

# Impact of COVID-19 vaccine on clinical characteristics and outcome of hospitalized COVID-19 patients during the fourth wave of the pandemic in Tuzla Canton, Bosnia and Herzegovina

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## ABSTRACT

**Aim** To evaluate clinical and epidemiological characteristics and outcome of patients with COVID-19, and impact of vaccine against COVID-19 on them.

**Methods** This retrospective study included 225 patients treated from COVID-19 in the period from 1 to 30 September 2021 at the Clinic for Infectious Diseases, University Clinical Centre Tuzla (UCC Tuzla). For the diagnosis confirmation of Covid-19, RT-PCR was used. Patients were divided in two groups: fully vaccinated with two doses of vaccine, and non-vaccinated or partially vaccinated.

**Results** Of 225 patients, 120 (53.3%) were females, and 105 (46.7%) males. Mean age was 65.6 years. There were 26 (11.6%) fully vaccinated patients. Most common symptoms in unvaccinated patients were fatigue (70.9%), cough (70.4%) and fever (69.8%), and in vaccinated fever (76.9%), fatigue (69.2%) and cough (46.2%). Cough was more common in unvaccinated patients ( $p=0.013$ ). Fatal outcome happened in 84 (37.3%) patients. Transfer to the Intensive Care Unit (ICU) and older age had a higher risk of death ( $p<0.001$ ). Older age patients were more likely to have comorbidities like atrial fibrillation ( $p=0.017$ ), hypertension ( $p<0.001$ ) and diabetes mellitus ( $p=0.002$ ). Atrial fibrillation ( $p<0.001$ ), hypertension ( $p<0.001$ ), diabetes mellitus ( $p=0.009$ ) and history of stroke ( $p=0.026$ ), were related to fatal outcome in unvaccinated patients, also did a shorter duration of illness prior to hospitalization ( $p<0.001$ ) and shorter length of hospitalization ( $p=0.002$ ).

**Conclusion** Older patients with comorbidities, as well as those who were not vaccinated against COVID-19, were at higher risk for severe form of the disease and poor outcome.

**Key words:** age, comorbidities, COVID-19, symptoms, vaccination

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## INTRODUCTION

COVID-19 is a severe acute respiratory infection (SARI) that emerged in early December 2019 in Wuhan, China (1). It rapidly spread worldwide and the World Health Organization (WHO) gave the name COVID-19 for the disease and SARS-CoV-2 to the causative virus. It was declared global pandemic by WHO on 11th March 2020 (2).

The incubation period of the disease is 1–14 days, usually 3–7 days, and can even reach 24 days, making it difficult to screen for infections. Additionally, the disease is mainly spread by respiratory droplets and contact (3).

Most patients show clinical symptoms in 5 to 6 days (4). Typically, reported clinical symptoms are fever, dry cough, fatigue, dyspnoea, anosmia, ageusia, or some combination of these (1,4,5).

Majority of the patients have a good prognosis, while a few are in a critical condition, especially the elderly and those with underlying chronic conditions such as cardiac disease and diabetes (6).

Sepsis is the most frequently observed complication, followed by respiratory failure, acute respiratory distress syndrome (ARDS), heart failure, and septic shock (7).

As there is no evidence of pre-existing human SARS-CoV-2 immunity, all people are believed to be susceptible to SARS-CoV-2 infection, especially infants, children, pregnant women and the elderly (8). The older adult population suffers from increased rates of hospitalization and higher fatality rates compared to the younger population (9,10).

To date, nucleic acid detection in nasal and throat swab samples or other respiratory tract samples by real-time (RT) PCR has been the gold-standard method for the clinical diagnosis of COVID-19, which is then further confirmed by next-generation sequencing (11,12).

As of 16 December 16, the outbreak of the COVID-19 has been confirmed in over 220 countries and territories. The virus infected almost 273 million people worldwide, and the number of deaths reached over 5.3 million. The most severely affected countries include the U.S., Brazil, and India (13).

In Bosnia and Herzegovina (B&H), the first imported cases of COVID-19 occurred on 5 March 2020 in the Republic of Srpska, and on 9 March

2020 in the Federation of B&H (14). In the Tuzla Canton, north-eastern part of B&H, the first registered case was on 28 March 2020 (15).

The WHO has emphasized that a vaccine against COVID-19 is a “vital tool” to counter the current pandemic (16).

A COVID19 vaccine is intended to provide acquired immunity against SARSCoV2 (17). The approved vaccines use a range of different platforms (mRNA, viral vector, protein/peptide and inactivated virus) (18). As of 25 January 2022 882,641, (27.1%) people in B&H received the first dose with 1,553,874 doses totally administered (19).

There are many studies around the world relating an impact of the COVID-19 vaccine on the severity of the disease in different age groups, as well as on people with different comorbidities, and on the outcome of the disease. In B&H there has been no published data.

The aim of this study was to evaluate demographic, clinical and epidemiological characteristics and outcomes of patients with COVID-19 admitted to UCC Tuzla, Tuzla Canton, Bosnia and Herzegovina.

## PATIENTS AND METHODS

### Patients and study design

In this retrospective research, medical records and data from all patients aged 18 years and older treated for COVID-19 at the Clinic for Infectious Diseases, University Clinical Centre (UCC) Tuzla, from September 01 to September 30 2021 were analysed.

The patients were divided in seven categories by age: 18-29, 30-39, 40-49, 50-64, 65-74, 75-85 and seventh 85+ years.

The patients were divided in two groups according to the vaccine against SARS-CoV-2 status: fully vaccinated (with two doses of vaccine), and non-vaccinated or partially (with one dose) vaccinated.

This study was approved by the Ethics Committee of the UCC Tuzla.

### Methods

All of the patients had some, or all of the symptoms of COVID-19 (fever, dry cough, headache, sore throat, myalgia, fatigue, dyspnoea, anosmia, ageusia, diarrhea, vomitus, loss of appetite).

For confirmation of COVID-19, the diagnostic RT-PCR method for detecting SARS-CoV-2 virus from the respiratory tract (by nasal and/or oropharyngeal swab) was used.

Laboratory analyses for all patients were performed: complete blood count (CBC), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), ferritin, urea, creatinine, blood gas analysis, electrolytes, D-dimer, creatin kinase (CK), creatin kinase-MB (CK-MB), troponin and chest radiography. For patients who had an elevated D-dimer value above 4.4 chest computerized tomography (CT) scan and CT angiography of pulmonary artery was done. Additionally, comorbidities (diabetes mellitus, chronic pulmonary diseases, heart conditions, kidney disease, obesity, cancer, hematologic disorders, neurological disorders, rheumatological disorders) as well as length of hospitalization and outcome were recorded.

The patients were treated with oxygen, corticosteroids, low weight molecular heparin, or in moderate to severe cases when patients needed more than 15 L/min of oxygen (high flow oxygen therapy, non-invasive ventilation, or invasive ventilatory support) they were transferred to the Intensive Care Unit (ICU).

**Statistical analysis**

Standard methods of descriptive statistics (measures of central tendency, dispersion measures) were used. For each risk factor, sensitivity, specificity and positive and negative predictive value were tested. To test statistical significance of the differences among the groups (age, gender, symptoms, comorbidities, risk factors, complications, outcome) parametric and nonparametric significance tests, as well as the linear correlation method, were used. The p < 0.05 was considered statistically significant.

**RESULTS**

In the period between 1 September and 30 September 2021, 225 patients were treated at the Clinic for Infectious Disease of which 120 (53.3%) were females, and 105 (46.7%) males. Most patients belonged to the age group 50-64 years, 71 (31.6%), and 65-74 years, 68 (30.2%). Twenty-five (11.1%) patients were younger than 50 years of age, and 200 (88.9%) were older than 50 years of age. Mean age was 65.6±13.9 years (range 18-93, median 67).

Of 225 patients, 26 (11.6%) were fully vaccinated, and 199 (88.4%) were unvaccinated or partially vaccinated (with one dose). Fever (p=0.003), cough (p=0.005), and pulmonary embolism (PE) (p=0.016) were more present in patients who re-

**Table 1. Symptoms, demographics and pulmonary embolism (PE) as a complication and their influence on outcome of COVID-19 patients**

Characteristic	No (%) of all patients (n=225)			No (%) of unvaccinated patients (n =199)			No (%) of vaccinated patients (n =26)		
	Fatal outcome	Recovery	p	Fatal outcome	Recovery	p	Fatal outcome	Recovery	p
Cough	48 (57.1)	104 (73.8)	0.010	46 (59)	94 (77.7)	0.005	2 (33.3)	10 (50)	0.652
Dyspnoea	14 (16.7)	23 (16.3)	0.945	12 (15.4)	21 (17.4)	0.715	2 (33.3)	2 (10)	0.218
Fever	51 (60.7)	108 (76.6)	0.011	45 (57.7)	94 (77.7)	0.003	6 (100)	14 (70)	0.280
Fatigue	57 (67.9)	102 (72.3)	0.475	51 (65.4)	90 (74.4)	0.173	6 (100)	12 (60)	0.132
Heavy breathing	51 (60.7)	68 (48.2)	0.070	46 (59)	62 (51.2)	0.285	5 (83.3)	6 (30)	0.054
Loss of smell and taste	4 (4.8)	7 (5)	1	4 (5.1)	6 (5)	1	0 (0)	1 (5)	1
Loss of appetite	35 (41.7)	54 (38.3)	0.617	32 (41)	46 (38)	0.671	3 (50)	8 (40)	1
Pulmonary embolism	1 (1.2)	14 (9.9)	0.011	1 (1.3)	12 (9.9)	0.016	0 (0)	2 (10)	1
Transferred to ICU	41 (48.8)	11 (7.8)	0.000	38 (48.7)	10 (8.3)	0.000	3 (50)	1 (5)	0.028
<b>Age and gender (No of patients)</b>	84 (37.3)	141 (62.7)	0.000	78 (39.2)	121 (60.8)	0.000	6 (23)	20 (77)	0.507
0-17 (0)	-	-	-	-	-	-	-	-	-
18-29 (4)	0 (0)	4 (2.8)	0.300	0 (0)	4 (3.3)	0.157	-	-	-
30-39 (5)	0 (0)	5 (3.5)	0.160	0 (0)	5 (4.1)	0.159	-	-	-
40-49 (16)	0 (0)	16 (11.3)	0.001	0 (0)	16 (13.2)	0.001	-	-	-
50-64 (71)	7 (8.3)	64 (45.4)	0.000	6 (7.7)	56 (46.3)	0.000	1 (16.7)	8 (40)	0.380
65-74 (68)	36 (42.9)	32 (22.7)	0.001	33 (42.3)	26 (21.5)	0.002	3 (50)	6 (30)	0.628
75-85 (44)	28 (33.3)	16 (11.3)	0.000	27 (34.6)	11 (9.1)	0.000	1 (16.7)	5 (25)	1
85+ (17)	13 (15.5)	4 (2.8)	0.001	12 (15.4)	3 (2.5)	0.001	1 (16.7)	1 (5)	0.415
Males (108)	38 (45.2)	67 (47.5)	0.740	36 (46.2)	54 (44.6)	0.833	2 (33.3)	13 (65)	0.348
Females (120)	46 (54.8)	74 (52.5)		42 (53.8)	67 (55.4)		4 (66.6)	7 (35)	

ICU, Intensive Care Unit

covered and were unvaccinated. Vaccinated patients who died showed heavy breathing more frequently but without statistical significance ( $p=0.054$ ). Patients transferred to ICU had a higher risk of fatal outcome ( $p=0.000$ ). Patients who belonged to older age groups, and who were not vaccinated had a higher risk of death ( $p=0.001$ ) (Table 1).

The most common symptoms in unvaccinated group of patients were fatigue in 70.9% (141/199), cough in 70.4% (140/199) and fever in 69.8% (139/199), and in the vaccinated group fever in 76.9% (20/26), fatigue in 69.2% (18/26) and cough in 46.2% (12/26) of patients. Cough was more common in unvaccinated patients ( $p=0.013$ ). Pulmonary embolism was detected in 13 (out of 199; 6.5%) unvaccinated, and in two (out of 199; 7.7%) vaccinated patients ( $p=1$ ). Forty-eight (out of 199; 24.1%) unvaccinated,

and four (out of 26; 15.4%) vaccinated patients were transferred to ICU ( $p=0.320$ ). Fatal outcome was noticed in 84 (37.3%) patients with mean age of 74.92 years (range 55 to 90; median 74 years). In unvaccinated group fatal outcome was noticed in 78 (out of 199; 39.2%), and in vaccinated group in six (out of 26; 23.1%) patients ( $p=0.110$ ) (Table 2).

There was no statistically significant difference in fatal outcome according to gender: 38 (out of 105; 36.2%) males and 46 (out of 120; 38.3%) females died (Table 1).

Patients from the older age group were more likely to have comorbidities, atrial fibrillation ( $p=0.017$ ), hypertension ( $p<0.001$ ) and diabetes mellitus ( $p=0.002$ ).

Females had chronic diseases more frequently than males, 94 (out of 120; 78.3%), and 72 (out of 105; 68.6%), respectively.

Shorter duration of illness prior to admission was related with poor outcome in the unvaccinated group of patients ( $p<0.001$ ). Atrial fibrillation was related to poor outcome in the unvaccinated group of patients, eight (4%) ( $p<0.001$ ), as did hypertension, 126 (63.3%) ( $p=0.001$ ), diabetes mellitus, 56 (28.1%) ( $p=0.009$ ), and history of stroke 11 (5.5%) ( $p=0.026$ ). Length of hospitalization varied from one to 33 days in the unvaccinated group of patients, and from two to 23 days in vaccinated group of patients. Shorter length of hospitalization was correlated to fatal outcome in unvaccinated group of patients ( $p=0.011$ ) (Table 3).

**Table 2. Symptoms, complications, transfer to the Intensive Care Unit (ICU) and outcome in 225 patients with COVID-19**

Variable	No (%) of patients			p
	Total	Unvaccinated and partially vaccinated (n =199)	Vaccinated (n =26)	
Cough	152 (67.6%)	140 (70.4)	12 (46.2%)	0.013
Dyspnoea	37 (16.4)	33 (16.6)	4 (15.4)	1
Fever	159 (70.7)	139 (69.8)	20 (76.9)	0.456
Fatigue	159 (70.7)	141 (70.9)	18 (69.2)	0.864
Heavy breathing	119 (52.9)	108 (54.3)	11 (42.3)	0.250
Loss of smell and taste	11 (4.9%)	10 (5.0)	1 (3.8)	1
Loss of appetite	89 (39.6)	78 (39.2)	11 (42.3)	0.760
Pulmonary embolism	15 (6.7%)	13 (6.5)	2 (7.7)	0.687
Fatal outcome	84 (37.3)	78 (39.2)	6 (23.1)	0.110
Transfer to ICU	52 (23.1)	48 (24.1)	4 (15.4)	0.320

**Table 3. Risk factors and comorbidities to less favourable outcome**

Variable	No (%) of all patients (n=225)			No (%) of unvaccinated patients (n =199)			No (%) of vaccinated patients (n =26)		
	Fatal outcome	Recovery	p	Fatal outcome	Recovery	p	Fatal outcome	Recovery	p
Obesity	17 (20.2)	27 (19.1)	0.842	17 (21.8)	25 (20.7)	0.848	0 (0)	2 (10)	1
Smoking	0 (0)	5 (3.5)	0.160	0 (0)	4 (3.3)	0.157	0 (0)	1 (5)	1
Duration of illness prior to admission	6.18±0.78 (84)	8.7±0.575 (141)	0.000	6.14±0.82 (78)	8.64±0.545 (121)	0.000	6.67±3.85 (6)	9.05±2.52 (20)	0.322
Atrial fibrillation	9 (10.7)	2 (1.4)	0.003	8 (10.3)	0 (0)	0.000	1 (16.7)	2 (10)	1
Hypertension	68 (81)	77 (54.6)	0.000	62 (79.5)	64 (52.9)	0.000	6 (100)	13 (65)	0.146
Diabetes mellitus	33 (39.3)	32 (22.7)	0.008	30 (38.5)	26 (21.5)	0.009	3 (50)	6 (30)	0.628
Malignant diseases	2 (2.4)	5 (3.5)	1	1 (1.3)	2 (1.7)	1	1 (16.7)	3 (15)	1
Thyroid gland diseases	4 (4.8)	4 (2.8)	0.475	4 (5.1)	3 (2.5)	0.436	0 (0)	1 (5)	1
Neurological disorders	2 (2.4)	3 (2.1)	1	1 (1.3)	2 (1.7)	1	1 (16.7)	1 (5)	0.415
History of stroke	9 (10.7)	3 (2.1)	0.011	8 (10.3)	3 (2.5)	0.026	1 (16.7)	0 (0)	0.231
Rheumatologic diseases	4 (4.8)	1 (0.7)	0.066	4 (5.1)	1 (0.8)	0.078	-	-	-
Chronic kidney diseases	4 (4.8)	1 (0.7)	0.066	4 (5.1)	1 (0.8)	0.078	-	-	-
Haematological diseases	0 (0)	1 (0.7)	1	-	-	-	0 (0)	1 (5)	1
Chronic pulmonary diseases	4 (4.8)	3 (2.1)	0.429	3 (3.8)	2 (1.7)	0.382	1 (16.7)	1 (5)	0.415
Length of Hospital Stay	7.32±1.39 (84)	9.79±0.92 (141)	0.004	7.46±1.48 (78)	9.7±0.96 (121)	0.011	5.5±3.91 (6)	10.3±3.01 (20)	0.149

## DISCUSSION

Vaccination against COVID-19 in Bosnia and Herzegovina started slowly in February 2021, with a higher number of vaccines arriving to our country about three months later. During the summer 2021, low patient admission regarding COVID-19 was recorded, and at the end of the August climbed again. For this investigation we chose September as the first month of the fourth COVID-19 pandemic wave, where we could observe and compare characteristics of vaccinated and unvaccinated patients.

This study analysed 225 hospitalized patients treated from COVID-19. Females were predominant, in 53.3%. In many other studies males was more prevalent, 55.2% - 61.77% (20-22). Current evidence on the receptors for SARS-CoV-2 suggests that ACE 2 are the responsible receptors for SARS-CoV-2 (23,24). Males have higher plasma ACE2 level than females, and a recent study of patients with heart failure showed that plasma ACE2 concentrations were higher in males than in females, possibly reflecting higher tissue expression of the ACE2 receptor for SARS-CoV infections (25). A study conducted in the Chinese population found that the expression of ACE 2 in human lungs was extremely more expressed in Asian male than female patients (26). Women, especially during their reproductive years, are at increased risk of developing autoimmune diseases, but they are more resistant to infection than males. This is possibly mediated by several factors including sex hormones (27). Our study is the only one that we could find with higher prevalence of females hospitalized for COVID-19 than males. One of our findings which could be a possible explanation is that females had higher prevalence of underlying diseases and lower prevalence of vaccination comparing to males.

Mean age for our patients was  $65.6 \pm 13.9$  years, and most of them (88.9%) were older than 50 years of age. In a study made by Conway et al. (28), majority of patients (75%) were  $\geq 75$  years old. In a similar study done in Bulgaria (29) mean age of patients was 52.9 years, and in an Iranian study the average age was  $56.9 (\pm 15.7)$  years. Mean age of our patients was higher than in other studies, probably because in our country old population was represented with high prevalence, 16.22% of people are  $\geq 65$  years (30). Addition-

ally, there are some differences in admission criteria comparing to other countries/hospitals. Boston Medical Center criteria for admission for COVID-19 confirmed cases are: any patient with dyspnoea or increased respiratory rate ( $>30$  breaths per min), any patient with oxygen saturation  $<94\%$ , clinical concern by an emergency doctor attending for a risk of outpatient failure based on high risk for complications from severe COVID-19 (31). In our hospital some of the criteria for admission are age, comorbidities and the need for supplementary oxygen.

Clinical trials of COVID-19 vaccines currently authorized for emergency use in the United States (Pfizer-BioNTech, Moderna, and Janssen - Johnson & Johnson) indicate that these vaccines have high efficacy against symptomatic disease, including moderate to severe illness (32-34). The results of our study showed 11.6% fully vaccinated (two doses) and 88.4% unvaccinated and partially vaccinated. In Tenforde et al. (35) study, among 1,197 patients hospitalized with COVID-19, 11.9% were vaccinated breakthrough cases and 88.1% were unvaccinated. An analysis of the UK data (36,37) showed that of 40,000 patients with covid-19, who were admitted to hospital between December 2020 and July 2021, 84% had not been vaccinated.

The latest report on 60,109 hospitalized cases of COVID-19 across 43 countries found that the three most common symptoms at admission were history of fever (68.7%), cough (68.5%), and/or shortness of breath (65.8%), and that 92% of those admitted experienced one or more of these (36). In most studies results are similar, with slight differences of symptom distribution in some countries with different population demographics, and also with social, cultural and environmental differences (21,22,28,29).

Dominant symptoms and laboratory markers in vaccinated and in unvaccinated groups of patients are different in published studies (37,38), but the data are still scarce especially for vaccinated people. This does not allow us to compare our results.

Shorter duration of illness prior to hospital admission was one of the markers of poor outcome, especially in the unvaccinated group of our patients. Length of hospitalization in our study varied: 1-33 days in unvaccinated, and 2-23 days

in vaccinated group of patients; in unvaccinated group of patients with shorter length of hospitalization it was correlated with bad outcome.

The most presented comorbidities in our study were hypertension (64.4%) and diabetes mellitus (28.9%). It is in concordance with results of other authors: in Naganathan et al. study (21), hypertension (23.8%), diabetes mellitus (23.2%), and obesity (20.8%) were the top three comorbidities, and in Perez et al. study (39) it was hypertension (40%), diabetes mellitus (16%) and cardiopathy (14%). Patients with advanced age and comorbid conditions (obesity, diabetes mellitus, chronic lung disease, cardiovascular disease, chronic kidney disease, chronic liver disease, and neoplastic conditions) are at risk of developing severe COVID-19 and its associated complications (40).

Since the beginning of the COVID-19 pandemic, serious thrombotic complications have been reported in infected patients especially those that were critically ill. Early reports suggested a venous thromboembolism (VTE) rate of 27% in critically ill COVID-19 hospitalized patients (41). In a large study that involved over 3000 individuals admitted to the hospital, most of whom received prophylactic-dose anticoagulation, risk factors for VTE were older age, male sex, Hispanic ethnicity, coronary artery disease, prior myocardial infarction, and higher D-dimer (>500 ng/mL) (42). Pulmonary embolism (PE) in our study was detected in 6.7% patients (6.5% in unvaccinated group and 7.7% in vaccinated group), and it was not correlated to bad outcome in neither of the groups, probably because of the small number of patients.

In study by Alwafi et al. fever, cough, shortness of breath, nausea/vomiting, headache, loss of taste and smell, sputum were more common across severe and critical cases compared to others (43), and in a study by Li et al. shortness of breath, chest distress, muscle or joint ache, and dry cough were significantly enriched among patients classified as severe (44). In our study fever and cough were more present in unvaccinated patients who survived, and heavy breathing almost had statistical significance in unvaccinated patients who died.

Our results showed that 39.1% patients were transferred to the ICU. In a Bulgarian study 29.65% passed through the ICU. This high rate to the ICU

admission in our patients was probably caused by older age than in other studies, many comorbidities, and longer prehospitalization period. In a study from Pakistan, ICU admission was needed for 59% of patients (45). Also, our patients transferred to the ICU had higher risk of fatal outcome, and patients with hypertension had greater chance to be transferred to the ICU. In a study by Cummings, 20-40% of the hospitalized COVID-19 patients required ICU admission (46), and in a study by Botta et al. (47) 35-50% of these patients have a fatal outcome.

From the first published series, it has been observed that advanced age and comorbidities entail a higher risk of death (48-50). In an Israeli study mortality rate reached 22% (51), 15.8% in the USA, (52) in France 31% (53), in Pakistan 36% (54). In our study total mortality rate was 37.3% and it was higher in the unvaccinated group compared to the vaccinated group (39% vs 23%) suggesting a need to continue working to promote vaccination.

The age, cancer, chronic obstructive pulmonary disease, chronic kidney failure or an immunocompromised state were associated with in-hospital mortality in older individuals (55,56). There was a 2.5-fold increase in the risk of severe COVID-19 in those with a history of cerebrovascular disease (57). Also, vaccine effectiveness was lower in people older than 70 years and in those with multiple co-morbidities (58). In our study older age and unvaccinated patients had a higher risk of fatal outcome, as did the patients with comorbidities such as hypertension, diabetes mellitus, atrial fibrillation and the patients with history of stroke.

In conclusion, vaccines against COVID-19 have a beneficial effect on the outcome of patients and shorten the time of hospitalization. They are especially important for elderly patients with comorbidities, which basically make up the majority of hospitalized patients.

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Conflicts of interest: None to declare.

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