ORIGINAL RESEARCH

THE IMPORTANCE OF VACCINATION AGAINST COVID-19 ON THE OUTCOME OF CRITICALLY ILL COVID-19 PATIENTS

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Abstract

Introduction. The development of the coronavirus disease 2019 (COVID-19) vaccine marked the beginning of the end of the pandemic and the understanding of the disease as something that is part of clinical practice. The aim of this study was to investigate, assess, and demonstrate the significance of vaccination on the outcome of severely ill patients treated in intensive care units.

Methods. A retrospective study was conducted on a sample of patients hospitalized at the Clinic for Infectious Diseases of the Clinical Center of the University of Sarajevo during 2022.

Results. Participants who were vaccinated against COVID-19 had a lower mortality rate and a higher chance of survival compared to unvaccinated participants. Additionally, disease outcomes were significantly influenced by oxygen saturation and platelet count at admission.

Conclusion. COVID-19 vaccination significantly reduced the mortality rate, with vaccinated participants having a higher chance of survival compared to unvaccinated participants.

Keywords: Coronavirus disease 2019, vaccination, treatment, prognosis.

INTRODUCTION

The clinical manifestation of coronavirus disease 2019 (COVID-19) is not specific and is very similar to other viral infections (1). After an incubation period of around 4 to 14 days, the infection can develop with mild to severe symptoms, which can also be fatal. COVID-19 is clinically classified as mild to moderate illness (without pneumonia or with pneumonia), severe illness (dyspnea, respiratory rate above 30/min, oxygen saturation below 93%, partial pressure of oxygen in arterial blood (PaO2)/ inspiratory oxygen concentration (FiO2) ratio less than 300, and/or lung infiltrates covering 50% of the lung surface within 24 to 48 hours), and critical illness (respiratory failure, multi-organ failure, sepsis) (2-4). All patients who experienced a severe clinical course of the disease had chronic conditions such as cardiovascular diseases, pulmonary pathology, chronic kid-

ney disease, or were oncology cases (5-9). COVID-19 vaccines that have been analyzed or approved for clinical studies include inactivated vaccines, live attenuated vaccines, vector vaccines, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), protein subunit-based vaccines, and virus-like particle vaccines (10,11). The primary goal of the vaccine was to prevent the development of severe clinical disease, i.e., to reduce mortality and morbidity rates and to slow the spread of the virus (11). After the first vaccines were approved and vaccination began, it was observed that the spread of this severe infection slowed down (11). Clinicians noticed that vaccinated patients, compared to unvaccinated patients, had a milder course of the disease, shorter hospital stays, and a lower percentage of fatal outcomes in the vaccinated population (11).

The aim of the study was to determine the vaccination status of critically ill COVID-19 patients admitted to intensive care units (ICU), to assess the significance of vaccination on the outcome of critically ill COVID-19 patients, to establish the average values of vital parameters at admission in patients admitted to ICUs, to determine the average values of non-specific inflammation and blood count parameters, and to assess their significance on the outcome of critically ill COVID-19 patients, as well as to compare independent predictors at admission on the outcome of critically ill COVID-19 patients.

METHODS

Patients and study design

The study utilized data obtained from clinical data records, temperature charts, laboratory findings, and discharge letters. A total of 110 patients (57 male, 53 female) hospitalized in the ICU at the Clinic for Infectious Diseases of the Clinical Center of the University of Sarajevo (CCUS) between January 1, 2022, and December 31, 2022, were included in the study. The analyzed variables were: gender, age, comorbidities, vaccination status (number of doses and vaccine manufacturer), assessment of the patient's general condition, vital parameters (oxygen saturation (sO2), blood pressure, heart rate), laboratory parameters (values of leukocytes, neutrophils, erythrocytes, hemoglobin, hematocrit, platelets, C-reactive protein (CRP)), duration of treatment (in days), and disease outcome.

Methods

The study was designed as a retrospective cohort study. Approval for the review and processing of data from patients was obtained from the Institute for Scientific Research at CCUS. The study was conducted in accordance with the Convention on Human Rights (Oviedo Convention), the Helsinki Declaration on the Rights of Patients in Biomedical Research and its latest revision, as well as national laws on patient rights (Law on the Rights, Obligations, and Responsibilities of Patients of the Federation of Bosnia and Herzegovina, Law on the Protection of Personal Data of Bosnia and Herzegovina, and the Rulebook on Regulations and Records in the Field of Health Care of the Federation of Bosnia and Herzegovina).

Statistical Methods

Upon completion of the study, statistical data analysis was performed. The statistical analysis of the data was conducted using the SPSS for Windows software package (version 19.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (version 11, Microsoft Corporation, Redmond, WA, USA). The Kolmogorov-Smirnov test was used to determine the distribution of continuous variables (for a sample size greater than 50 participants). For variables that showed a statistically significant deviation from normal distribution, average values were presented using the median and interquartile range (25th-75th percentile), and the Mann-Whitney U test was used for their comparison. Binary logistic regression was applied to

examine whether independent predictors/variables in the study had an influence on the disease outcome univariately. Subsequently, multivariate regression analysis was used to assess the combined influence of variables that were identified as statistically significant predictors in univariate analysis. The Chi-square test of independence was employed to examine the dependency of disease outcomes on the vaccination status of participants. A significance level of $\alpha=0.05$ was set for statistical analysis. Decisions to accept or reject hypotheses in the relevant tests were made based on the p-value of the statistical test (if $p \geq \alpha$, the hypothesis was accepted; if $p < \alpha$, the hypothesis was rejected). The results were thoroughly detailed and documented, presented in absolute numbers, relative numbers, and statistical values using statistical indicators, and displayed in simple and understandable tables and graphs.

RESULTS

The average age of participants hospitalized in the ICU during this period was 75.5 (67.75-83), with the youngest participant being 22 years old and the oldest 93 years old. The average age of male participants was 76.0, while the average age of female participants was 75.0, and no statistically significant difference in age between genders was found (p=0.434). The most common pre-existing cardiorespiratory risk factors were present in 74 participants (63.7%), followed by endocrinological pathology in 34 participants (30.9%), urological pathology in 23 participants (20.9%), and gastrointestinal pathology in 3 participants (2.7%). Regarding vaccination status, a larger number of participants, 59 (53.6%), were unvaccinated, while 51 (46.4%) were vaccinated. Among the 51 vaccinated participants, four had received one dose, 37 had received two doses, and 10 participants had received a booster—a third dose. The majority of participants had a moderately severe clinical presentation, 73 (66.4%), while 30 participants (27.3%) had a severe clinical presentation, and 7 participants (6.4%) were in critical condition upon admission. The average oxygen saturation level of participants was 91% (86-95%), with a minimum value of 60% and a maximum of 99%.

The average systolic blood pressure was 125 mmHg (110-135.25 mmHg), and the average diastolic blood pressure was 76 mmHg (69.75-85 mmHg). The average heart rate was 84 beats/min (76-97), with a minimum of 36 and a maximum of 150 beats/min. Table 1 shows the values of non-specific inflammatory and blood parameters.

The average value of CRP was 86 mg/L (29.75-137 mg/L), with a minimum of 1 mg/L and a maximum of 310 mg/L. The average leukocyte count was 7.2 x 10^9/L (5.275-10.275 x 10^9/L), with a minimum of 1 x 10^9/L and a maximum of 38 x 10^9/L. The average erythrocyte count was 4.3 x 10^{12}/L, with a minimum of 2 x 10^{12}/L and a maximum of 22.6 x 10^{12}/L. The average hemoglobin level was 127 g/L, with a minimum of 57 g/L and a maximum of 166 g/L.

Table 1. Average values of non-specific inflammatory and blood parameters

	N	Minimum	Maximum	Percentiles		
				25th	50th (Median)	75th
C-reactive protein (mg/L)	110	1	310	29.75	86.00	137.50
Leukocytes x 10^9/L	110	1.0	38.0	5.275	7.200	10.275
Erythrocytes x10^{12}/L	110	2.0	22.6	3.700	4.300	4.700
Hemoglobin g/L	110	57	166	107.00	127.00	140.25
Hematocrit L/L	110	3	58	34.00	39.00	42.25
Thrombocytes x10^9/L	110	13	525	129.00	168.00	220.25
Neutrophiles %	71	11	94	64.40	75.80	85.50

N - number of data

Table 2. The impact of participants' vaccination status on disease outcome

		B	Wald	Df	p	Exp (B)	95.0%C.I.for Exp (B)	
							Lower	Upper
Step 1 (a)	Vaccination status	1.390	8.161	1	0.004	4.016	1.547	10.424
	Constant	0.448	2.817	1	0.093	1.565		

B – estimated logit coefficient; Wald –Wald test; Df – Degrees of freedom; p-level of significance; Exp(B)- odds ratio; CI - Confidence Interval

The average duration of treatment for participants in the ICU was 7 days (5-10 days), with a minimum duration of one (1) day and a maximum of 21 days. Out of the total number of participants included in the study, 30 (27.3%) had a fatal outcome, while 80 (72.7%) had a positive outcome, meaning they recovered. Univariate binary logistic regression was used to examine the influence of independent predictors on disease outcome (survived - 1; did not survive - 0), with age and gender of the participants not proving to be statistically significant predictors of survival (p>0.5). The presence or absence of pre-existing comorbidities also did not have a statistically significant predictive value (p>0.05).

Univariate binary logistic regression was used to examine the impact of vaccination status on disease outcomes. Vaccination status was found to be a significant predictor (p=0.004, Exp(B)= 4.0) of disease outcome (Table 2). Vaccinated participants had a fourfold greater chance of survival compared to unvaccinated participants, with the survival chance in this population ranging from 1.5 to 10 times higher. The univariate binary logistic regression also demonstrated that oxygen saturation (O2%) upon admission had a statistically significant impact on disease outcome (p=0.019, Exp(B)=1.07). For every one percent increase in oxygen saturation at admission, the chance of survival increased by 7% in our sample, with the range in such a population being between 1% and 14%. The impact of systolic and diastolic blood pressure, as well as heart rate, was also examined using univariate binary logistic regression, but no statistically significant influence on disease outcome was found (p>0.05). Values of non-specific acute inflammation markers such as CRP, leukocytes, and the percentage of neutrophils at admission did not show a statistically significant impact on disease outcome (p>0.05). However, platelet count was found to be a significant predictor (p=0.009, Exp(B)=1.08) of disease outcome. If the platelet count at admission was higher by 10 ($x10^9$/L), the chance of survival increased by 8% in our sample, with the survival chance in such a population ranging between 2% and 14%. Multivariate logistic regression was used to examine the impact of independent predictors (which were found to be significant in the univariate analysis) on disease outcomes. Multivariate regression analysis showed that all three independent factors had a statistically significant impact on disease outcomes (p<0.05). Among them, platelet count at admission had the greatest impact (Wald=6.69), followed by vaccination status (Wald=5.58) and peripheral oxygen saturation percentage (Wald=4.58). The Hosmer

Table 3. The impact of independent predictors (vaccination status, peripheral oxygen saturation, and platelets) on disease outcomes at admission

	B	Wald	Df	p	Exp(B)	95.0% CIfor EXP(B)	
						Lower	Upper
Vaccination status (yes/no)	1.222	5.589	1	0.018	3.392	1.232	9.340
O2 saturation %	0.072	4.583	1	0.032	1.075	1.006	1.148
Thrombocytes x 109/L	0.085	6.699	1	0.010	1.089	1.021	1.161
Constant	-7.337	5.440	1	0.020	0.001		

B – estimated logit coefficient; Wald – Wald test; Df – Degrees of freedom; p-level of significance; Exp(B)- odds ratio; CI - Confidence Interval

and Lemeshow test supports the assertion that the model is a good fit, with a χ^2 value of 9.115 and p=0.329. Out of 59 unvaccinated participants, 36 (61%) survived, while 23 (39%) had a fatal outcome. In the vaccinated group (n=51), 44 (86.3%) survived, and 7 (13.7%) had a fatal outcome. The chi-square test of independence showed a significant association between treatment outcome and vaccination status (χ^2=8.7, p=0.003).

DISCUSSION

In our study, data were analyzed for 52% male patients and 48% female patients. Compared to similar studies, our study had a similar gender distribution (12) as the retrospective cohort study by Nachtigall et al. in Germany (2021), which included 51% male and 49% female participants (12). Other studies showed different gender distributions, such as Kautzky-Willer et al. (2022) in Austria, which included 65% male and 35% female patients (13), or Jirak et al. (2022), also in Austria, which included 72% male and 28% female participants (14). The average age of our participants was 75.5 (67.75-83), similar to the study by Jung et al. (2021), where the average age was 75 (15). Other studies showed different age structures, such as Bruni et al., where the average age was 65 (16). The age structure by gender in our study was 76 for males and 75 for females, which is similar to the study by Meijis et al., where the age structure was 64 for females and 66 for males (17). Among the participants in our study, the most common comorbidities were cardiorespiratory, affecting 67.7% of patients, followed by endocrine (30.9%), urological (20.9%), and gastrointestinal (2.7%) comorbidities. Our study had similar comorbidities compared to other studies of similar design (17,18). In our sample of 110 patients in the intensive care unit, 46.4% were vaccinated against COVID-19, while 53.6% were unvaccinated. Among those vaccinated, 7.8% received one dose, 72.5% received two doses, and 19.7% received a booster dose. In contrast, Bruni et al. (2022) in Italy found that 41% of participants were vaccinated, with 38% receiving two doses and 62% receiving a booster dose (16). Lorenzoni et al. (2022) in Italy reported that 18% of patients in the intensive care unit were vaccinated, 8% were partially vaccinated, and 74% were unvaccinated. Vaccinated patients were more likely to be over 80 years old compared to partially vaccinated and unvaccinated patients (19). Uzun et al. (2022) found 53.1% unvaccinated and 46.9% vaccinated participants, with 12.5% receiving one dose, 74.2% receiving two doses, and 13.3% receiving a booster dose (20). In our study, vaccination status was a significant predictor of disease outcome. Vaccinated participants had a fourfold increased chance of survival compared to unvaccinated participants, with chances ranging from 1.5 to 10 times higher in our population. Conversely, Lorenzoni et al. found that vaccinated patients received their second dose on average 5 months before admission to the intensive care unit, while partially vaccinated patients waited for their second dose. They observed a significant increase in admissions to the intensive care unit only among unvaccinated patients. Their data also indicated higher mortality among vaccinated compared to unvaccinated patients, and a higher proportion of patients over 80 years old among the vaccinated (19). Uzun et al. demonstrated that vaccination reduces the severity of the disease and, consequently, the mortality rate among vaccinated compared to unvaccinated patients (20). For every 10(x 10^9/L) increase in platelet count upon admission, the chance of survival increased by 8% in our sample. In contrast, Wang et al. (2021) found that a higher leukocyte value was associated with higher mortality rates. They observed that 23% of patients had a white blood cell count below the normal range, 12% had a count above the normal range, and about 50% had a reduced lymphocyte count (21). Aly et al. also demonstrated that lymphocyte count, platelet count, neutrophils, and CRP

are significant predictors of disease outcome in their sample (22). Data suggest that thrombocytopenia and lymphopenia in COVID-19 patients are associated with prolonged hospitalization and worse outcomes. Patients with SARS have a higher percentage of lymphopenia (68-90%) and thrombocytopenia (20-45%) compared to those with COVID-19. Thrombocytopenia and lymphopenia have previously been associated with increased mortality risk in patients with COVID-19 (22). The limitations of the study are a small patient sample, not differentiating patients based on vaccine type, and lack of virus strain analysis, therefore a larger sample size, differentiation of patients based on vaccine type, and analysis of the infective strain could provide more significant conclusions.

CONCLUSION

It has been found that in critically ill COVID-19 patients, vaccination status has significant effects on the course of the disease**.** It was discovered through statistical research that patients who were vaccinated have a higher chance of survival compared to non-vaccinated patients. Besides the vaccination status, the patient's platelet count upon admission, followed by their immunization history and, finally, their oxygen saturation %, have the most statistical relevance on the disease's course.

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REFERENCES

1. Albtoosh AS, Farah R, Al Oweidat K, Hussein OM, Obeid AA, Hamila HM, et al. Presenting clinical symptoms of post-COVID-19 breakthrough infection: Predictors of mortality in a Middle Eastern population. Vaccine X. 2024;18:100495. doi: 10.1016/j.jvacx.2024.100495.
2. Liira H, Garner P, Malmivaara A, Kanerva M, Kvarnström K, Sainio M, et al. Prognosis of patients with post-Covid-19 condition: Prospective cohort cluster analysis at one year. J Psychosom Res. 2024; 182:111808. doi: 10.1016/j.jpsychores.2024.111808.
3. Cascella M, Rajnik M, Aleem A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2023 Aug 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/
4. Meyerowitz EA, Scott J, Richterman A, Male V, Cevik M. Clinical course and management of COVID-19 in the era of widespread population immunity. Nat Rev Microbiol. 2024;22(2):75-88. doi: 10.1038/s41579-023-01001-1.
5. Chen CL, Teng CK, Chen WC, Liang SJ, Tu CY, Shih HM, et al. Clinical characteristics and treatment outcomes among the hospitalized elderly patients with COVID-19 during the late pandemic phase in central Taiwan. J Microbiol Immunol Infect. 2024;57(2):257-68. doi: 10.1016/j.jmii.2024.01.006.
6. Fabiani G, Cogozzo C, De Paris A, Di Maria V, Lagomarsini A, Masotti O, et al. Clinical characteristics of patients hospitalized for COVID-19: comparison between different age groups. BMC Geriatr. 2024;24(1):51. doi: 10.1186/s12877-023-04626-2.
7. Begic E, Iglica A, Gojak R, Baljic R, Begic Z, Durak-Nalbantic A, et al. Pericardial Effusion in Postcoronavirus Disease Patients with Preserved Ejection Fraction of the Left Ventricle and Normal Values of N-Terminal-Pro B-Type Natriuretic Peptide-Link with C-Reactive Protein and D-Dimer. Int J Appl Basic Med Res. 2022;12(3):157-60. doi: 10.4103/ijabmr.ijabmr_802_21.
8. Mujakovic A, Kovacevic T, Begic E, Fajkic A, Baric G, Jamakosmanovic A, et al. High Flow Nasal Cannula Versus Noninvasive Positive Pressure Ventilation as Initial Respiratory Support in Patients with Chronic Obstructive Pulmonary Disease and Covid-19: Exploratory Analysis in Two Intensive Care Units. Acta Med Acad. 2022;51(3):199-208. doi: 10.5644/ama2006-124.389.
9. Pasic M, Begic E, Kadic F, Gavrankapetanovic A, Pasic M. Development of neural network models for prediction of the outcome of COVID-19 hospitalized patients based on initial laboratory findin-

gs, demographics, and comorbidities. J Family Med Prim Care. 2022;11(8):4488-95. doi: 10.4103/jfmpc.jfmpc_113_22.
10. Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006–. COVID-19 Vaccines. 2024 Aug 15.
11. Soraci L, Lattanzio F, Soraci G, Gambuzza ME, Pulvirenti C, Cozza A, et al. COVID-19 Vaccines: Current and Future Perspectives. Vaccines (Basel). 2022;10(4):608. doi: 10.3390/vaccines10040608.
12. Nachtigall I, Bonsignore M, Thürmann P, Hohenstein S, Jóźwiak K, Hauptmann M, et al. Sex Differences in Clinical Course and Intensive Care Unit Admission in a National Cohort of Hospitalized Patients with COVID-19. J Clin Med. 2021;10(21):4954. doi: 10.3390/jcm10214954.
13. Kautzky-Willer A, Kaleta M, Lindner SD, Leutner M, Thurner S, Klimek P. Sex Differences in Clinical Characteristics and Outcomes of Patients with SARS-CoV-2-Infection Admitted to Intensive Care Units in Austria. J Pers Med. 2022;12(4):517. doi: 10.3390/jpm12040517.
14. Jirak P, Mirna M, Van Almsick V, Shomanova Z, Mahringer M, Lichtenauer M, et al. Gender-Specific Differences in the Intensive Care Treatment of COVID-19 Patients. J Pers Med. 2022;12(5):849. doi: 10.3390/jpm12050849.
15. Jung C, Flaatten H, Fjølner J, Bruno RR, Wernly B; COVIP study group. The impact of frailty on survival in elderly intensive care patients with COVID-19: the COVIP study. Crit Care. 2021;25(1):149. doi: 10.1186/s13054-021-03551-3.
16. Bruni A, Longhini F, Macheda S, Biamonte E, Pasqua P, Neri G; Calabria COVID-ICU Network authors. Characteristics of unvaccinated and vaccinated critically ill COVID-19 patients in calabria region (Italy): A retrospective study. Front Med (Lausanne). 2022;9:1042411. doi: 10.3389/fmed.2022.1042411.
17. Meijs DAM, van Bussel BCT, Stessel B, Mehagnoul-Schipper J, Hana A, Scheeren CIE; CoDaP investigators. Better COVID-19 Intensive Care Unit survival in females, independent of age, disease severity, comorbidities, and treatment. Sci Rep. 2022;12(1):734. doi: 10.1038/s41598-021-04531-x.
18. Djaharuddin I, Munawwarah S, Nurulita A, Ilyas M, Tabri NA, Lihawa N. Comorbidities and mortality in COVID-19 patients. Gac Sanit. 2021;35(2):S530-2. doi: 10.1016/j.gaceta.2021.10.085.
19. Lorenzoni G, Rosi P, De Rosa S, Ranieri VM, Navalesi P, Gregori D; COVID-19 VENETO ICU Network. COVID-19 Vaccination Status Among Adults Admitted to Intensive Care Units in Veneto, Italy. JAMA Netw Open. 2022;5(5): e2213553. doi: 10.1001/jamanetworkopen.2022.13553.
20. Uzun O, Akpolat T, Varol A, Turan S, Bektas SG, Cetinkaya PD,et al. COVID-19: vaccination vs. hospitalization. Infection. 2022;50(3):747-52. doi: 10.1007/s15010-021-01751-1.
21. Wang L, Cheng X, Dong Q, Zhou C, Wang Y, Song B, Li W, et al. The characteristics of laboratory tests at admission and the risk factors for adverse clinical outcomes of severe and critical COVID-19 patients. BMC Infect Dis. 2021;21(1):371. doi: 10.1186/s12879-021-06057-z.
22. Aly MH, Rahman SS, Ahmed WA, Alghamedi MH, Al Shehri AA, Alkalkami AM, Hassan MH. Indicators of Critical Illness and Predictors of Mortality in COVID-19 Patients. Infect Drug Resist. 2020;13:1995-2000. doi: 10.2147/IDR.S261159.