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VACCINE BREAKTHROUGH INFECTIONS IN COVID-19 PATIENTS - SINGLE CENTER STUDY IN THE REPUBLIC OF NORTH MACEDONIA

КОВИД-19 ИНФЕКЦИИ НА ПРОБИВ КАЈ ВАКЦИНИРАНИ ПАЦИЕНТИ - СТУДИЈА ОД ЕДЕН ЦЕНТАР ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Abstract

Our study evaluates vaccine breakthrough infections in Coronavirus Disease 2019 (COVID-19) patients who presented for medical examination at a tertiary care hospital in Skopje, Republic of North Macedonia. We retrospectively evaluated medical files of 249 completely vaccinated patients who presented at the hospital since June 2021 till October 2021, with a clinical picture of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. The average time from complete vaccination to symptom onset was 79.8±41.8 days. Out of 249 patients, 158(63.45%) were treated as outpatients, and 91(36.55%) were hospitalized. From the hospitalized patients, 61(67.03%) were discharged and 30(32.97) died. Breakthrough infections occurred in the Sinopharm vaccine group in 45.78%, Sinovac in 20.08%, Pfizer in 14.86%, AstraZeneca in 10.84% and Sputnik in 7.23%. The highest mortality was found in patients vaccinated with mRNA1273 vaccine, followed by inactivated virus containing vaccine and with non-replicating viral vector vaccine, while the lowest mortality was found in those vaccinated with either BNT162b2 vaccine or human adenovirus vector-based COVID-19 vaccine. Male gender (p=0.006), age over 65 years (p=0.002) and presence of comorbidities (p=0.006) were major contributing factors for a poor outcome in vaccinated hospitalized patients with COVID-19. Due to the uneven distribution of the samples in our patient cohort it would be misleading to look at breakthrough cases, disease severity and outcome by vaccine brand due to different representation of vaccine brands. Breakthrough infection, hospitalization, and death from COVID -19 could differ across different vaccination profiles.

Keywords: COVID-19, SARS-CoV-2, vaccination, breakthrough infection, outcome

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Апстракт

Студијата ги евалуира инфекциите на вакцинален пробив кај Корона вирусната болест 2019 (КОВИД-19) кај пациенти кои се појавиле на преглед во терциерна болница во Скопје, Република Северна Македонија. Ретроспективно се еваулирани медицинските истории на 249 комплетно вакцинирани пациенти кои дошле на преглед на Клиниката за инфективни болести и фебрилни состојби, Скопје во периодот јуни 2021 до октомври 2021 година со клиничка слика на акутен тежок респираторен коронавирус 2 синдром (САРС-КоВ-2 инфеција). Средното време после комплетна вакцинација до појава на симптоми на болеста изнесуваше 79.8±41.8 дена. Од вкупно 249 пациенти, 158(63.45%) беа третирани амбулантски, додека 91 (36.55%) беа хоспитализирани. Од хоспитализираните пациенти 61(67.03%) оздравеа, додека (32.97%) починаа. Кај пациентите вакцинирани со Sinopharm инфекции на вакцинален пробив имало кај 45.78%, со Sinovac кај 20.08%, Pfizer кај 14.86%, AstraZeneka кај 10.84%, со Sputnik кај 7.23%. Највисока смртност имале пациентите вакцинирани со mRNA1273 вакцината, потоа вакцинираните со вакцини кои содржат инактивиран вирус и не-репликативна вирусна векторна вакцина, додека најмала смртност е утврдена кај пациентите вакцинирани или со BNT162b2 вакцината или со хумани аденовирус базирана КОВИД-19 вакцината. Машкиот пол (p=0.006), возраст над 65 години (p= 0.002) и присуство на коморбидитет (p=0.006) се главни фактори за смртен исход кај вакцинираните, хоспитлизирани пациенти со КОВИД-19. Како резултат на нееднаквата распределност на примерокот кај пациентите, би било погрешно да се евалуира појавата на вакцинален пробив, тежината и исходот на болеста според типот на вакцината, поради различната застапеност на истите. Инфекциите на вакцинален пробив, хоспитализацијата и смртноста поради КОВИД-19 можат да бидат различни кај различни профили на вакцини.

Клучни зборови: КОВИД-19, САРС-КоВ-2, вакцина-

ција, инфекции на вакцинален пробив, исход

Introduction

With the appearance of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, first detected in Wuhan, China causing highly infectious Coronavirus Disease 2019 (COVID-19), a new global pandemic was unleashed spreading worldwide [1]. Numerous global efforts had been undertaken since the beginning of the pandemic in order to reduce the virus transmission and mortality via different measures including social distancing, wearing facemasks, hand hygiene and restricting interpersonal contact to outdoor settings; widespread testing to identify individuals infected with the virus; different governmental actions including school and workplace closures, bans on public gatherings, travel restrictions and stay-at-home orders in order to mitigate the pandemic [2]. Despite all the measures and efforts, SARS-CoV-2 continues to spread causing very high morbidity (above 225 million confirmed cases) and mortality (more than four and a half million deaths) worldwide as of September 15, 2021 [3]. The development of safe and efficacious vaccine against SARS-CoV-2 was the only possible way to fight the virus and to prevent its spread, together with effective therapy for COVID-19 patients [4]. Recently published meta-analysis of eight COVID-19 vaccines, that have published the data of phase 3 randomized controlled trials (RCTs), reported excellent efficacy (pooled Risk Ratio (RR) to prevent symptomatic disease of 0.17; 95% Confidence Interval (CI): 0.09-0.32)[5]. People who are fully vaccinated against COVID-19 have a significantly reduced risk of severe illness but despite the high level of vaccine efficacy some hospitalizations and deaths have been reported even in fully vaccinated people with breakthrough COVID-19 infections [6-11]. In the Republic of North Macedonia, the vaccination campaign started in February 2021. Vaccination process stared with the vaccination of medical personnel, elderly, as well as immunocompromised individuals as priority target groups [12]. The first vaccines used against SARS-CoV-2 infection in the Republic of North Macedonia were Bnt162b2 (Pfizer/BionTec) vaccine, COVID-19 Vaccine (Vero Cell), Inactivated/Coronavac™ (Sinovac), SARS-CoV-2 Vaccine (Vero Cell), Inactivated (lnCoV) (Sinopharm) followed by Sputnik V and AZD1222 Vaxzevria (AstraZeneca). At the time when this study was conducted, October 2021, the distribution of the vaccines was as presented in Table 1 [13]. By October 2021, only 38% of the population (2.083 million by the census of year 2020) were completely vaccinated, 35% had received only one dose of vaccine, and 53% of individuals over 40 years of age were completely vaccinated, whereas 33% of the population aged 18-39 years were vaccinated with one dose of vaccine [14]. The aim of this study was to evaluate vaccine breakthrough infections and outcome in patients with SARS-CoV-2 breakthrough infection.

Table 1. Number of vaccinated persons in Republic of North Macedonia

Vaccine	First dose	Second dose	Third dose	Grand Total
ChAdOx1-S recombinant, AZD1222 - AstraZeneca COVID-19 Vaccine	66.142	61.000		127.142
COVID-19 vaccine (Vero Cell), Inactivated (Sinovac)	247.227	235.541		482.768
Gam-COVID-VAC (Sputnik V)	22.912	22.549		45.461
Pfizer - BioNTech COVID-19 Vaccine	309.511	285.073	894	595.478
SARS-CoV-2 Vaccine (Vero Cell), Inactivated (Sinopharm)	150.606	149.337	1	299.944
Grand Total	796.398	753.500	895	1.550.793

Material and methods

A retrospective cohort study was undertaken in the period between June 2021 till October 2021 at the University Clinic for Infectious Diseases and Febrile Conditions, Skopje, Republic of North Macedonia. The study included 249 patients with breakthrough infections that had come for a medical checkup at the Clinic due to symptoms of COVID-19 disease (fever, sore throat, headache, fatigue, cough, nasal congestion, ageusia or anosmia). All participants were fully vaccinated with one of the available vaccines in the Republic of North Macedonia with two doses in an interval period as recommended by the manufacturer: Bnt162b2 (Pfizer/BionTec) vaccine, COVID-19 Vaccine (Vero Cell), Inactivated/Coronavac™ (Sinovac), SARS-CoV-2 Vaccine (Vero Cell), Inactivated (lnCoV) (Sinopharm), Sputnik V and AZD1222 Vaxzevria (AstraZeneca).

Patients were considered fully vaccinated if the final dose of the vaccine was administered at least 14 days before symptom onset or a positive RT-PCR (reverse transcriptase-polymerase chain reaction) test for SARS-CoV-2. Breakthrough infections were detected by nasopharyngeal swabs, obtained at any point if a patient had suggestive symptoms for COVID-19 as described above. The swabs were obtained by trained physicians and RT-PCR test for COVID-19 detection was done using either one of the following test: 2019-nCoV "Allplex™, 13BGI, 14 Nucleic Acid Diagnostic Kit"-Sansure Biotech, 15, Charite-Diagnostic detection of Wuhan coronavirus 2019 by real-time RT-PCR,16 RealTime SARS-CoV-2"-EUROIMMUN, 17 TaqMan 2019-nCoV Assay Kit v1,18SARS-CoV-2 Fluorescent PCR"-Maccura 19 "TaqPath™ COVID-19 CE-IVD RT-PCR Kit", 20 SARS-CoV-2/Influenza Multiplex DNA-Technology, 21 Genrui SARS-CoV-2 Detection Kit RT-PCR22, according to manufacturers' protocol.
Inclusion criteria for the patients were evidence for complete vaccination against SARS-CoV-2 infection, positive nasopharyngeal swabs for SARS-CoV-2 infection and age of 18 years or older. Complete vaccination was defined as a period of at least two weeks after receiving two doses of a given vaccine in a time period as described by the manufacturer. Exclusion criteria: pregnancy and age bellow 18 years.
Demographic data, chronic medical conditions, vaccine type, severity of COVID-19 and outcome of the patient were recorded.

Statistical analysis

Kolmogorov-Smirnov test was used to verify the normality of distribution of continuous variables. Categorical variables were expressed as numbers and percentages and analyzed using the chi-square and Fisher exact test when necessary. Normally distributed variables are presented as mean (SD) and non-normally distributed variables as median and range. Difference testing between groups was performed using the Student's t-test when data were normally distributed. When normality was rejected, nonparametric Mann-Whitney U-test was used for independent groups. Data were analyzed with SPSS 24.0 software (SPSS, Chicago, IL).

Results

We evaluated the medical files of 249 completely vaccinated patients who presented with a clinical picture of SARS CoV-2 infection, confirmed by a positive nasopharyngeal swab at the University Clinic for Infectious Diseases, in Skopje, Republic of North Macedonia, since June 2021 until October 2021. This is the only tertiary care hospital for infectious diseases in the whole country. The average time from complete vaccination to symptom onset was 79.8±41.8 days. Out of 249 completely vaccinated patients with breakthrough infection 123(49.4%) were male, and 126(50.6%) were female. In our cohort, 125 patients (50.2%) were younger than 65 years, and 124(40.8%) were 65 years and older. In terms of comorbidities, 172 patients (69%) had one and/or more comorbidities, and 77 patients (31%) were without any comorbidity. General characteristic of analyzed patients are presented in Table 2.

Table 2. General characteristics of analyzed patients

Variable	All patients n=249	Survivors n=219 (87.9%)	Nonsurvivors n=30 (12.1%)	P value
Male, n (%)	123(49.4)	101(82.1)	22(17.9)	0.006
Female, n (%)	40(48.2)	118(93.7)	8(6.3)	
Age (years)				
<65, n (%)	125(50.2)	118(94.4)	7(5.6)	0.002
≥ 65, n (%)	124(49.8)	101(81.5)	23(18.5)	
Without comorbidity n (%)	77(33)	74(33.8)	3(10.0)	
With comorbidity n (%)	172(69)	145(66.2)	27(90.0)	0.006

According to the vaccine brand, most vaccine breakthrough infections occurred in the Sinopharm (45.78%) and Sinovac group (20.08%), followed by those vaccinated with Pfizer (14.86%), AstraZeneca (10.84%) and Sputnik (7.23%) (Table 3). Although at the time of this study the Republic of North Macedonia did not have mRNA-1273 (Moderna) vaccine, the three patients vaccinated with Moderna vaccine and included in our study were vaccinated in third EU countries and had come during the summer holidays for visiting their relatives in North Macedonia when illness occurred. The absolute number and percentages of breakthrough infection by vaccine brand are as presented in Table 3.

Table 3. Breakthrough infections of SARS CoV-2 by different vaccine brand

Vaccine brand	Frequency	Percent
Sinopharm	114	45.8
AstraZeneca	27	10.8
Pfizer	37	14.9
Sputnik	18	7.2
Sinovac	50	20.1
Moderna	3	1.2
Total	249	100.0

After examination and admission to the hospital, patients were categorized according to COVID-19 disease severity classification as per the WHO definition [15]. From the 249 vaccinated patients who were examined, 53(21.3%) had severe/critical form of COVID-19, 65 (26.1%) had moderate and 131(52.6%) had mild form of the disease. Among those with severe and/or critical illness, the mean age was 71.2±9.8 years. In the group of patients with severe and/or critical illness 27(50.94%) patients survived and 26 (49.06%) died. Distribution of disease severity according to vaccine brand is presented in Table 4.

Table 4. Disease severity in breakthrough infection of SARs CoV-2 according to vaccine brand

		Sinopharm	AstraZeneka	Pfizer	Sputnik	Sinovac	Moderna	Total	P value
Disease severity	Mild, n (%)	53(40.5)	13(9.9)	31(23.7)	10 (7.6)	24 (18.3)	0	131(52.6)	P=0.001
	Moderate, n (%)	31(47.7)	9(13.8)	4(6.2)	6 (9.2)	15 (23.1)	0	65(26.1)	
	Severe/ Critical, n (%)	30(56.6)	5(9.4)	2(3.8)	2 (3.8)	11(20.8)	3(5.7)	53(21.2)	
Total	n (%)	114(45.8)	27(10.8)	37(14.9)	18 (7.2)	50(20.1)	3(1.2)	249(100)	

As presented in Table 4, there was a significant statistical difference between the type of vaccine and the severity of the clinical picture in vaccinated patients who had a breakthrough infection, but due to the uneven distribution of the samples this significance cannot be taken reliably.

Of the 249 patients, 158 patients (63.45%) were treated as outpatients, and 91(36.55%) were hospitalized. Of the 91 hospitalized patients, 30 patients (32.97%) died, and 61(67.03%) were discharged. In the group of patients who died, 22 patients were male (17.9%) and 8(6.3%) were female (Table 2). There was a statistical significance between genders and outcome of COVID-19 disease in vaccinated patients with breakthrough infection; namely, male gender had a statistically greater chance for fatal outcome compared to female (P=0.006). Although there was almost equal number of patients < 65 and ≥65 years of age, 125(50.2%) and 124(49.8%), respectively, only 7(5.6%) patients died in the age group younger than 65 years and 118(94.4%) recovered, while in the patient group 65 years and older 23(18.5%) died, and 101(81.5%) survived. (Table 2). In terms of age, there was a statistically significant difference for negative clinical outcome for patients older than 65 years, who despite the vaccination had acquired COVID-19, compared to patients younger than 65 years (P= 0.002). Regarding comorbidities, the majority of our patients, 172(69.07%) had comorbidities, and 77(30.92%) were without any comorbidity (Table 2). In the patients' group with comorbidities, majority of patients had at least two or more comorbidities. The most common comorbidities were hypertension, diabetes mellitus, bronchial asthma, cardiovascular disease, chronic obstructive pulmonary diseases, cerebrovascular diseases and hypothyreosis. In the patients' group with comorbidities, 27(90.0%) died, whereas in the patients' group without comorbidities only 3(10.0%) died. Concerning comorbidities, there was a statistical significance for negative clinical outcome of COVID-19 breakthrough infection in the patients' group with comorbidities (P= 0.006). The mean age of the deceased was 71.27±9.79 years, and of the survived 58.83±15.3 years. There was a statistical significance between the age of the deceased and survived patients in vaccine breakthrough COVID-19 infection. Patients older than 71 years had statistically higher chances for lethal outcome compared to patients younger than 59 years (P=0.0001). We tried to evaluate if there was a connection between the disease outcome and the type of vaccine. Table 5 demonstrates the association between the disease outcomes in terms of mortality according to vaccine brand.

Table 5. COVID-19 disease outcome in vaccinated patients with breakthrough infection and type of vaccine

			Vaccine brand						
			Sinopharm	Astra Zeneka	Pfizer	Sputnik	Sinovac	Moderna	P value
Outcome	Deceased	N(%)	15(50.0)	6(20.0)	0(0.0)	0(0.0)	8 (26.7)	1(3.3)	P=0.031
	Survived	N(%)	99(45.2)	21(9.6)	37(16.9)	18(8.2)	42(19.2)	2 (0.9)	
Total		N(%)	114(45.8)	27(10.8)	37(14.9)	18(7.2)	50(20.1)	3(1.2)	

As presented in Table 5, there was a statistical signifycance between the clinical outcome and the vaccine type, but due to the uneven distribution of the samples, this significance cannot be taken reliably.

Discussion

Vaccination against COVID-19 was the most promising prospect of putting the pandemic under control and bringing it to an end. With the emergence of the SARS-CoV-2 virus in a relatively short period of time, various vaccine platforms were established and different va-

ccines were produced, with different vaccine efficacy [5,16]. Despite the great progress in the science, a perfect vaccine has not yet been found, a vaccine which would be 100% effective in 100% of the time and in 100% of the population. In our cohort of patients, majority of vaccine breakthrough infections occurred in the Sinopharm and Sinovac groups, followed by those vaccinated with Pfizer, AstraZeneca and Sputnik (45.8; 20.1%, 14.9%, 10.8% and 7.2%, respectively). The three Moderna vaccinated (1.2%) and evaluated patients were vaccinated abroad. In the literature, the mRNA vaccines led to the notable finding of ~95% efficacy for prevention of symptomatic COVID-19 two months after the second dose, which is more than in our cohort of patients. Adenovirus vectored vaccines showed a lower protection against infection with SARS-CoV-2, but achieved >90% protection against severe disease, while Sinopharm showed 79% efficiency against symptomatic disease and hospitalization [17]. According to WHO, in those vaccinated with Sinovac [18], it has an efficacy of 51% for preventing symptomatic disease and 100% for preventing hospitalization, contrary to the findings in our study. It has to be noted that according to the vaccine campaign plan of the government of North Macedonia [12] and the available vaccine brands at the time [13], individuals over 65 years of age had priority for vaccination and were mostly vaccinated with Sinovac and Sinopharm vaccines; therefore the difference of breaktrough infection in different vaccine groups in our cohort of patients might be simply a representation of the majority of vaccinated people. Additionaly, the vaccination campaign in the Republic of North Macedonia started in March 2021 and first to be vaccinated with the available vaccines were health care workers, people necessary for maintaining critical infrastructure, individuals over 65 years of age, people with comorbidities and those at a high risk of developing severe/critical illness [12]. As mentioned in some reports [19], the clinical waning of immunity after the first 2 months is particularly notable in people over 60 years of age, in whom susceptibility increased for both symptomatic infections and hospitalizations. Thus, it has to be further evaluated whether this larger occurrence of breakthrough infections in Sinopharm and Sinovac vaccinated group in our patient cohort was due to the vaccine (in)efficacy, waning of immunity or simply was a corresponding share of the total vaccine representation. The average time from complete vaccination to symptom onset in our cohort was 79.8 ±41.8 days, similar to the findings in other studies [19], which can also be explained with the expected waning of immunity after two months of vaccination but it still has to be further explored. Our study found that male gender, age ≥65 years and presence of comorbidities were major contributing factors for poor outcome in vaccinated hospitalized patients with COVID-19 vaccine breakthrough infection. Similar to our findings, other studies indicated that male gender was a risk factor for serious COVID-19 disease, which is explained by the differences in immunity response, the role of sex hormones, and gender-related behavior [20,21]. Similar to the study of Scobie [22], in our study older age despite vaccination still represented a risk factor for hospital admission or death compared to younger people. The mean age of patients with breakthrough infections and lethal outcome in our study cohort was 71.2±9.8 years, as indicated in other clinical reports that age of the patients is an independent risk factor significantly associated with severe COVID-19 outcomes [23,24]. Similar to the findings in the literature, our study showed that more vaccine breakthrough infections occurred in patients with comorbidities compared to patients without comorbidities, and there was a statistically significant difference in mortality of patients with and without comorbidities (90.0% and 10.0%, respectively). Namely, studies show that patients with comorbidities are more susceptible to infection with SARS-CoV-2 *per se* [25]. Also, it has been shown in different studies that individual characteristics of patients including older age, immunosuppression, comorbidities such as chronic cardiovascular, pulmonary, renal, liver and neurological diseases, advanced pregnancy, and heavy smoking are associated with a higher incidence of severe illness infected with SARS-CoV-2 infection [22,26]. In our cohort hospitalization rate due to SARS-CoV-2 breakthrough infections (36.55%) was higher compared to other studies, as shown through Case Investigation and Reporting of the Centers for Disease Control and Prevention (CDC) [27], which might be a result of different vaccine brands used for immunization, as well as the lower overall health status of our population in general. A study by O'Driscoll [28], accentuates that the risk for SARS-CoV-2 infection grows proportionally with age, and older individuals are at disproportionately higher risk of developing severe COVID-19, and patients over 65 are responsible for 80% of COVID-19 hospitalizations and suffer from a 20-fold higher COVID-19 fatality rate compared to those less than 65 years old. Similar to these findings and other findings in the literature [28-30], in our study vaccinated patients older than 65 years of age had statically significant higher chances for negative clinical outcome compared to patients younger than 65 years.

Our study showed that there was a significant difference between the type of vaccine and the severity of COVID-19 in the vaccinated patients with a breakthrough infection and that the highest mortality was found in patients vaccinated with inactivated virus containing vaccine, followed by a non-replicating viral vector vaccine and the lowest mortality was found in those vaccinated with either mRNA vaccine or human adenovirus vector-based COVID-19 vaccine. In both cases, due to the uneven distribution of the samples,

this significance cannot be taken reliably into account. There are several meta-analyses that have compared vaccine efficacy and presented different findings [31-34]. Unlike the findings in these studies, due to the uneven distribution of the samples in our cohort it would be misleading to look at breakthrough cases by vaccine brand since we received and administered more of some brands than others. Some vaccine profiles had only a small number of participants which might overestimate the outcome if the outcome occurred. These factors make it difficult to directly compare numbers of breakthrough cases, the severity of clinical picture and disease outcome among vaccine brands used for vaccination in our patients. Nevertheless, the differences in the incidence of breakthrough cases based on vaccine type are of interest and will need further investigation.

Our study had several limitations: firstly, some of the vaccines were not available or very not equally represented at the moment of the study, hence they were not included in the analysis. Secondly, the causative variants of SARS-CoV-2 were not determined in each COVID-19 case, but according to the SARS-CoV-2 variant surveillance report by the Institute of Public Health of R.N. Macedonia [35], the delta variant had prevailed in the region during the study period. Another limitation is that the vaccine may mitigate the symptoms of the SARS-CoV-2 infection; therefore, some asymptomatic people escaped from the COVID-19 screening and were not included in the study as vaccine breakthrough infections. Additionally, comparing the severity outcomes with unvaccinated individuals warrants further investigation.

Conclusion

Our study revealed a difference in vaccine breakthrough infection with SARS-CoV-2 in terms of vaccine types, as well difference in the severity of the clinical picture and outcome, but due to the uneven representation of the samples and different vaccine representation it would be misleading to draw any conclusion. Nevertheless, our investigation showed that gender, age and comorbidities are associated with the severity and negative clinical outcome of SARS-CoV-2 infection even in vaccinated patients. Therefore, boosting immunity for vulnerable patient groups in addition to maintaining and promoting preventive measures are essential to prevent severe cases of breakthrough infections of COVID-19. At the same time identifying subgroups of high-risk patients for severe breakthrough infections can help prioritizing early preventive treatment or prophylaxis for SARS-CoV-2 infection.

Conflict of interest statement. None declared.

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