to increase its ability to respond to health and other future crises. These calls are usually misinterpreted as a pursuit for "more state". However, it is an aspiration for a different type of state that will have adequate capacities and capabilities to activate stakeholders from all governance levels and make them integral parts of a comprehensive process of transformation and adaption to turbulences. In that regard, the IHR effectiveness could also be provided considering the ongoing policy debate of revisiting the WHO international standards towards an approach based on integrated coordination of rights and responsibilities, as well as fair distribution of burdens, both at the international and national levels, including also the level of organizations.

While resilience in the healthcare system has been mostly analyzed in the literature on the level of individual employees, as well as some comparisons between personal and organizational level practices, there is a relative lack of analysis of the organizational structure and practice factors. The contribution of this study to the existing knowledge is in providing insights into building resilience in the healthcare sector focused on organizational-level practices, processes, decision-making, and structures in turbulent environments.

ACKNOWLEDGMENT

This paper was written as part of the 2023 Research Program of the Institute of Social Sciences, Belgrade, Serbia with the support of the Ministry of Science, Technological Development and Innovation of the Republic of Serbia.

Conflict of interest: None declared.

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Увиди у управљање сектором здравствене заштите у турбулентном окружењу – ка приступу добре праксе

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САЖЕТАК

Пандемију ковида 19 је карактерисало да се шири великом брзином, са изненадним променама ситуације, високом варијабилношћу и непредвидивошћу, стварајући неизвесност која је отежавала надлежним институцијама да предвиде, планирају и припреме мере сузбијања и превентиве на конвенционалан начин. Владе широм света морале су да пронађу нова свеобухватнија и комплекснија решења како да управљају здравственим системом у турбулентном окружењу.

Циљ овог рада је анализа различитих организационих решења у одговору на кризу ковида 19 како би се ојачала отпорност система, те идентификовали примери добре праксе. Надлежни у здравственом систему треба да размотре примену „новог модела управљања", који се не ослања на само један приступ и који карактерише мање хијерархије и формализма у управљању са равнијом управљачком структуром. Државе које су имале више успеха у сузбијању кризе ковида 19 примениле су приступ „динамичне отпорности", који подразумева децентрализацију у одлучивању, већу улогу нижих хијерархијских нивоа који непосредно пружају услугу пацијентима, високу транспарентност и флексибилност које омогућавају континуирано прилагођавање брзим променама услова.

Кључне речи: управљање турбулентним ситуацијама; управљање кризама; динамичка отпорност; трансформационо лидерство

UDC: 613.86(497.11)"1963/2023"

CONGRESS AND SCIENTIFIC MEETING REPORT / ИЗВЕШТАЈ СА КОНГРЕСА

Sixty years of the Institute of Mental Health

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SUMMARY
In April 2023, the Institute of Mental Health celebrated 60th anniversary. During this year several activities were dedicated to this important jubilee – first, a music concert was organized at the Atrium of the National Museum, named "The Sounds of the Soul", then several movies projection were organized at the Yugoslav film archive in Belgrade with topic related to mental health issues and followed by discussion of professionals from the movie industry and mental health. There were eight clinical lessons organized within the Institute of mental health during 2022 and 2023 dedicated to the contemporary issues in psychiatry, and finally, the X Forum was organized under the title "60 years of the Institute – the past and future are here". It was an excellent opportunity to present the work of one of the most significant psychiatric institutions in the Balkans.
Keywords: mental health; jubilee; psychiatry; institution

INTRODUCTION

Today, dealing with mental health is imperative. Data from 2019 indicated that one in eight people in the world has a psychiatric disorder, i.e., about 970 million people [1]. These data clearly indicates that any institution which dedicates its work to the care and treatment of mental health problems has not only public health importance, but also affects the functioning of society. The Institute of Mental Health has been an example of good practice for years, and the celebration of its sixty years of existence demands that it be recorded in the annals of Serbian medicine. On a significant jubilee, from April 19–21, 2023, the X Forum of the Institute of Mental Health was organized under the title "60 years of the Institute - the past and the future are here". The forum was an occasion to present the work of the Institute from its establishment until today, five symposia were organized, five satellite symposia with domestic and foreign students (Professor Bruno Fallisard, Professor Andrea Raballo, Prof. Aleksandar Dimitrijević), and a monograph with all the papers was published [2]. We dedicate this paper to this event (Figure 1).

HISTORY

Caring for people with mental health problems in Serbia began more than 160 years ago, with the opening of Doctor's Tower, as

Figure 1. The Institute of Mental Health, 2023

Received • Примљено: July 17, 2023
Accepted • Прихваћено: August 24, 2023
Online first: August 30, 2023

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Figure 2. Founders of Institute of Mental Health. Standing, from left to right, top row: Dr Dragoslav Ercegovac, Dr Predrag Kaličanin, Valta Erdeljan, Head of accounting, Dr Milan Popović, Assistant Director Slobodan Gavrić, Dr Dušan Petrović, Dr Jovan Potrebić, social worker and Dr Mića Damjanović. Bottom row, from left to right: Dr Kosara Barjaktarević, Dr Slavka Morić Petrović, Dr Nataša Stanojević, Dr Vera Velimirović head nurse, Dr Jovan Bukelić

the first psychiatric institution in Serbia. By the decree signed by Prince Mihailo, on March 3, 1861, the "Home for those who went out of their minds" (orig. "Dom za s uma sišavše") was formed. With the establishment of this first psychiatric hospital, the previous practice of treating the mentally ill by psychics, witch doctors, and monasteries was abandoned [3].

One hundred years after the opening of the first psychiatric institution in Serbia, Professor Dr Slavka Morić-Petrović, with the help of Alliance of Fighters Associations of. People's Liberation Wars fighters, founded the Institute of Mental Health – the first day hospital in Belgrade city center, the first of its kind in Yugoslavia and this part of the Balkans. It was a historic step to improving the approach to people with mental illnesses because treatment in day hospitals provided a new perspective to those in existing institutions; instead of isolating patients from the environment, the emphasis was on staying in the community. In 1963, a daily newspaper published an article referring to the "Madhouse in the center of the city" – how great was the misunderstanding of the new work concept is best illustrated by the fact that the Institute was said to be where "cosmetologists" work in psychiatry.

The Institute's primary task was to provide primary, secondary, and tertiary mental health care on the territory of the city of Belgrade, as this million-strong city represented an ideal terrain for the introduction of new types of services such as outpatient services, transitional, and open psychiatric wards. Since its establishment, the Institute has been oriented towards the outpatient units. Apart from that, many different departments were there since the beginning, including day hospitals, the electroencephalography cabinet, a laboratory, and the teaching-epidemiological department. The Institute's principle of work was the joint, cross-departmental treatment of patients. It is especially important to point out the establishment of sociotherapy clubs for rehabilitated patients, called "Fridays at 6 PM" and "Saturdays at 6 PM", as well as the existence of workshops with the protected work for psychiatric patients. The work of the Institute was also devoted to educational activities. Employees of the Institute were among the first to organize ten-day courses in social psychiatry and mental hygiene for general practitioners.

Other cooperation with other institutions was also significant, both through educational and scientific activities, as well as through providing more comprehensive support to patients. In this way, the Institute of Mental Health opened a new path to psychiatric practice from the very beginning, aiming to bridge the gap between psychiatric hospitals on one hand and the community on the other, thus becoming an "experimental laboratory for social psychiatry" [4]. With time, the Institute has grown its reputation, becoming a modern health and scientific institution, as well as the teaching base for several Belgrade faculties.

SIGNIFICANT PEOPLE OF THE INSTITUTE

Professor Dr Slavka Morić-Petrović was one of the founders of the Institute (Figure 2). In 1966, she founded the Laboratory for Human Cytogenetics at the Institute, and later the Genoprophylaxis Clinic. She was very active in the social and political life of the country at that time – the bearer of the partisan memorial in 1941, the Order of the

Republic with a silver wreath, she received the October Award of the City of Belgrade (1976) and the Seventh of July Award of the Federal Republic of Serbia (1978). Professor Jovan Bukelić described her as "a woman who has coastal stoutness and beauty" and who was "a revolutionary student, a brave illegal, a patriot, a creator of unquenchable scientific curiosity, a tireless seeker of the new, a doctor with dresses for every soul". The involvement of Professor Morić-Petrović in the organization of home treatment was especially significant – home visits to mothers in labour and women who had children with Down syndrome in the territory of municipalities Stari Grad and Vračar. From today's perspective, such a method appears to be a forerunner of the Institute's current engagement in the implementation and organization of the family-oriented early intervention programme for children with developmental disabilities, which is implemented in cooperation with UNICEF and other organizations.

Professor Dr Predrag Kaličanin was one of the founders of the Research Department of the Institute. He worked in the fields of epidemiology in psychiatry, genetics, social psychiatry and was a teacher of exceptional moral purity. He was a consultant to the World Health Organization on mental health and researched community mental health care, the role of psychiatry in major accidents and disasters. He worked with refugees and exiles, and his publishing work was particularly fruitful – he published 48 monographs, textbooks and manuals.

Professor Dušan Petrović was also one of the founders of the Institute. He advocated for the introduction of teamwork in psychiatry and the improvement of outpatient psychiatric care. He dealt with the rehabilitation of psychiatric patients, psychogeriatric protection, psychosocial support to refugees. He founded the Geriatrics Counseling Centre within the Institute's Dispensary, which at the time was the only counselling center of its type in the country.

Professor Dr Jovan Bukelić worked in the field of addiction disorders and obtained the first doctoral dissertation in this field in the Balkans. He published many essays, feuilletons, and original literary works in literary newspapers. in 1988, he opened the day hospital for children up to 12 years of age at the Institute.

Professor Dr Petar Opalić pointed out the inextricable links between sociology and psychiatry, pointing to existentialism both as a philosophical direction and as a psychotherapeutic direction.

Academician Dr Dušica Lečić-Toševski founded the Stress Clinic, Day Hospital for Adolescents, Departments for the Third Age, Forensic Psychiatry, and Perinatal and Reproductive Psychiatry, Journal Club for young people, as well as the Culture Circle on Wednesdays for hospitalized patients at the Institute. Under her leadership, the Institute for Mental Health was appointed as a Collaborative Center for Education by the World Health Organization in 2009, and based on the analysis of the results, it was appointed again for the period 2013-2017 and 2017–2021. She concluded a cooperation agreement with one of the most prestigious psychiatric institutions in the world – the Institute of Psychiatry of the Maudsley Hospital in London.

In addition to the aforementioned leaders of the Institute, many other famous professors, scientists, doctors, and therapists worked at the Institute: Dr Nevenka Tadić, Dr Svetomir Bojanin, Dr Veronika Išpanović-Radojković, Dr Dragoslav Ercegovac, Dr Ivana Timotijević, Dr Marko Munjiza, Dr Ljubomir Erić, Dr Zorka Lopičić, Dr Smiljka Popović-Deušić, Dr Ivan Dimitrijević, Dr Žarko Martinović, Dr Andreja Krajger-Guzina, Dr Miroslav Antonijević, Dr Branko Ćorić, Dr Tomislav Sedmak, and many others. To date, 1,685 health workers and associates have worked at the Institute – neuropsychiatrists, psychiatrists, child and adolescent psychiatrists, neurologists, pediatricians, psychologists, special pedagogues, defectologists, social workers, pharmacists, molecular biologists, senior nurses and technicians, nurses and technicians, pediatric nurses, pharmaceutical and laboratory technicians, lawyers, economists, graduate managers, economic, mechanical and legal technicians, qualified workers. Each of them is important for the successful work of the Institute.

THE WORK OF THE INSTITUTE TODAY

The work of the Institute for Mental Health is based on three pillars:

1) treatment;
2) education;
3) research [5].

The Institute is a tertiary-level health institution that offers highly specialized outpatient and inpatient health services in the fields of adult psychiatry, developmental psychiatry, addictions, clinical psychology, epileptology and clinical neurophysiology, psychopharmacology, psychotherapy, prevention of mental disorders, as well as protection and improvement of mental health, medical biochemistry and medical supply – pharmaceutical activities.

The Institute is the teaching base of several faculties: the Faculty of Medicine of the University of Belgrade, the Faculty of Special Education and Rehabilitation, the Faculty of Political Sciences, the Department of Psychology and Social Protection of the Singidunum University, as well as schools: Colleges for Social Work, Secondary, Higher and Higher Medical schools of professional studies. The Institute has established cooperation with many other institutions, and through cooperation agreements, it carries out various activities. The Institute currently has 242 employees, of which 51 are specialists in psychiatry, child and adolescent psychiatry and neurology, 15 doctors on specialization, 16 psychologists, seven graduated social workers, two biologists, four occupational therapists, 111 nurses and technicians, two pharmacists, three defectologists, five special pedagogues, four laboratory and pharmaceutical technicians, 22 members of the economic and legal service. There are 24 Doctors of Science, nine masters, eight subspecialists and 12 medicus primus working at the Institute (Figure 3).

As part of its activities, the Institute approaches the treatment of mental disorders through applying established professional and doctrinal criteria, that is, the principles

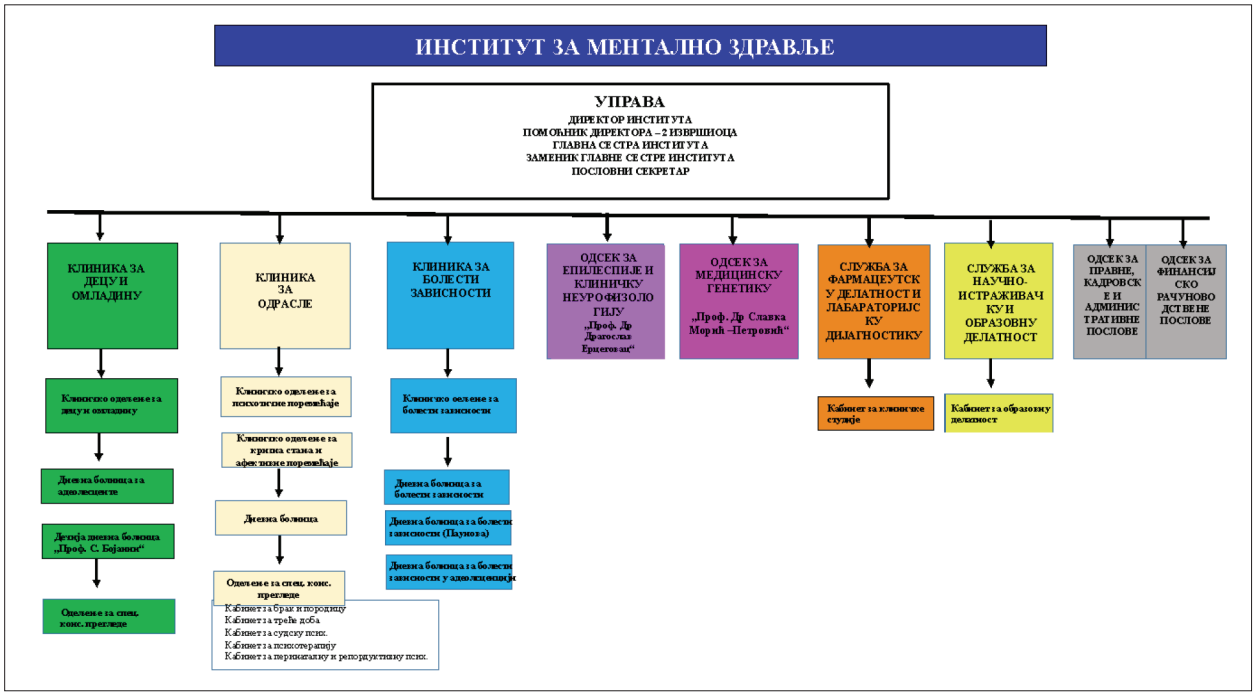

Figure 3. Current structure of Institute of Mental Health

of good clinical practice; prevention of mental disorders and improvement of mental health; education (basic and postgraduate studies), continuous education, specialization and subspecialization for its associates, as well as health workers and health associates of other health institutions and other legal entities; research in all areas of psychiatry, psychology and related disciplines according to the principles of good scientific practice. It also focuses on the implementation of measures to prevent possible complications and adverse consequences in healthcare, as well as general security measures during the stay of citizens at the Institute, ensuring constant control of the implementation of these measures. The Institute's accreditation with the Agency for Accreditation of Healthcare Institutions of Serbia was carried out in 2020 and will be valid for seven years.

Over 50,000 dispensary examinations and over 2,000 hospitalizations with an average length of treatment of 21.4 days are performed annually at the Mental Health Institute.

When it comes to addictions, the Institute has a Day Hospital for Addiction in Adolescence, which was founded in 2003, and is a unique day hospital for the population of young people aged 12–18 years with addiction problems in Serbia. The day hospital works according to the principles of systemic group family therapy, which implies that, in addition to adolescents, parents must be involved in the therapeutic process, not as companions, but as co-patients.

Apart from this day hospital, the Day Hospital for Children "Prof. Dr Svetomir Bojanin" for diagnosis and treatment of children with complex developmental and emotional problems. Children aged 2–12 are admitted to the Children's Day Hospital. The work of the Children's Day Hospital is based on collaborative, cross-departmental diagnostic assessment, daily educational playroom group activities for young children conducted by the teachers of the "Savski venac" preschool institution, and other group and individual treatments for children and parents. The Day Hospital for Adolescents, which also has a unique programme, offers partial hospitalization for adolescents and young people with psychological problems and difficulties in the identity formation, aged 15–25. Treatment includes pharmacotherapy, individual, group, family, and "Milieu" therapy.

What sets the Institute apart from other psychiatric institutions is the fact that children and adults are treated under the same roof, as well as its special organizational units that do not exist in other institutions – the Cabinet for Marriage and Family; Cabinet for Reproductive and Perinatal Psychiatry; Cabinet for Forensic Psychiatry; Cabinet for the Third Age; Cabinet for Psychotherapy and Cabinet for Clinical Studies.

RESEARCH

The first scientific research of the Institute was conducted in the Experimental Laboratory for Social Psychiatry from 1963 to 1969 [6]. An assessment of the psychological, social, and professional characteristics of psychiatric patients was carried out, as well as the determination of the value of certain rehabilitation methods, that is, which methods and procedures are most suitable for patients. Until today, the Institute has carried out national and international research projects, the last of which relates to the COVID-19 pandemic. In the "CoV2Soul.rs" project (2021–2022), the prevalence of the most common psychiatric disorders among a representative population of adults in the Republic of Serbia was examined for the first time using an in-depth clinical interview conducted by experts in the field [7]. In this way, the long tradition of

Figure 4. The future of Institute of Mental Health – young specialists, residents, and psychologists of the Institute

epidemiological research at the Institute was continued. In addition to epidemiological, the Institute also conducts other types of research. On average, about 30 research outputs per year are conducted at the Institute, as part of the post-graduate training of academics or larger, multidisciplinary research groups.

EDUCATION AND TRAINING

Improving the competence of experts through education, by strategically and systematically promoting educational activity and organizing scientific gatherings and symposiums is one of the strategic goals of the Institute. Educational courses, seminars, symposia and psychotherapy education are organized regularly. Since 2009, more than 220 programs have been accredited, and an average of 200 participants from the country and abroad complete the training each year.

The Institute for Mental Health is accredited by the European Association for Psychotherapy as a Training Institute for educating experts in the field of systemic family therapy and psychoanalytic psychotherapy. In addition, the Institute conducts over 20 different educational programs every year. The Institute highlights several of them, which have existed almost since its foundation – Mental Hygiene of the Developmental Age and Psychomotor Reeducation, as well as newer ones, such as the School of Clinical Neuropsychology, organized since 2021. Ten Forums of the Institute for Mental Health have been organized so far, with the participation of experts from the Institute, as well as from other institutions in the country, as well as well-known European and international institutions.

In addition to external training, the Institute also conducts internal training. "Lessons," which are traditionally organized twice a month (since 2005), and are intended for all employees of our institution, while the "Book club", Clinical classes, Continuous development of scientific and professional youth and "Conversations with experts" are intended for younger colleagues currently specializing in psychiatry, clinical psychology, defectology, etc. Numerous lectures within the framework of these educational activities are available on the Institute's official YouTube channel.

In cooperation with other related institutions and as a teaching base of several faculties (e.g. Faculty of Medicine, Faculty of Philosophy, Faculty of Special Education and Rehabilitation, Faculty of Political Sciences, etc.), colleges, higher and secondary schools, our employees contribute significantly to the education of health workers and health associates as lecturers and teachers.

PUBLICATIONS

Since 1969, the Institute has published the journal "Annals of the Institute for Mental Health," which was renamed to "Psychiatry Today" in 1975. In 2022, the Institute launched the quarterly "Scientific Bulletin of the Institute of Mental Health," available in in Serbian and English. Six new publications were published for the 60th anniversary of the Institute. The Institute has so far published 73 books or monographs by its employees [8, 9, 10].

THE FUTURE OF THE INSTITUTE

Psychiatry is undergoing major changes. In the modern world, the well-being of people with psychiatric disorders and their relatives depends not only on the cooperation of experts of different profiles, but also on intersectoral cooperation and available resources [11]. The evolution of modern psychiatry is in the direction of greater integration of scientific concepts: a deeper study of the classifications of psychiatric disorders, a more systematic and comprehensive diagnostic evaluation, personalized psychopharmacology, as well as further improvement of psychotherapy is necessary [12]. The value of the Institute lies in the continuous striving for the new, as well as in the wealth of diverse fields we work in. The Institute's plan is to continue pursuing contemporary trends and to continue active participation in the development of psychiatry as a scientific and clinical discipline. Work with young people, continuation of training programs and their constant enrichment, modernization of work through the introduction of new technologies, continuation of scientific research projects are just some of the plans for the future (Figure 4). The possibilities for a better future are limitless. Regardless, it is certain that the fundamental doctor/expert–patient relationship will remain a constant that will preserve the integrity of psychiatry as a profession.

This article was written in accordance with the ethical standards of the institution and the journal.

Conflict of interest: None declared.

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Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh).*

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

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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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ISSN 0370-8179
ISSN Online 2406-0895
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ISSN 0370-8179
ISSN Online 2406-0895
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61(497.11)

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