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The effect of vaccination against the COVID-19 on the course and outcomes of a new coronavirus infection: a retrospective analysis of laboratory and clinical indicators of hospitalized patients

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ABSTRACT

BACKGROUND: The Gam-COVID-Vac vaccine was proven effective in preventing the severe course and adverse outcomes of COVID-19 during different periods of the pandemic. However, the effect of vaccination on laboratory marker levels in hospitalized patients during the spread of the omicron variant of SARS-CoV-2 has not been sufficiently studied.

AIM: To assess the effect of vaccination on the severity and outcomes of COVID-19 in hospitalized patients during the dominance of the SARS-CoV-2 omicron variant in Russia.

MATERIALS AND METHODS: This case–control study included adult patients diagnosed with COVID-19 (U 07.1) and hospitalized in infectious hospitals in Moscow between February 1, 2022, and July 31, 2022 (n = 119). The main group included individuals vaccinated with two doses of Sputnik V vaccine (n = 59). The control group included individuals who were not vaccinated (n = 60). The median patient age was 66 [interquartile range, 41–66] years, and 58.8% were female. The chi-square test for categorical variables and the Mann–Whitney test for continuous variables were used for the analysis. P-values < 0.05 were considered statistically significant.

RESULTS: Viral pneumonia was less likely to develop in the vaccinated group than in the unvaccinated group (46.7% and 18.6%, respectively, p = 0.007). The proportion of patients without lung damage (0 CT-severity scores) in the vaccinated group (72.0%) was significantly higher than that in the unvaccinated group (42.9%) (p = 0.003). In the vaccinated group, the levels of C-reactive protein on admission were lower (29.1 [7.4–68.6] mg/L and 75.1 [32.4–104.0] mg/L, p < 0.001), and the highest level was recorded during hospitalization (38.2 [12.0–84.0] mg/L and 92.2 [45.3–137.4] mg/L, p < 0.001). The D-dimer levels before discharge were lower in the group of patients vaccinated <6 months ago than in the unvaccinated group (157.0 [107.0–297.0] ng/mL and 316.0 [125.0–556.0] ng/mL, respectively, p = 0.014). The frequency of deaths in the control group (11.7%) was 6.9 times higher than that in the main group (1.7%) (p = 0.030).

CONCLUSION: Completion of the primary vaccination course of Sputnik V vaccine resulted in lower levels of prognostic markers of severe COVID-19 (C-reactive protein and D-dimer) and a decrease in the frequency of pulmonary and fatal outcomes than in the unvaccinated group during the dominance of the omicron variant of SARS-CoV-2.

Keywords: SARS-CoV-2; COVID-19; vaccination; outcomes; C-reactive protein; D-dimer.

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Влияние вакцинации против COVID-19 на течение и исходы новой коронавирусной инфекции: ретроспективный анализ клинико-эпидемиологических и лабораторных показателей у госпитализированных пациентов

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АННОТАЦИЯ

Обоснование. Вакцина «Гам-КОВИД-Вак» доказала свою эффективность для профилактики тяжёлого течения и неблагоприятных исходов новой коронавирусной инфекции в разные периоды пандемии COVID-19, однако влияние вакцинации на уровни лабораторных маркеров у госпитализированных пациентов в период распространения варианта Омикрон SARS-CoV-2 изучено недостаточно.

Цель исследования — оценить влияние вакцинации против COVID-19 на тяжесть течения и исходы новой коронавирусной инфекции у госпитализированных пациентов в раннем периоде распространения варианта Омикрон SARS-CoV-2 в России.

Материалы и методы. В исследование были включены 119 взрослых пациентов (58,8% женщин, медиана возраста — 66 лет), госпитализированных в инфекционную клиническую больницу № 2 г. Москвы с 1 февраля 2022 года по 31 июля 2022 года с диагнозом COVID-19 (U 07.1). В основную группу вошли пациенты, вакцинированные 2 дозами вакцины «Гам-КОВИД-Вак» (n=59), в контрольную — невакцинированные (n=60). Статистическую значимость отличий определяли для количественных переменных с помощью критерия Манна–Уитни, для категориальных — с помощью критерия χ^2 (уровень статистической значимости p <0,05).

Результаты. Вирусная пневмония реже развивалась у вакцинированных лиц по сравнению с невакцинированными (46,7 и 18,6% соответственно, p=0,007). Доля пациентов без поражения лёгких (КТ0) среди привитых (72,0%) была значительно выше, чем среди непривитых пациентов (42,9%) (p=0,003). Уровень С-реактивного белка при поступлении был ниже в группе вакцинированных по сравнению с невакцинированными (29,1 [7,4–68,6] мг/л и 75,1 [32,4–104,0] мг/л соответственно, p <0,001), как и максимальный уровень С-реактивного белка за период госпитализации (38,2 [12,0–84,0] мг/л и 92,2 [45,3–137,4] мг/л соответственно, p <0,001). Уровень D-димера перед выпиской был ниже у вакцинированных <6 месяцев назад по сравнению с невакцинированными (157,0 [107,0–297,0] нг/мл и 316,0 [125,0–556,0] нг/мл, p=0,014). Частота летальных исходов среди непривитых против COVID-19 (11,7%) была в 6,9 раза выше по сравнению с привитыми (1,7%) (p=0,030).

Заключение. У пациентов с завершённым первичным курсом вакцинации вакциной «Гам-КОВИД-Вак» наблюдались достоверно более низкие уровни С-реактивного белка, D-димера, а также снижение частоты поражения лёгких и летальных исходов по сравнению с невакцинированными пациентами в период распространения варианта BA.2 Омикрон SARS-CoV-2.

Ключевые слова: SARS-CoV-2; COVID-19; вакцинация; исходы; С-реактивный белок; D-димер.

Как цитировать

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ЭКО•ВЕКТОР

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BACKGROUND

In January 2020, an infection caused by the novel SARS-CoV-2 coronavirus was identified in countries outside the People's Republic of China, where the first cases were reported. As of January 2023, there have been more than 656 million confirmed cases of Coronavirus disease 2019 (COVID-19) worldwide, with more than 6.6 million resulting in fatalities [1]. In the Russian Federation, over three years of COVID-19 pandemic, more than 1.8 million cases and over 393,000 deaths from COVID-19 were documented [2].

SARS-CoV-2 infection is known to cause respiratory complications, including acute respiratory distress syndrome [3]. In COVID-19, complications from other systems and organs are not uncommon, the most common being blood clotting disorders (7.4%–14.7%), heart disease (6.8%–22.3%), liver injury (22.8%), and kidney (7%–19.5%) injury [3–8].

Elderly people and those with chronic diseases are at higher risk for severe disease progression and COVID-19 complications [3]. Reduced platelet and lymphocyte count and high levels of C-reactive protein (CRP), D-dimer, lactate dehydrogenase, ferritin, and procalcitonin in laboratory tests were found to be predictors of adverse COVID-19 outcomes [9, 10]. Criteria for respiratory failure include dyspnea, decreased saturation (SpO2), and hypercapnia [11, 12].

Vaccination is an effective way to prevent severe COVID-19 disease and its adverse outcomes. Many studies demonstrated that vaccination against COVID-19 reduces the incidence of severe disease, hospitalization, and mortality, particularly in at-risk groups [13–15]. Vaccination was effective during periods of prevalence of several virus variants, including Omicron [14, 16, 17]. Several foreign studies showed that the patients vaccinated against COVID-19 have significantly lower levels of laboratory markers of adverse disease outcomes and less severe lung damage observed on computed tomography (CT) scans [14, 15, 18].

In the Russian Federation, there were studies to assess the epidemiologic efficacy of COVID-19 vaccines, which showed a decrease in the incidence of disease during different periods of the pandemic in the vaccinated versus unvaccinated individuals [19–21]. Additionally, the severity of disease course in COVID-19 vaccinated and unvaccinated individuals and the levels of laboratory parameters (white blood cells, lymphocytes, CRP, D-dimer, ferritin, fibrinogen, lactate dehydrogenase, and interleukin 6) were compared according to vaccination history [22–25].

AIM

To evaluate the effect of vaccination against COVID-19 with two doses of Gam-COVID-Vac vaccine on the severity of course and outcomes of a new coronavirus infection in hospitalized patients during the initial period of the spread of the Omicron variant of SARS-CoV-2 in Russia.

MATERIALS AND METHODS

Study design

A single-center, retrospective, case-control study was conducted among adult patients hospitalized at Clinical Hospital of Infectious Diseases No. 2 in Moscow from February 1, 2022 to July 31, 2022. This period coincided with the spread of the SARS-CoV-2 Omicron sub-variant BA.2. A total of 181 patients were initially included in the study and evaluated according to the developed list of inclusion and non-inclusion/exclusion criteria. Based on the evaluation results, 62 patients included in the primary sample were excluded, resulting in a final sample of 119 patients. The study group, comprising patients who had received the vaccination against the novel coronavirus, included 59 patients, while the control group, consisting of unvaccinated individuals, included 60 patients. The data used in the study were drawn from the electronic medical records of patients.

The severity of the disease course and the severity of pulmonary changes as observed on CT scans were determined in accordance with the Interim Guidelines for the Prevention, Diagnosis, and Treatment of a Novel Coronavirus Infection (COVID-19), version 15.

Eligibility criteria

The inclusion criteria were as follows: age ⩾18 years; established diagnosis of COVID-19 (ICD-10 code U07.1) confirmed by detection of SARS-CoV-2 ribonucleic acid (RNA) by polymerase chain reaction or detection of SARS-CoV-2 antigen by immunochromatography; vaccination history; and hospitalization between February 1, 2022 and July 31, 2022.

The exclusion criteria were as follows: age <18 years; no data on vaccination history; vaccination with a single dose of COVID-19 vaccine; vaccination with vaccines other than Gam-COVID-Vac; revaccination against COVID-19; and HIV infection.

Patients vaccinated with two doses of Gum-COVID-Vac with at least 42 days between the first dose of vaccine and hospitalization were considered vaccinated. If these criteria were not met, the patients vaccinated against COVID-19 were excluded from the study.

Study setting

The study was conducted at Clinical Hospital of Infectious Diseases No. 2 of the Moscow City Health Department (Clinical Hospital of Infectious Diseases No. 2, Moscow Russia).

Study duration

The study included patients admitted to the hospital from February 1, 2022 to July 31, 2022.

Main study outcomes

Patients were assessed according to the following clinical and laboratory parameters:

- CRP and D-dimer levels (upon admission, before discharge, and maximum values during hospitalization);

- Respiratory rate (RR), saturation level (SpO_2), severity of pulmonary changes according to CT scan, NEWS2 (National Early Warning System) scale, and qSOFA (quick Sequential Organ Failure Assessment) scale (on admission)
- Disease outcome.

Subgroup analysis

To evaluate the clinical characteristics of patients vaccinated against COVID-19, depending on the time from the first dose of vaccine to hospitalization, the study group was subdivided into two subgroups: up to six months (<182 days, *n* = 20) and six or more months (⩾182 days, *n* = 39).

The characteristics of patients at risk for severe COVID-19 (aged 65 years and older) were also analyzed depending on their vaccination history [vaccinated (*n* = 28), unvaccinated (*n* = 38)].

Outcomes registration

The data on the demographic, epidemiologic, and clinical characteristics of the study participants, as well as the results of the laboratory and instrumental tests, were obtained from the electronic medical records of Clinical Hospital of Infectious Diseases No. 2.

Ethical review

The study protocol was approved by the Ethical Committee of Clinical Hospital of Infectious Diseases No. 2.

Statistical analysis

The sample size was not pre-calculated.

The statistical analysis of the obtained data was performed using IBM SPSS Statistics 19 and Microsoft Excel 2020 software packages. The results were presented using median and interquartile ranges (IQR) for quantitative variables and percentages for categorical variables. The Mann–Whitney test was used for quantitative variables, and the $\chi 2$ test was used for categorical variables to assess the statistical significance of differences. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Study participants

The median age of all patients included in the study was 66 years (IQR: 41–66) and the predominant sex was female (58.8%). The majority of patients (91.6%) had moderate disease severity. The proportion of patients who had previously had COVID-19 was 16%. Additionally, 6.7% had been in contact with a person with a laboratory-confirmed case of COVID-19.

The study and control groups were comparable in terms of sex, comorbidities, and the proportion of patients with reinfection ($p \geqslant 0.05$). The median age was slightly higher in the study group, but the ratio of age groups was comparable (Table 1).

Primary results

The prevalence of respiratory system complications among unvaccinated individuals was markedly higher (63.3%) compared to the study group (32.2%) ($p = 0.001$). The most prevalent respiratory complication among hospitalized patients was viral pneumonia (ICD-10 code J12.8), occurring in 46.7% of the unvaccinated group and 18.6% of the vaccinated group ($p = 0.007$). Furthermore, among patients aged 65 years and older, the incidence of respiratory system complications was higher among the unvaccinated (84.2%) compared with the vaccinated (39.3%) ($p < 0.001$).

However, no significant differences were found in the incidence of extrapulmonary complications of COVID-19 between the study and control groups, both in the total sample and in the patients aged 65 years and older (13.6% vs. 20.0%; 10.7% vs. 26.3%, respectively; $p \geqslant 0.05$).

Table 1. Demographic, clinical and epidemiological characteristics of hospitalized patients with COVID-19

Parameter	Study group (*n* = 59)	Control group (*n* = 60)	*p*
Age, years (median)	60.0 [35.0–75.0]	69.0 [48.3–82.0]	=0.022
Proportion of persons aged ⩾65 years	47.5%	63.3%	⩾0.05
Sex (female/male)	59.3%/40.7%	58.3%/41.7%	⩾0.05
Presence of comorbidities:	86.4%	91.7%	⩾0.05
• Cardiovascular disease	61.0%	68.3%	⩾0.05
• Endocrine disease	35.6%	30.0%	⩾0.05
• Oncology	8.5%	11.7%	⩾0.05
• Urinary disease	11.9%	18.3%	⩾0.05
Reinfection	15.3%	16.7%	⩾0.05
Contact with a laboratory-confirmed case \ of COVID-19	6.8%	6.7%	⩾0.05

The proportion of patients without pulmonary lesions was 72.0% in the study group and 42.9% in the control group. Consequently, the proportion of patients with pulmonary lesions (CT1–CT4) was lower in the study group ($p = 0.003$) (Fig. 1). Similar results were observed in patients aged 65 years and older, with 65.2% and 21.9%, respectively ($p = 0.001$).

The parameter values that allow evaluating the state of the patient's respiratory system and the severity of the disease course (RR and SpO_2) showed significant differences both in the total sample ($p = 0.005$ vs. $p = 0.034$, respectively) and in the patients aged 65 years and older ($p = 0.015$ vs. $p = 0.011$, respectively) (Table 2).

Significant differences in CRP levels were observed between patients in the study and control groups. The median CRP level on admission was 2.6 times lower in the study group (29.1 mg/L) than in the control group (75.5 mg/L) ($p < 0.001$). In addition, the median peak CRP levels during hospitalization were lower in the study group ($p < 0.001$). There were no statistically significant differences in D-dimer levels between the groups compared ($p \geq 0.05$).

The analysis of laboratory parameters reflecting the severity of the disease course in patients aged 65 years and older showed no statistically significant differences between the groups ($p \geq 0.05$), except for the maximum value of CRP ($p = 0.009$).

The severity of patients in the study and control groups at hospitalization based on NEWS2 score had no statistically significant differences, with the proportion of patients with a low score (0–4) being 76.4% and 63.0%, respectively ($p \geq 0.05$).

In the hospitalized patients, the qSOFA score demonstrated no statistically significant differences between the study and control groups. In the majority of patients, the sum of scores did not exceed one unit (100% and 97.1%, respectively; $p \geq 0.05$).

In elderly patients, the severity of disease course based on NEWS2 and qSOFA scores was also not significantly different in the studied subgroups. The proportion of patients with a low NEWS2 score (0–4) was 68.1% in the vaccinated and 54.9% in the unvaccinated patients. The proportion of patients with a qSOFA score of 0–1 was 100% and 95.3%, respectively ($p \geq 0.05$).

Significant differences in CRP levels (at hospital admission and maximum during hospitalization) were found between the unvaccinated and the vaccinated <6 months, as well as between the unvaccinated and the vaccinated ≥6 months before the development of COVID-19 (Table 3). In addition, D-dimer levels before hospital discharge were significantly different between the unvaccinated and the vaccinated <6 months groups ($p = 0.014$). No statistically significant differences in the levels of the evaluated

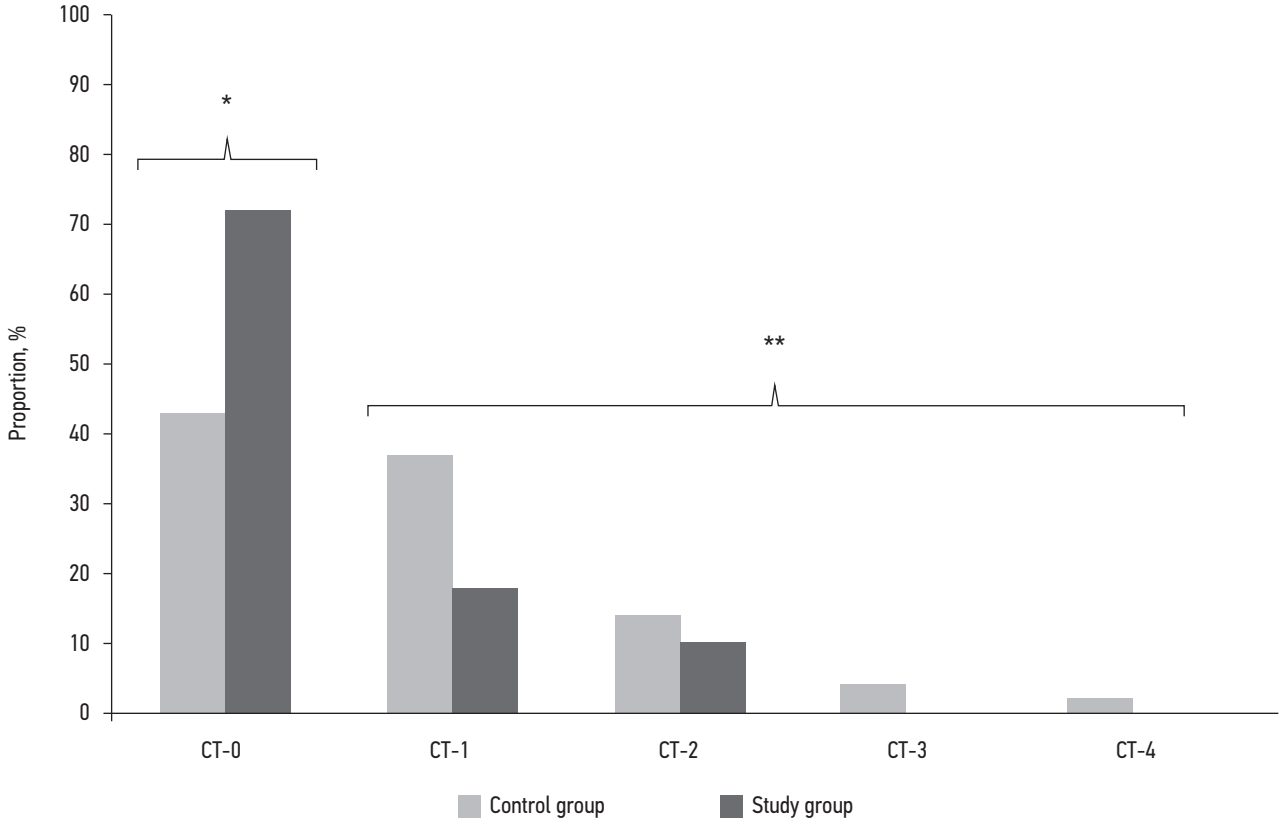

Fig. 1. Severity of lung changes according to the results of computed tomography (CT) among vaccinated and unvaccinated patients with COVID-19. * A proportion of patients with 0 CT-severity scores was significantly higher in the main group (Chi-Square test, $p < 0.05$). ** A total proportion of patients with 1–4 CT-severity scores was significantly lower in the main group (Chi-Square test, $p < 0.05$).

Table 2. Clinical and laboratory parameters in patients with new coronavirus infection depending on the vaccination status

Parameter	All patients			Patients aged ≥65 years		
	Study group (*n* = 59)	Control group (*n* = 60)	*p*	Study group (*n* = 28)	Control group (*n* = 38)	*p*
Clinical indices						
Duration of hospitalization, days	8 [6–11]	9 [7–12]	$p \geq 0.05$	8 [7–10]	10 [8–14]	$p = 0.009$
Respiratory rate, per min	19 [18–20]	20 [19–21]	$p = 0.005$	20 [18.5–20.0]	21 [19–22]	$p = 0.015$
SpO_2, %	97 [96–98]	96 [93–98]	$p = 0.034$	97 [95–98]	95 [90–96]	$p = 0.011$
Laboratory values						
CRP on admission, mg/L	29.1 [7.4–68.6]	75.5 [35.1–117.9]	$p < 0.001$	68.2 [15.6–91.5]	75.1 [32.4–104.0]	$p \geq 0.05$
Maximum CRP during hospitalization, mg/L	38.2 [12.0–84.0]	92.2[45.3–137.4]	$p < 0.001$	47.2 [13.8–88.4]	87.7[40.0–130.1]	$p = 0.009$
CRP before discharge, mg/L	6.0 [2.0–11.3]	8.3 [2.5–18.2]	$p \geq 0.05$	6.5 [4.3–12.9]	6.0 [2.0–13.8]	$p \geq 0.05$
D-dimer on admission, ng/mL	294.5 [166.0–628.5]	399.0 [206.0–822.0]	$p \geq 0.05$	386.0 [245.0–982.0]	439.0 [261.0–832.0]	$p \geq 0.05$
Maximum D-dimer during hospitalization, ng/mL	446.0 [220.0–1045.0]	567.5 [322.0–1358.0]	$p \geq 0.05$	623.5 [360.0–1280.0]	723.0 [394.0–1542.0]	$p \geq 0.05$
D-dimer before discharge, ng/mL	214.0 [117.0–421.5]	303.5 [206.0–533.0]	$p \geq 0.05$	350.0 [178.0–657.0]	351.0 [244.0–682.0]	$p \geq 0.05$

Table 3. Laboratory parameters of unvaccinated patients with a new coronavirus infection, patients vaccinated <6 months ago and ≥6 months ago

Parameter	Study group		Control group (*n* = 60)	*p*1	*p*2
	<6 months (*n* = 20)	≥6 months or more (*n* = 39)			
CRP on admission, mg/L	49.3 [10.1–69.6]	27.9 [6.3–68.6]	75.5 [35.1–117.9]	$p = 0.001$	$p < 0.001$
Maximum CRP value, mg/L	49.3 [15.2–84.0]	34.4 [10.9–52.3]	92.2[45.3–137.4]	$p = 0.002$	$p < 0.001$
CRP before discharge, mg/L	6.0 [1.4–16.1]	5.3 [2.0–9.3]	8.3 [2.5–18.2]	$p \geq 0.05$	$p \geq 0.05$
D-dimer on admission, ng/mL	284.0 [126.0–451.0]	305.0 [169.0–670.0]	399.0 [206.0–822.0]	$p \geq 0.05$	$p \geq 0.05$
Maximum D-dimer, ng/mL	441.0 [208.0–952.0]	556.0 [233.0–1060.0]	567.5 [322.0–1358.0]	$p \geq 0.05$	$p \geq 0.05$
D-dimer before discharge, ng/mL	157.0 [107.0–297.0]	316.0 [125.0–556.0]	303.5 [206.0–533.0]	$p = 0.014$	$p \geq 0.05$

Note: *p*1, control group and vaccination less than 6 months ago; *p*2, control group and vaccination 6 months or more; Mann–Whitney test.

laboratory parameters were found between the groups of patients vaccinated before six and six or more months ago ($p \geq 0.05$).

The incidence of fatal outcomes among the patients in the total sample was 6.7%. Most of the patients who died were not vaccinated against COVID-19 ($n = 7$), representing 11.7% of the control group. At the same time, only one fatality occurred among the vaccinated patients (1.7%; $p = 0.03$).

DISCUSSION

Discussion of the primary study results

Since February 2022, the Omicron variant has been the predominant strain of the SARS-CoV-2 virus in the Russian Federation [26, 27]. This variant was found to exhibit higher contagiosity and the capacity to evade immune responses compared to previously circulating

variants. A meta-analysis revealed that the effectiveness of immunization with two doses of different vaccine types against COVID-19 was 55.9% for the Omicron variant, which was 21.9% and 32.1% lower than for the Delta and Alpha variants, respectively [28]. However, vaccination during the initial period of the Omicron variant was still effective in preventing severe and fatal infections. The severity of COVID-19 was shown to be less severe in patients vaccinated against novel coronavirus infection with mRNA vaccines (Tozinameran or mRNA-1273), regardless of the SARS-CoV-2 strain [29]. The Gam-COVID-Vac vaccine protected against more severe forms of disease and hospitalization during the spread of the Omicron variant in Russia [17].

In addition, the results of our study demonstrate the effectiveness of vaccination against COVID-19 during the initial period of the spread of the Omicron variant in the Russian Federation. Hospitalized vaccinated patients were less likely to develop pneumonia and had a lower incidence of fatal outcomes, which is consistent with the results of Russian and foreign studies [14, 15, 22–24, 30].

In the scientific literature, there are conflicting data regarding CRP and D-dimer levels in the vaccinated and unvaccinated COVID-19 patients. While some studies show lower D-dimer levels in the vaccinated patients, other studies show the opposite [22, 25]. In our study, the test for D-dimer levels did not show statistically significant differences between the study and control groups. However, the patients vaccinated <6 months ago had significantly lower D-dimer levels before discharge compared with the unvaccinated group.

Moreover, the group of individuals vaccinated against COVID-19 exhibited significantly reduced levels of CRP, both at the time of hospital admission and at the maximum level observed throughout the entire hospitalization period. Furthermore, the studies conducted at the Alexandrovskaya City Hospital (St. Petersburg) during different periods of the pandemic demonstrated reliable differences in CRP levels between the vaccinated and unvaccinated patients. The values of this indicator were consistently lower in patients vaccinated against COVID-19 on admission to the hospital, on Day 3 after admission, and at the time of discharge or death [23, 24]. According to the study of CRP levels in patients of City Clinical Hospital No. 52 in Moscow during the spread of the Omicron variant, no significant differences were found between the groups of those vaccinated and unvaccinated against COVID-19 [22]. Similar results were described in the work of Fatima et al [15].

An analysis of the incidence of COVID-19 respiratory complications in the subgroup of patients aged 65 years and older, one of the risk groups for severe disease, showed that the vaccinated patients developed complications less frequently than the unvaccinated. No significant differences in the levels of laboratory markers in the patients aged 65 years and older were found, except for the maximum level of CRP during hospitalization, probably due to the small size of this group.

Study limitations

The small number of subgroups in terms of time since completion of the vaccination course does not allow a full assessment of the impact of COVID-19 vaccination on disease progression. Furthermore, scientific literature indicates that vaccine effectiveness is enhanced with booster vaccination; however, the present study assessed the characteristics of patients who received primary vaccination only. The median age of the vaccinated participants was higher than that of the unvaccinated participants, which may have had some effect on the levels of the laboratory markers. In view of the above and the results obtained in the study cohort, the effect of COVID-19 vaccination on the levels of prognostic markers of severe disease needs to be further investigated in larger samples and in the revaccinated group.

CONCLUSIONS

The initial course of vaccination with the Gam-COVID-Vac vaccine was associated with significantly lower levels of CRP, an important laboratory marker of disease severity and progression, as well as incidence of lung damage and death, in hospitalized patients with COVID-19 and a history of vaccination, compared with the unvaccinated patients. In the patients who received the Gam-COVID-Vac vaccine less than six months prior to the disease onset, D-dimer levels were significantly lower in those who were discharged from the hospital compared to the unvaccinated patients. These findings illustrate the clinical efficacy of the Gam-COVID-Vac vaccine in preventing adverse outcomes associated with the SARS-CoV-2 Omicron BA.2 sub-variant during its spread in the Russian Federation.

ADDITIONAL INFORMATION

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