CLINICAL SCIENCE

EFFECT OF VACCINATION AND NUMBER OF DOSES ON DISEASE SEVERITY AND MORTALITY IN COVID-19 POSITIVE HOSPITALIZED PATIENTS

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Abstract

The COVID-19 pandemic, caused by the novel SARS-CoV-2 virus, started in December 2019 in the city Wuhan, province Hubei in the Republic of China. The disease quickly became pandemic and infected 48.539.872 people and had a mortality of 1.232.791 in 215 countries all over the world resulting in economic and healthcare collapse. On 11-th of March the World Health Organisation declared COVID 19 as pandemic. SARS-CoV-2 (severe form of acute respiratory syndrome coronavirus 2) as the cause of COVID 19 is the member of the coronavirus family along with MERS-CoV and SARS-CoV-1which cause severe respiratory infections that are highly contagious and have very high mortality. The pandemic character, the high morbidity and mortality and rehabilitation resulted in a massive vaccine production as an attempt to control the spread of the SARS CoV-2 virus and reduce the morbidity and mortality, especially in the most vulnerable population groups. The aim of the study was to evaluate the association between vaccination status, number of doses and disease severity, length of hospital stay and mortality. Material and Methods: In this case-control study we included 230 male and female patients admitted in the Covid Centre in Acibadem Clinical Hospital in Skopje from March 2021 to February 2022. Patients were divided in two groups according to their vaccination status. Data about patients demographics, comorbidities, vaccination, number of doses received, type of oxygen and ventilation support, length of stay and patient outcome were collected. Results: A total of 230 COVID-19 positive hospitalized patients participated in the study. 50.4% of them were vaccinated, of which 86.2% received two doses, 11.2% received one and 2.6% received three doses of vaccines. A significant association was registered between lethal outcome and vaccination (PearsonChi-square: 5.32523, p=.021019), association with number of doses of vaccination (PearsonChi-square: 7.66262, p=.043524), association with type of ventilation - NIV, HFO, IMV (PearsonChi-square: 177.399, df=3, p=0.00000), associationwithcomorbidity (3.90770, p=.048065). Conclusion: Vaccination against Covid-19 and number of doses have a significant impact on disease severity, progression and outcome of the disease.

КЛИНИЧКИ ИСТРАЖУВАЊА

ВЛИЈАНИЕТО НА ВАКЦИНАЛНИОТ СТАТУС И БРОЈОТ НА ДОЗИ НА ТЕЖИНАТА НА КЛИНИЧКАТА СЛИКА И СМРТНОСТА ОД COVID-19

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Извадок

COVID-19 како инфективно заболување за првпат се појави во декември 2019 година, а првите заразени беа во градот Вухан, област Хубеи во Н.Р.Кина. Болеста доби пандемиски карактер и за брзо доведе до 48.539.872 заразени луѓе и предизвика 1.232.791 смртни случаи во 215 земји во светот, доведувајќи до глобален здравствен и економски колапс на светското население. На 11 март 2020 година Светската здравствена организација прогласи COVID-19 пандемија. SARS-CoV-2 (тешка форма наакутен респираторен синдром коронавирус 2) како предизвикувач на COVID-19 претставува корона вирус кој што исто како и останатите два корона вируси MERS-CoV и SARS-CoV-1 се одговорни за предизвикување на акутни респираторни инфекции кои се многу контагиозни по природа и доведуваат до висок морталитет. Пандемискиот карактер на болеста, високиот морбидитет, морталитет и долгата рехабилитација доведоа до масовно производство на вакцини со цел превенирање и спречување на инфекција со SARS-CoV-2 вирусот,намалување на морбидитетот и морталитетот, особено кај ранливата популација со имунокомпромитираност и имунодефицит. Целта на оваа студија беше да се испита поврзаноста помеѓу вакцинлниот статус и бројот на примени дози против COVID-19 и тежината на болеста, должината на болничкиот престој и смртноста. Материјали и методи: Во оваа студија беа вклучени 230 пациенти од машки и женски пол, кои беа третирани во Covid центарот при Инфективниот оддел на Клиничката болница Аџибадем Систина во периодот од март 2021 година до февруари 2022 година. Пациентите беа поделени во две групи според вакцинлниот статус. Податоци за демографските карактеристики, коморбидитетите, вакцинацијата, бројот на примени дози, типот на кислородна и вентилаторна поддршка, должината на престој во болница, исходот од лекувањето беа следени и забележани. Резултати: Во студијата учествуваа 230 хоспитализирани COVID-19 позитивни пациенти. Вакцинирани беа50,4% од хоспитализираните, од кои 86,2% примиле две дози, 11,2% примиле една и 2,6% примиле три дози вакцини. Беше регистрирана значајна поврзаност помеѓу смртоносниот исход и вакцинацијата (PearsonChi-square: 5.32523, p=.021019), поврзаноста со бројот на дози на вакцинацијата (PearsonChi-square: 7.66262, p=.043524), поврзаноста со типот на вентилација (PearsonChi-square: 177.399, df=3, p=0.00000), и поврзаноста со присуството на коморбидитети (3.90770, p=.048065). Заклучок: Вакцинлниот статус и бројот на примени дози во нашата студија покажа значителен заштитен ефект за развој на тежок облик на болеста и летален исход.

Introduction

SARS-CoV-2 is a member of the coronavirus family, a group of enveloped single-stranded RNA viruses. First reported infections were in 2019, and since then the SARS-CoV-2 virus (COVID-19) pandemic has spread globally in almost every country in the world[1]. Although most commonly attacking the respiratory system, all systems can be affected. Signs and symptoms can differ from asymptomatic, mild illness to very severe and critical disease requiring intensive care unit admission and death[2].

COVID-19 mortality and morbidity are affected by many different factors, i.e., gender, age and several chronic diseases such as chronic respiratory disease/asthma, heart arrhythmias, hypertension, coronary disease, diabetes and neoplasma[3]. Vaccination against SARS-CoV-2 has become crucial for limiting disease transmission and reducing its severity, hospitalization and mortality[4]. More specifically, data from systematic reviews underline the efficacy of vaccination in terms of clinical severity and mortality[5]. Despite universal acceptance, vaccine hesitancy is still significant[6]. Finally, the occurrence of the new variants can change all previous data in relation to previous emerging virus strains. In light of all these factors, analysis of real-world data concerning disease severity and mortality of COVID-19 and vaccination is important for making future national health policy.

The aim of the study was to evaluate the association between vaccination status, number of doses and disease severity, length of hospital stay and mortality of COVID-19.

Materials and Methods

After receiving an approval from the local Ethics Committee, we performed a case-control study, including 230 male and female Covid-19 positive patients, aged from 34 to 90 years admitted to the Covid center at the Clinical Hospital Acibadem, Skopje from March 2021 to February 2022. Patients were either on oxygen support with 5-15 liters of oxygen per minute, high-flow oxygen support (HFO), non-invasive mechanical ventilation (NIMV) or invasive mechanical ventilation (IMV) and were divided in two groups according to their vaccination status: Group 1 included 116 patients vaccinated with 1, 2 or 3 doses of vaccine against SARS-CoV-2 regardless of the manufacturer at least 14 days before admission, and Group 2 was the control group with 114 unvaccinated patients.

All patients tested positive to PCR test for SARS-CoV-2 virus. Patients' data regarding age, sex, vaccination, number of doses, comorbidities, symptoms, duration of disease and therapy were collected from questionaries submitted by the patients or their families, and from the CEREBRAL patient system at Clinical hospital Acibadem from Skopje.

Results

A total of 230 COVID-19 positive hospitalized patients participated

in the study, of which 54.3% were men and 45.7% women. The percentage difference registered between the sexes was statistically non-significant for p>0.05 (Difference test, p=0.0651) (Table 1).

50.4% of the hospitalized patients were vaccinated, of which 86.2% received two doses, 11.2% received one and 2.6% received three doses of vaccines (Table 1).

Comorbidities were registered in 84.8% of patients, with more than two comorbidities registered in 40.0%. Cerebrovascular disease (CVD) was registered in 69.1%, endocrine diseases (diabetes mellitus, Addison's disease, hypothyroidism) in 36.5%, immunocompromising conditions in 10.0%, chronic obstructive pulmonary disease (COPD) and asthma in 8.7% and obesity in 6.1% (Table 1).

In the largest percentage (72.2%), patients ended up on oxygen support with face mask, 26.9% on non-invasive ventilation and high-flow oxygen support and 0.9% (two patients) on mechanical ventilation (Table 1).

The average age of males was 62.4±13.9 (minimum32, maximum 92 years), and of females 66.3±11.7 (minimum34, maximum 90 years) (Table 1). The difference registered between the average age according to gender was significant, for <0.05 (t-test=2.27101, p=0.024080).

Table. 1. Demographic characteristics and comorbidities of participants

Gender	Number	Percent
M	125	54.3
F	105	45.7
Vaccination		
no		
yes		
Dose		
I	13	11.2
II	100	86.2
III	3	2.6
Comorbidity		
yes	195	84.8
no	35	15.2
comorbidity>=2		
yes	92	40.0
no	138	60.0
CVD		
yes	159	69.1
no	71	30.9

DM, hypotireosis, Adison's disease		
yes	84	36.5
no	146	63.5
HBI, HD		
yes	10	4.3
no	220	95.7
Immunocompromising		
yes	23	10.0
no	207	90.0
COPD, asthma		
yes	20	8.7
no	210	91.3
Obesity		
yes	14	6.1
no	216	93.9
Type of oxygen support		
OM	166	72.2
NIV/HFO	62	26.9
	2	0.9
MV		
age	***Average***	***SD***
M	62.4	13.9
F	66.3	11.7

Table 2. Patient characteristics according to vaccination status

Vaccination	**yes**		**no**	
sex	Number	Percent	Number	Percent
M	65	56.0	60	52.6
F	51	44.0	54	47.4
age				
>67	61	52.6	53	46.5
<67	55	47.4	61	53.5
Comorbidity				
yes	98	84.5	97	85.1
no	18	15.5	17	14.9
Oxygen support type				
OM	93	80.2	73	64.0
NIV/HFO	23	19.8	39	34.2
IMV	0	0	2	1.8

No gender difference in vaccination status was registered, for p>0.05 (PearsonChi-square: 0.268343, p=0.604445). 52.6% of vaccinated patients were older than 67 years, and 46.5% of unvaccinated. There was no association between the age above and below 67 years and the vaccination status, for p>0.05 (PearsonChi-square: 0.854422, p=0.355304). Comorbidity was registered in 84.5% of the vaccinated, and 85.1% of the unvaccinated. There was no association between registration of comorbidity and vaccination status, for p>0.05 (PearsonChi-square: 0. 016310, p=0.898379). 80.2% of the vaccinated patients were on oxygen mask, 19.8 % on NIV/HFO. None of the patients in vaccinated group were on IMV. 64.0% of the unvaccinated were on an oxygen mask; 32.4% were on NIV/HFO and 1.8% on IMV. An association was registered between the type of ventilation and the vaccination status, for p<0.05 (PearsonChi-square: 8.53979, p=0.0360).

Table 3. Length of hospitalization according to vaccination

Mean yes	Mean no	t-test	df	p	Valid N yes	Valid N no	Std.Dev. yes	Std.Dev. no
8.775	11.403	-3.402	228	0.0007	116	114	4.852	6.724

Vaccinated patients were hospitalized for an average of 8.8±4.8 days, and those who were not vaccinated were hospitalized for 11.4±6.7 days; the difference between the average length of hospitalization was significant, for p<0.05.

Vaccinated patients with one dose were hospitalized for 9.3±8.4 days, with two doses 8.7±4.3 days and with three doses 7.7±4.0 days. According to the Analysis of Variance test, the difference between the average hospitalization between unvaccinated and those vaccinated with three doses was significant, for p<0.0 (F=3.901, p=0.0095).

21.7% (50) of hospitalized patients died. The profile of patients who had fatal outcome were men, not vaccinated, or vaccinated with only one dose, with registered comorbidities; they had ended on NIV, HFO, IMV, and they were with anaverage age of 67 years, i.e., 50% were older than 67.5 years (mean=67.5 years) (Table4).

A significant association was registered between lethal outcome and vaccination status (Pearson Chi-square: 5.325, p=.0210), association with number of doses of vaccination (PearsonChi-square: 7.662, p=.0435), association with type of ventilation - NIV, HFO, IMV (PearsonChi-square: 177.399, df=3, p=0.000), association with comorbidity (3.907, p=.0480).

Table 4. Age, gender, vaccination and type of ventilation in patients with fatal outcome

Gender	Number	Percent
M	28	56.0
F	22	44.0
Vaccination		
no	32	64.0
yes	18	36.0
Dose		
I	32	64.0
II	4	8.0
III	14	28.0
Comorbidity		
yes	42	84.0
no	8	16.0
Ventilation type		
NIV/HFO/MV	48	96.0
MV	2	4.0

age	*Average*	*SD*
live	63.4	13.0
deceased	66.9	13.0

Accordingto the binary logistic regression, non-vaccination was a predictor of lethal outcome in hospitalized patients (Table 5).

Table 5. Binary logistic regression

Variables in the equation

Vaccination		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	no	.754	.330	5.201	1	.023	2.125	1.112	4.060
	Constant	-1.695	.256	43.669	1	.000	.184		

a. Variable(s) enteredonstep 1: ref.yes

Variables in the equation

sex		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	no	.085	.322	.070	1	.791	1.089	.580	2.046
	Constant	-1.328	.240	30.660	1	.000	.265		

a. Variable(s) enteredonstep 1: female

Variables in the equation

Type of ventilation		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]				.000	3	1.000		.000	
	MV	42.406	28591.418	.000	1	.999	260975880129586330 0.000		
	NIV/HFO	22.676	3119.579	.000	1	.994	7049344222.542	.000	
	Constant	-21.203	3119.579		1	.995			

a. Variable(s) enteredonstep 1: ref.OM

Variablesintheequation

Comorbidities		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	no	-.076	.439	.030	1	.862	.926	.392	2.189
	Constant	-1.216	.403	9.131	1	.003	.296		

a. Variable(s) enteredonstep 1: yes

Variablesintheequation

age		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	>67	.227	.321	.502	1	.479	1.255	.669	2.352
	Constant	-1.397	.233	35.992	1	.000	.247		

Variable(s) enteredonstep 1: ref.<67years

Discussion

COVID-19 is the first disease where a large number of institutions and companies have been engaged in research to produce effective multiplatform vaccines. By the end of 2020, more than 60 vaccines had entered clinical trials, of which 13 were in phase 3 clinical trials[7]. Among them, mRNA vaccines (Pfizer-BioNTech, Moderna), recombinant adenoviral vectored vaccines (AstraZeneca, Cansino, Gamaleya, Johnson Pharma) and inactivated vaccines (Sinopharm, Sinovac) achieved the fastest progress. By the end of 2020, nine candidate vaccines have been approved for human use in many countries[8–15]. The first generation of COVID-19 vaccines developed for emergency use showed promising results for controlling the pandemic 16. The SARS-CoV-2 virus during the several waves showed a large number of mutations, some of which were marked as “of concern”,

because they could have an impact on health policies of public interest, monitoring and immunization strategies[17]. In addition, the development of vaccines in such a short period of time has also led to doubts about the safety and efficacy of vaccines. Several studies have examined the efficacy and safety of vaccines. In a recent systematic review of 42 original studies, the authors analyzed the efficacy of various licensed vaccines and concluded that vaccines successfully reduce the number of infections, the severity of the disease, the need for hospitalization, the number of hospital days and mortality. The Pfizer-BioNTech vaccine is the most studied of the available vaccines and shows an effectiveness greater than 90%, followed by Moderna with an effectiveness greater than 80%[18].

In our case-control study, it was shown that unvaccinated patients had higher in-hospital mortality than vaccinated ones. It was also shown that vaccination and vaccine dose were significantly associated with shorter hospitalization compared to unvaccinated patients. The incidence of comorbidities was similar in the groups of vaccinated and unvaccinated patients. No significant statistical difference was found in terms of sex, age and vaccination status of patients. We found an association with unvaccinated status and type of oxygen support and the need for invasive mechanical ventilation.

There are studies that examined the effect of vaccination against COVID-19 and their impact on the clinical picture and the outcome of hospitalization, with results that are similar or coincide with ours. José M. Ruiz-Giardin et al. conducted a retrospective comparative studyof 500 hospitalized patients,of which 15.4% fully vaccinated, 17.2% partially vaccinated and 67.4% unvaccinated COVID-19 positive patients. They showed that complete vaccination was associated with a milder form of COVID-19 and a shorter hospital stay[19].

Papaioannou et al. in their prospective study including 166 vaccinated and 416 unvaccinated COVID-19 positive patients showed that the mean number of days of hospitalization was higher in unvaccinated compared to vaccinated patients [7.0 (95% CI: 7.0-8.0) vs. 6.0 (95%CI: 5.0-7.0),p=0.02]. Also, age-adjusted analysis showed that hospitalized unvaccinated patients had a significantly higher risk of mortality compared to hospitalized vaccinated patients[20].

Giacomo Grasselli et al. in their Lombardy cohort study of 10 million inhabitants, during the study period analyzed 553 patients that required admission to an intensive care unit, of which 139 (25.1%) were vaccinated, while 414 (74.9%) were unvaccinated. Vaccinated patients were older, with more comorbidities and mostly men. Vaccinated patients had a significantly lower risk of intensive care unit admission than unvaccinated patients, but there was no significant difference in hospital and intensive care unit mortality[21].

Robert Whittaker et al. included 716 fully vaccinated and 2487 unvaccinated COVID-19 positive patients in their cohort study. Using cox proportional hazard model adjustment, they showed that vaccinated patients had a shorter hospital stay and a lower risk of intensive care admission compared to unvaccinated patients. On the other hand, when they were admitted to the intensive care unit, the length of stay and mortality was not significantly different[22].

Athina A. Samara's study conducted from June 1, 2021 to February 1, 2022 included 760 consecutive patients diagnosed with COVID-19 infection. Of them, 38.7% were vaccinated, and 11.7% were diagnosed with a severe form of the disease. Vaccination against the SARS-CoV-2 virus had a significant protective effect against the development of a severe form of the disease and mortality, but the comparison of the length of hospital stay was not statistically significantly different between vaccinated and unvaccinated patients[23].

The existence of comorbidities, hypertension, diabetes, chronic lung disease, heart disease and malignant tumors are associated with the development of a severe form of the disease[24]. Additionally acute and chronic renal failure, COPD, diabetes, hypertension, cardiovascular disease, malignancy, high d-dimers, high ferritin, age, male gender, obesity, and smoking are factors associated with higher mortality from COVID-19[25,26].

However,of particular importance is the fact that in certain studies it has been observed that vaccination modifies or reduces the association of these risk factors and the development of a severe form of the disease and death[22,23,27]. On the other hand,in the multicenter prospective study of Anna Motos et al. From Spain during the study period 1585 patients were admitted to the intensive care units of seven hospitals due to COVID-19. Of them, 1314 (82.9%) were unvaccinated, 161 (10.2%) had not completed the vaccination protocol, and 110 (6.9%) were fully vaccinated. Data from 81 (73.6%) fully vaccinated patients were available for analysis. Among fullyvaccinated patients, 45 (55.6%) were on mechanical ventilation, and only one patient required extracorporeal membrane oxygenation. In-hospital mortality was 34.6%, the meantime on mechanical ventilation was 19.0 (9.0–28.0) days, and the mean number of hospital-days was 11.0 (7.0–30.0)[28]. The main conclusion of this study according to the authors was that patients with specific comorbidities despite being fully vaccinated could develop a severe form of COVID-19. Important to say that only 7% of patients with severe COVID-19 were fully vaccinated. A comparison between vaccinated and unvaccinated patients with severe COVID-19 requiring intensive care showed a two-to three-fold higher prevalence of immunosuppression, chronic lung disease, diabetes, kidney disease, and hypertension. Similar results have been published by Tal Brosh-Nissimov et al.in their study of 152 COVID-19 positive patients from Israel requiring hospitalization[29].

Only 4% of patients had no comorbidities. Even 40% of patients were immuno compromised. Mortality in their study was 22% (34/152). The authors conclude that although in a small percentage of patients with COVID-19 who are fully vaccinated, the development of a severe form of the disease and death is possible, especially in those with multiple comorbidities. Compared to unvaccinated group of patients, these patients have more comorbidities and are immunocompromised.

The analysis of patients with a fatal outcome in our study also showed an association with the existence of comorbidities. Patients with a fatal outcome were mostly men over the age of 65, had more comorbidities, and were unvaccinated or vaccinated with a single dose. The association of age and gender as risk factors for a severe form of the disease and death outcome has also been shown in other studies. In a 2020 population-based cohort study from Sweden, the authors analyzed 758,932 patients. Patients were couples, men and women, with an age difference of no more than 5 years and living together. The authors concluded that men had a higher risk of developing severe, intensive care unit admission, developing complications, and death compared to women, and that risk varied with age and was greatest inp atients aged 50 to 59 years 30. The relationship between age, sex and vaccination status and the number of doses received has been shown in other-studies as well[31,32].

Conclusion

Data from our study suggest that vaccination against Covid-19 and booster doses provide protection against the development of a severe form of COVID-19 and death. In addition, vaccination and the number of doses received affect the type of oxygen support and the need for mechanical ventilation. Vaccinated patients have a shorter hospital stay and a faster recovery from the sequelae of the disease.

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