

Infectious Diseases Clinic, University Clinical Center of Vojvodina, Novi Sad¹ Original study

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CLINICAL CHARACTERISTICS OF COVID-19 IN FULLY VACCINATED VERSUS UNVACCINATED PATIENTS TREATED AT THE INFECTIOUS DISEASES CLINIC OF THE UNIVERSITY CLINICAL CENTER OF VOJVODINA

KLINIČKE KARAKTERISTIKE COVID-19 KOD KOMPLETNO VAKCINISANIH U ODNOSU NA NEVAKCINISANE PACIJENTE LEČENE NA KLINICI ZA INFektivNE BOLESTI UNIVERZITETSKOG KLINIČKOG CENTRA VOJVODINE

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Summary

Introduction. COVID-19 vaccines have demonstrated high effectiveness in preventing hospitalization, severe disease and death. However, a minority of fully vaccinated adults still experience breakthrough infections. This study aims to evaluate the severity of breakthrough infections in the adult population. **Material and Methods.** A retrospective observational study was conducted from March 1, 2021, to June 30, 2021. We compared the clinical characteristics hospitalized patients who were fully vaccinated against SARS-CoV-2 with those who were not fully vaccinated. **Results.** During the study period, 216 patients were treated at the Infectious Diseases Clinic. Complete medical documentation was available for 120 patients, of which 20 (9.75%) were fully vaccinated. Vaccinated patients were older than unvaccinated patients (74 years vs. 60 years, $p < 0.001$) and had a statistically higher prevalence of hypertension ($p = 0.004$), previous cardiovascular diseases ($p < 0.001$), and diabetes mellitus ($p = 0.014$). A statistically significant higher proportion of bilateral pneumonias was observed in the unvaccinated group ($p = 0.042$). The final outcome of the disease did not differ between the two groups. **Conclusion.** Our research confirmed that a significantly smaller percentage of vaccinated patients required hospital treatment, with vaccination coverage in the population during that period being around 50%. Fully vaccinated patients were generally older and had more chronic underlying diseases. While individual differences in the clinical presentation and course of the disease were observed between the groups, the results showed no difference in the final outcome.

Key words: COVID-19; SARS-CoV-2; Unvaccinated Persons; COVID-19 Vaccines; Signs and Symptoms; Hospitalization

Sažetak

Uvod. Vakcine protiv SARS-CoV-2 infekcije pokazale su visoku efikasnost u smanjivanju broja hospitalizacija, težih formi bolesti i letalnih ishoda. Manji udeo potpuno vakcinisanih odraslih oboleo je od COVID-19 infekcije. Cilj studije bio je da proceni karakteristike i težinu bolesti kod potpuno vakcinisanih pojedinaca. **Materijal i metode.** Sprovedena je retrospektivna opservaciona studija u periodu 1. 3. 2021–30. 6. 2021. godine u kojoj smo upoređivali karakteristike kliničke slike pacijenata koji su vakcinisani i onih koji nisu vakcinisani protiv SARS-CoV-2 a oboleli su i njihovo stanje je zahtevalo hospitalno lečenje. **Rezultati.** Za dati vremenski period na Klinici za infektivne bolesti lečeno je 216 pacijenata. Potpuna medicinska dokumentacija bila je dostupna za 120 pacijenata, od kojih 20 (9,75%) spada u grupu potpuno vakcinisanih obolelih i hospitalizovanih pacijenata. Vakcinisani pacijenti bili su stariji u odnosu na nevakinisane (74 godine vs. 60 godina, $p < 0,001$), sa statistički značajno većim procentom hipertenzije ($p = 0,004$), prethodnim kardiovaskularnim događajima ($p < 0,001$) i dijabetesom melitus ($p = 0,014$). Potvrđen je statistički značajan veći udeo bilateralnih pneumonija kod nevakinisane grupe ($p = 0,042$). Konačni ishod bolesti nije se razlikovao. **Zaključak.** Istraživanje je potvrdilo da je značajno manji procenat vakcinisanih pacijenata bilo neophodno hospitalizovati (u tom trenutku obuhvat vakcinacijom bio je oko 50% populacije). Potpuno vakcinisani pacijenti bili su stariji i opterećeniji hroničnim bolestima. Potvrđene su pojedinačne razlike u kliničkoj prezentaciji i toku bolesti između ispitivanih grupa, ali nije potvrđena razlika u krajnjem ishodu hospitalizovanih vakcinisanih i nevakinisanih pacijenata.

Ključne reči: COVID-19; SARS-CoV-2; nevakinisane osobe; COVID-19 vakcine; znaci i simptomi; hospitalizacija

Introduction

In December 2019, an increased incidence of atypical pneumonia of unknown etiology was observed in the city of Wuhan, Hubei Province, China. The situation, which began with sporadic cases, soon gained global proportions. The etiological

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Abbreviations

COVID-19	– Corona Virus Disease 2019
SARS-CoV-2	– Severe Acute Respiratory Syndrome Coronavirus 2
mRNA vaccines	– messenger RNA vaccines
UCCV	– University Clinical Center of Vojvodina
ARDS	– acute respiratory distress syndrome
IL-6	– interleukin-6
AST	– aspartate aminotransferase
ALT	– alanine aminotransferase
GGT	– gamma-glutamyltransferase
ICU	– Intensive Care Unit
CPAP	– continuous positive air pressure
ACE 2 receptors	– angiotensin-converting enzyme 2 receptors

agent, a virus, was identified as SARS-CoV-2, and the World Health Organization named the disease COVID-19 [1].

Despite a large number of patients exhibiting mild clinical symptoms, it has been shown that in some cases, the health condition of patients infected with SARS-CoV-2 progresses from pneumonia to acute respiratory distress syndrome (ARDS), which can potentially lead to disseminated intravascular coagulation, multiple organ dysfunction syndrome, and death [2–4]. Older age, male gender, and the presence of comorbidities such as hypertension and diabetes mellitus are risk factors for a more severe form of the disease [5, 6]. Subsequent studies of the pathogenetic mechanisms of the disease have indicated that a cytokine storm, part of the pathogenetic process, is responsible for severe forms and represents an excessive host response to infection, drawing parallels with certain occurrences in sepsis [7].

In 2020, a rapid global effort was undertaken to develop vaccines against SARS-CoV-2 infection. The goal was to increase population immunity through vaccination, thereby preventing severe forms of the disease and mitigating the ongoing health crisis worldwide [8]. This effort led to the development of new vaccine platforms, including vector vaccines, mRNA vaccines, and DNA vaccines [9]. In the Republic of Serbia, mass vaccination began in December 2020 (Official Gazette of the RS, No. 155/2020). The available vaccines included vector vaccines (Gam-COVID-Vac and ChAdOx1 nCoV-19), an mRNA vaccine (BNT162b2) and an inactivated vaccine (BBIBP-CorV) [10].

Large, multicenter randomized clinical trials published in the first half of 2021 showed encouraging results regarding the effectiveness of vaccination [8, 11–13]. An observational study by Haas et al. in 2021 demonstrated that vaccination contributed to a reduction in the incidence of SARS-CoV-2 infection, hospitalization, and deaths at the national level in Israel [14]. However, research has also documented cases of disease in fully immunized individuals, referred to as breakthrough infections [15, 16]. This study aims to compare the clinical characteristics, severity, course, and outcome of COVID-19 between fully vaccinated and non-vaccinated patients treated at the Infectious Diseases Clinic of the University Clinical Center of Vojvodina.

Material and Methods

This study includes patients treated at the Infectious Diseases Clinic of the University Clinical Center of Vojvodina (UCCV) from March 1, 2021, to June 30, 2021, with a confirmed diagnosis of COVID-19. Positive results were obtained from upper respiratory tract samples and confirmed by reverse transcription polymerase chain reaction and/or rapid antigen testing. Data on the subjects were retrospectively analyzed from available medical records, with the approval of the UCCV Ethics Committee (approval number: 00-150/2021).

Based on an epidemiological survey, patients were categorized into a fully vaccinated group and a control group of non-vaccinated subjects. Vaccinated patients confirmed anamnistically upon admission to inpatient care that they had received both recommended doses of one of the SARS-CoV-2 vaccines available in the Republic of Serbia, and that at least 14 days had passed since the second dose of the vaccine and the appearance of the first symptoms.

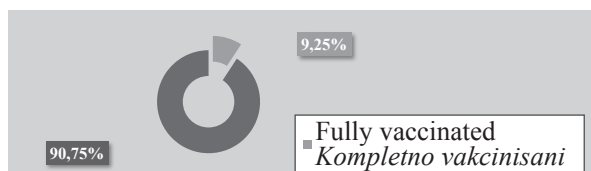
A total of 216 confirmed cases were treated at the Clinic during the specified period. Complete medical documentation was available for 120 patients at the time of data processing. The first group of completely vaccinated patients included 20 subjects, while the unvaccinated group consisted of 100 consecutive unvaccinated patients for whom complete medical documentation was available. Upon examination of the medical histories, data were obtained on age, sex, comorbidities, date of onset of symptoms, date of hospitalization, disease symptoms, use of antibiotic therapy before hospitalization, and the final outcome of hospitalization for all patients. The values of vital parameters at admission (body temperature measured axillary using a digital thermometer, pulse, respirations per minute, and systolic and diastolic blood pressure values), transcutaneous blood oxygen saturation (measured with a pulse oximeter) and lung X-ray findings were recorded. The following laboratory parameters were determined upon admission: complete blood count with leukocyte formula, C-reactive protein, procalcitonin, interleukin-6, fibrinogen, urea, creatinine, serum electrolytes (sodium and potassium), bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), activated partial thrombin time, prothrombin time, and D-dimer. Data on the course of treatment of patients (collected from the decursus) included information on the duration of fever in the hospital, implementation of the therapeutic protocol according to individual indications for each patient, admission to the Intensive Care Unit (ICU) and the length of treatment there, need for non-invasive ventilatory support (CPAP) and/or invasive mechanical ventilation together with the duration, the total length of hospitalization, and the final outcome of treatment (survived/deceased). All patients were treated according to the “Protocol for the treatment of patients with COVID-19” (versions 10 and 11) during the specified period. Information on

corticosteroid therapy (initial choice and dose of corticosteroids, length of intrahospital therapy, and whether the therapy was extended after discharge), low-molecular-weight heparin, types of antibiotics, oxygen therapy (whether it was received and its duration), intrahospital antibiotics, antiviral therapy (favipiravir), and immunomodulatory therapy (tocilizumab) was taken from the medical records for the purpose of the study.

For statistical data processing, SPSS software version 23.0 was used. Categorical variables are presented as n (%), and differences between groups were compared using the χ^2 -test. By testing the normality of the distribution of continuous variables, it was concluded that most variables significantly deviate from the normal distribution. Accordingly, measures of central tendency of continuous variables are presented in percentiles (median and interquartile range), and differences between groups were compared by using the Mann-Whitney test. Statistically significant differences were those with $p < 0.05$. The data are presented in tables and graphs.

Results

A total of 216 patients were treated at the Clinic during the specified period. Data on age, gender, and the final treatment outcome were available for all patients. There were 20 patients in the complete-



Graph 1. Ratio of fully vaccinated and unvaccinated patients hospitalized at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021

Grafikon 1. Udeo kompletno vakcinisanih među hospitalizovanim bolesnicima na Klinici za infektivne bolesti u periodu od 1. 3. 2021. do 30. 6. 2021. godine

ly vaccinated group and 196 patients in the non-vaccinated group. Therefore, the vaccinated group accounted for 9.25% of those treated at the Clinic during the specified period, while the non-vaccinated group accounted for 90.75% (**Graph 1**).

An analysis of the gender structure revealed that males were more prevalent among the hospitalized patients, but there was no statistically significant difference between the male and female genders between the two groups (**Table 1**). Vaccinated patients were statistically significantly older than non-vaccinated ones (74 years vs. 60 years, $p < 0.001$), with a significantly higher prevalence of hypertension, previous cardiovascular diseases, and diabetes mellitus ($p = 0.004$, $p < 0.001$, $p = 0.014$) (**Graph 2**, **Table 1**).

Table 1. Epidemiological characteristics, comorbidities, symptoms, vital parameters, laboratory analyzes, and lung X-ray findings in COVID-19 patients hospitalized at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021

Tabela 1. Epidemiološke karakteristike, komorbiditeti, simptomi, vitalni parametri, laboratorijski nalazi i nalazi radiograma grudnog koša kod obolelih od COVID-19 hospitalizovanih na Klinici za infektivne bolesti u periodu 1. 3. 2021–30. 6. 2021.

Characteristics/ <i>Karakteristike</i>	Vaccinated/ <i>Vakcinisani</i>		Total/ <i>Ukupno</i>	p/p
	Yes/ <i>Da</i> *	No/ <i>Ne</i> *	N/ <i>Br.</i> (%)	
Gender/ <i>Pol</i>				
Male/ <i>Muški</i>	13 (65)	124 (63.3)	137 (63.4)	0.878
Comorbidities/ <i>Komorbidityeti</i>				
Obesity/ <i>Gojaznost</i>	6 (30)	18 (18)	24 (20)	0.221
Hypertension/ <i>Arterijska hipertenzija</i>	16 (18)	45 (45)	61 (50.8)	0.004
MI or stent / <i>Akutni infarkt miokarda i/ili stent</i>	5 (25)	3 (3)	8 (6.7)	<0.001
COPD/ <i>HOBP</i>	1 (5)	5 (5)	6 (5)	1.000
Autoimmune diseases/ <i>Autoimune bolesti</i>	2 (10)	9 (9)	11 (9.2)	0.898
Malignant diseases/ <i>Maligne bolesti</i>	1 (5)	6 (6)	7 (5.8)	0.898
Symptoms before hospitalization/ <i>Simptomi pre hospitalizacije</i>				
Fever/ <i>Temperatura</i>	20 (100)	92 (92)	112 (93.3)	0.190
Headache/ <i>Glavobolja</i>	2 (10)	8 (8)	10 (8.3)	0.768
Muscle pain/ <i>Mialgije</i>	1 (5)	6 (6)	7 (5.8)	0.862
Back pain/ <i>Bolovi u leđima</i>	1 (5)	7 (7)	8 (6.7)	0.743
Sore throat/ <i>Gušobolja</i>	3 (15)	9 (9)	12 (10)	0.414
Rhinorrhea/ <i>Sekrecija iz nosa</i>	2 (10)	3 (3)	5 (4.2)	0.153
Cough/ <i>Kašalj</i>	14 (70)	74 (74)	88 (73.3)	0.712
Dyspnea/ <i>Dispnea</i>	6 (30)	27 (27)	33 (27.5)	0.784

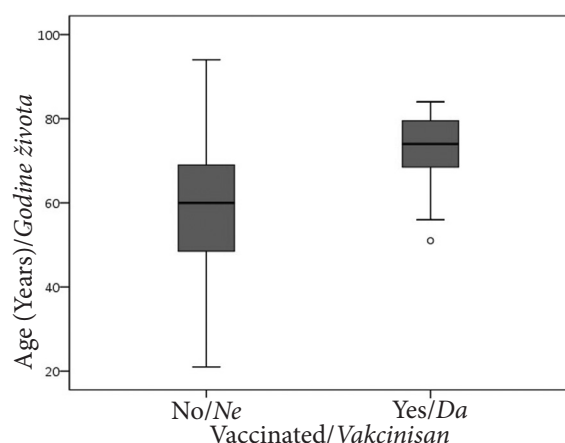
Chest pain/Bolovi u grudima	8 (40)	2 (2)	10 (8.3)	0.000
Hemoptysis/Hemoptizije	0 (0)	3 (3)	3 (2.5)	0.433
Nausea/Mučnina	0 (0)	10 (10)	10 (8.3)	0.140
Vomiting/Povraćanje	1 (5)	5 (5)	6 (5)	1.000
Diarrhea/Dijareja	2 (10)	11 (11)	13 (10.8)	0.895
Anosmia/Gubitak čula mirisa	0 (0)	2 (2)	2 (1.7)	0.524
Highest fever/Vrednosti najviše telesne temperature (°C)	38 (37.8-39.0)	38.7 (38.2-39.0)		0.008
Duration of fever (days)	5.5 (3-8)	8 (5-10)		0.041
Trajanje povišene telesne temperature (dani)				
Vital parameters on admission/Vitalni parametri pri prijemu				
Body temperature/Telesna temperatura (°C)	36.5 (36.5-37.8)	36.5 (36.5-37.7)		0.601
Systolic blood pressure/Sistolni krvni pritisak (mmHg)	130 (116-130)	120 (115-130)		0.394
Diastolic blood pressure/Dijastolni krvni pritisak (mmHg)	70 (66-80)	80 (70-80)		0.229
Heart rate/Srčana frekvencija (/min)	78 (67-90)	96 (81-106)		0.002
Respiratory rate/Broj udaha u minuti (/min)	16 (16-20)	16 (16-16)		0.335
Transcutaneous SpO ₂ /Transkutana SpO ₂ (%)	96 (93-97)	96 (93-97)		0.925
Chest X-ray findings on admission/Rendgenski nalaz grudnog koša pri prijemu				
No pneumonia/Bez pneumonije	0 (0)	5 (5.2)	5 (4.3)	
Unilateral pneumonia/Unilateralna pneumonija	5 (25)	7 (7.3)	12 (10.3)	0.042
Bilateral pneumonia/Bilateralna pneumonija	15 (75)	84 (87.5)	99 (85.3)	
ARDS/Akutni respiratorni distres sindrom	0 (0)	0 (0)	0 (0)	
Laboratory parameters on admission/Laboratorijski parametri pri prijemu				
Leukocytes/Leukociti (10 ⁹ /l)	6.1 (5.3-9.5)	6.0 (4.4-7.6)		0.422
Neutrophils/Neutrofili (%)	81.1 (67.7-83.0)	79.8 (68.8-85.8)		0.869
Lymphocytes/Limfociti (%)	13.4 (9.1-22.72)	15.3 (9.5-23.7)		0.408
Monocytes/Monociti (%)	5.6 (2.8-8.1)	4.6 (3.3-6.5)		0.477
Eosinophils/Eozinofili (%)	0.2 (0.0-0.7)	0.0 (0.0-0.2)		0.004
Erythrocytes/Eritrociti (10 ¹² /l)	4.1 (3.7-4.9)	4.7 (4.3-5.1)		0.007
Hemoglobin/Hemoglobin (g/l)	128 (117-145)	141 (128-150)		0.032
Thrombocytes/Trombociti (10 ⁹ /l)	163 (137-220)	190 (154-249)		0.120
C-reactive protein/C-reaktivni protein (mg/l)	77.8 (39.5-172)	56.2 (29.4-96.7)		0.218
Interleukin-6/Interleukin-6 (pg/ml)	25.2 (9.6-44.3)	28.1 (13.1-52.1)		0.702
Procalcitonin/Prokalciton (ng/ml)	0.07 (0.0-0.6)	0.08 (0.0-0.2)		0.967
Urea/Urea (mmol/l)	7.5 (6.1-12.6)	5.5 (4.2-7.2)		<0.001
Creatinine/Kreatinin (μmol/l)	100 (84-126)	91 (73-108)		0.312
Sodium/Natrijum (mmol/l)	137 (135-142)	139 (136-141)		0.753
Potassium/Kalijum (mmol/l)	4.3 (3.8-4.6)	4.1 (3.8-4.4)		0.384
Total bilirubin/Ukupni bilirubin (μmol/l)	8.4 (5.8-11.3)	8.6 (6.6-11.5)		0.775
Direct bilirubin/Direktni bilirubin (μmol/l)	2.6 (2.0-4.2)	3.1 (2.5-4.4)		0.256
Aspartate aminotransferase/Aspartat aminotransferaza (U/l)	32.5 (30.0-37.5)	42 (33.5-61.0)		0.007
Alanine aminotransferase/Alanin aminotransferaza (U/l)	29.0 (23.5-45.7)	41.0 (32.5-67.5)		0.001
Gamma-glutamyltransferase/Gama glutamil transferaza (U/l)	29.0 (22.0-45.0)	38.0 (29.0-64.0)		0.043
Activated partial thromboplastin time (R)	0.97	0.93		0.391
Aktivisano parcijalno tromboplastinsko vreme (R)	(0.82-1.07)	(0.85-1.00)		
Prothrombin time/Protrombinsko vreme (R)	0.97 (0.90-1.02)	0.97 (0.92-1.04)		0.781
D-dimer/D-dimer (ng/ml)	1190 (720-1333)	835 (555-1120)		0.058
Fibrinogen/Fibrinogen (g/l)	5.7 (4.5-6.4)	6.2 (5.6-6.9)		0.086

Legend: COPD - chronic obstructive pulmonary disease; ACE2 receptors - angiotensin-converting enzyme 2 receptors;

*Categorical variables are presented as n (%), measures of central tendency of continuous variables are presented in percentiles (median and interquartile range)

Legenda: HOBP - hronična opstruktivna bolest pluća; ACE2 - angiotenzin konvertujući enzim 2 receptori;

*Kategorijalne varijable su predstavljene kao Br (%), mere centralne tendencije kontinuiranih varijabli su prezentovane kao procenti (medijana i interkvartilni raspon).



Graph 2. Age structure of fully vaccinated and unvaccinated patients hospitalized at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021 ($p < 0.001$)

Grafikon 2. Starosna struktura kompletno vakcinisanih i nevakcinisanih pacijenata bolnički lečenih na Klinici za infektivne bolesti u periodu 1. 3. 2021–30. 6. 2021. ($p < 0.001$)

By examining the disease symptoms before admission to the hospital, a statistically significant difference between the vaccinated and non-vaccinated groups was recorded only for chest pain, which occurred more frequently in the vaccinated group ($p < 0.001$), while the frequencies of other symptoms did not differ. Before hospitalization, non-vaccinated patients experienced a longer duration of fever (expressed in days) and higher body temperature values ($p = 0.041$, $p = 0.008$) (**Table 1**).

Radiological findings revealed a statistically significant difference ($p = 0.042$) between the groups, with a higher proportion of bilateral pneumonia in the non-vaccinated group (**Table 1**).

Analysis of the complete blood count revealed that the mean values of erythrocytes, leukocytes, and platelets did not deviate from the reference values in either group. Although the values of erythrocytes and hemoglobin were slightly higher in the unvaccinated patients, this data is clinically irrelevant as they were within the range of reference values. A lower number of eosinophils was noted, which was more pronounced in the vaccinated group ($p = 0.004$), while the degree of lymphopenia did not differ between the groups (**Table 1**). Urea values were statistically significantly higher in

Table 2. Therapy administered to patients treated for COVID-19 at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021

Tabela 2. Primenjena terapija u lečenju COVID-19 na Klinici za infektivne bolesti u periodu 1. 3. 2021–30. 6. 2021.

Characteristics <i>Karakteristike</i>	Vaccinated/ <i>Vakcinisani</i>		Total/ <i>Ukupno</i>	p/p
	Yes/ <i>Da</i> *	No/ <i>Ne</i> *	n/ <i>Br.</i> (%)	
Intrahospital therapy/ <i>Intrahospitalna terapija</i>				
Oxygen therapy/ <i>Oksigenoterapija</i>	16 (80)	69 (69)	85 (70.8)	0.323
Corticosteroids/ <i>Kortikosteroidi</i>	18 (90)	99 (99)	117 (97.5)	0.090
Favipiravir	2 (10)	2 (2)	4 (3.3)	0.690
Tocilizumab	8 (40)	44 (44)	52 (43.3)	0.742

*Categorical variables are presented as n (%)/Kategorijalne varijable su predstavljene kao Br. (%).

Table 3. Course of the disease and treatment outcome in COVID-19 patients treated at the Infectious Diseases Clinic in the period from March 1, 2021 to June 30, 2021

Tabela 3. Tok bolesti i ishod lečenja COVID-19 kod pacijenata bolnički lečenih na Klinici za infektivne bolesti u periodu od 1. 3. 2021. godine do 30. 6. 2021. godine

Characteristics Karakteristike	Vaccinated/Vakcinisani		Total/Ukupno	p/p
	Yes/Da*	No/Ne*	n/Br. (%)	
Admission to the ICU/Prijem u Jedinicu intenzivne nege	4 (20)	21 (21)	25 (20.8)	0.920
CPAP	4 (20)	79 (79)	23 (19.2)	0.917
Mechanical ventilation/Mehanička ventilacija	4 (20)	8 (8)	12 (10)	0.102
Duration of hospitalization (days)/Dužina hospitalizacije (dani)	10 (7-16)	8 (7-11)		0.104
Duration of illness before hospitalization (days) Dužina bolesti pre hospitalizacije (dani)	7 (4-10)	9 (8-11)		0.033
Treatment outcome/Ishod lečenja				
Survived/Preživeli	3 (15)	21 (10.7)	24 (11.1)	0.561

Legend: CPAP - continuous positive air pressure

*Categorical variables are presented as n (%), measures of central tendency of continuous variables are presented in percentiles (median and interquartile range)

Legenda: CPAP – kontinuirani pozitivni pritisak vazduha u disajnim putevima

Kategorijalne varijable su predstavljene kao Br. (%), mere centralne tendencije kontinuiranih varijabli predstavljene su kao percentili (medijana i interkvartilni raspon).

the vaccinated group ($p < 0.001$). The values of aspartate AST ($p = 0.007$), ALT ($p = 0.011$), and GGT ($p = 0.043$) were statistically significantly higher in the unvaccinated group (**Table 1**). No significant difference was observed in other laboratory parameters between the groups.

The analysis of the use of antiviral and immunomodulatory therapy did not reveal statistically significant differences between the groups (**Table 2**).

The analysis of the duration of the disease (in days) before admission to inpatient care revealed a statistically significant difference ($p = 0.033$), with non-vaccinated patients experiencing a longer period of illness before hospitalization in comparison to vaccinated ones. In examining the progression of the disease, no statistically significant differences were observed in the frequency of ICU admission, the need for non-invasive or invasive mechanical ventilation, or the length of hospitalization. Additionally, there was no statistically significant difference in the treatment outcome between the two groups (**Table 3**).

Discussion

The most important findings of our study include:

- The percentage of vaccinated individuals among hospitalized patients was 9.75%, while the percentage of vaccinated individuals in the general population at that time was 47.8%, according to official data from the Ministry of Health [17].

- Vaccinated patients who required hospitalization were statistically significantly older than non-vaccinated patients.

- Vaccinated patients who required hospitalization had a statistically significantly higher burden of comorbidities, including hypertension, cardiovascular issues (myocardial infarction or cerebrovascular insult), and diabetes mellitus.

- Although individual differences in the clinical presentation and course of the disease were noted, they did not statistically significantly differ between vaccinated and non-vaccinated hospitalized patients.

According to official data from the Ministry of Health, by mid-June 2021, 47.8% of the population in the Republic of Serbia had been fully immunized [17]. That percentage was significantly lower, only 9.75%, among hospitalized patients, clearly indicating the protective effect of vaccination in reducing the number of patients with a more severe clinical picture [18].

A study by Gustafsson et al. demonstrated that changes in signaling and communication between lymphocytes, along with a shorter lifespan of memory cells, could explain the reduced response of the elderly population to vaccination, known as immunosenescence [19]. In addition to the altered immune response to the vaccine, age-related changes in the immune system also lead to a chronic low-grade inflammatory state. Since older age correlates with a higher prevalence of comorbidities, these factors together indicate a reduction in the reserve capacity of vital organs, putting older individuals at high risk for severe disease outcome [5]. This conclusion explains

the higher proportion of comorbidities such as hypertension, diabetes mellitus, or serious cardiovascular issues (e.g., acute myocardial infarction or coronary angioplasty) in the vaccinated group. Since both age and comorbidities are independent risk factors for COVID-19, and both were prevalent in the vaccinated population, it is logical that hospitalized fully vaccinated patients were older and chronically burdened with diseases compared to unvaccinated patients.

The interesting result regarding symptomatology differences, with an increased incidence of chest pain, was among the vaccinated group, may be linked to findings by Zhou et al. They note that cardiac complications (e.g., heart failure, new or worsening arrhythmia, acute myocardial infarction) are common in patients with pneumonia. Additional risk factors for cardiovascular issues following pneumonia include older age, preexisting cardiovascular comorbidities, and more severe pneumonia [20], all of which were prevalent in the vaccinated group. The higher incidence of anginal complaints in vaccinated patients can be interpreted as a potential worsening of cardiovascular status in the presence of SARS-CoV-2 infection. Additional clinical attention, including stricter monitoring of cardiovascular functions, is necessary for these patients to prevent unwanted cardiovascular complications.

The differences in the length of fever and the highest pre-hospital temperature can be understood in light of the age of the vaccinated population, which, as previously stated, was on average older. The geriatric population's response to infectious and inflammatory processes can be atypical, manifesting as confusion, falls, fatigue, incontinence and immobility [21]. The absence or reduction of fever could be an alternate response of the older vaccinated population to COVID-19. It would be unjustified to attribute these results to a potentially milder clinical presentation or reduced inflammatory processes due to vaccination, as the study focused on hospitalized patients with uniform criteria for hospitalization. Furthermore, as explained in the results, there were no significant differences in inflammatory laboratory parameters between the two groups. Rapid diagnosis and treatment of the geriatric population, considering the appearance of atypical symptoms, could prevent complications, shorten hospitalization and improve the quality of life for this age group [22].

In our analysis of radiological images at admission, we observed a higher percentage of bilateral pneumonia in the non-vaccinated population. The fact that the development of radiological findings is related to the duration of the disease since its onset can be a limiting factor of the results [23]. Our findings indicate that vaccinated patients were, on average, hospitalized earlier than non-vaccinated patients, which could partially affect the radiological findings at admission.

Laboratory analyses revealed elevated levels of urea in the serum of the vaccinated population. According to Ronco et al., renal dysfunction is common in COVID-19 patients, ranging from mild proteinu-

ria to acute renal failure, often occurring as part of multiple organ dysfunction syndrome requiring dialyses. Cardiovascular comorbidities and complications such as sepsis, hypovolemia, and nephrotoxins can impair renal function. COVID-19-induced heart failure may manifest as right-sided (causing renal congestion) or left-sided (leading to hypoperfusion), both of which could be pre-renal causes for elevated nitrogenous substances. The presence of ACE2 receptors in renal tissue may explain the direct renal impact of SARS-CoV-2 viremia [24]. The higher presence of cardiovascular comorbidities in the vaccinated group might explain the elevated urea levels, but we also observed that creatinine, another marker of renal function, did not follow this trend. The small sample size of vaccinated individuals may account for the limited specificity of these results. The isolated increase in urea may be due to SARS-CoV-2 binding to angiotensin-converting enzyme 2 receptors, activating the renin-angiotensin-aldosterone system, where water and sodium are absorbed, and causing passive reabsorption of urea from primary urine as a side effect [25]. Verified liver damage, indicated by increased aminotransferases, GGT and bilirubin activity, can predict more severe disease forms and worse outcomes [26, 27]. Potential liver and bile duct damage mechanisms include direct viral effects, cytokine storm, tissue ischemia and hypoxia, drug-induced liver injury or decompensation of pre-existing chronic liver disease [28]. The non-vaccinated group showed significant increases in AST, ALT and GGT upon hospital admission, with no significant differences in bilirubin levels. Since AST is found in tissues other than the liver (e.g., myocardium, skeletal muscles, kidneys), its value in interpreting the liver damage is less than that of ALT [27]. In severe COVID-19, which affects multiple

organ systems, AST better reflects systemic damage. No differences were observed in the use of corticosteroids, favipiravir, tocilizumab, and oxygen therapy.

Conclusion

The similar results of Intensive Care Unit admission, need for ventilatory support, and final treatment outcomes suggest that the most severe disease forms were equally represented in both groups. However, this result should be considered in light of several factors, including the comparison of hospitalized patient numbers, age structure, and comorbidities in both groups. Although the qualitative characteristics of the hospitalization were similar, the quantitative characteristics favored the vaccinated population. Vaccinated patients were, on average, older and had more pre-existing conditions requiring inpatient treatment, while the younger population showed protection from more severe forms of Corona Virus Disease 2019 due to vaccination.

The reduction in severe disease among those over 50 years, decreased mortality rate, fever Corona Virus Disease 2019 hospitalizations, protection of the working-age population, reduction of absenteeism, indirect prevention of long Corona Virus Disease 2019 and decreased need for rehabilitation treatments are some of the conclusions drawn from this research. These findings also highlight the reduced burden on healthcare systems and decreased use of antimicrobial agents.

Limitations of this study include the small patient sample, its retrospective nature, and data collection limited to the Infectious Diseases Clinic, excluding other inpatient Corona Virus Disease 2019 treatment centers in University Clinical Center of Vojvodina.

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