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Analysis of Influencing Factors of Different COVID-19 Vaccinations on COVID-19 Infected Patients in Shanghai

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ABSTRACT

Vaccination with COVID-19 vaccine can reduce the incidence of severe coronavirus infection and death. Different vaccinations have different impacts on patients who suffered COVID-19. However, the correlation between the dose and times of vaccination and the natural course of disease after infection has not been determined. The objective of this study was to analyze the correlation between the type, dose, times of vaccination and the time of negative turning, clinical symptoms and the natural course of disease. Retrospective analysis was adopted for which the patients who tested positive for COVID-19 nucleic acid in the study according to the consensus opinion of China's COVID-19 infection were included. A total of 210 asymptomatic and mild COVID-19 patients, 116 males and 94 females, with an average age of 46 years, BMI of 24.43±5.62, were enrolled in this study from March 21 to April 8, 2022 in Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. Novel coronavirus asymptomatic infections were 126 cases, and mild patients were 84 cases. The patients were grouped according to the dose of COVID-19 vaccine before infection. The gender, age, BMI, symptoms, complications, vaccine manufacturer, the interval between the last vaccination and COVID-19 infection, and the duration of disease were analyzed. We found that the average age of patients in the unvaccinated group was significantly higher than that in the other groups, and the duration of the disease was slightly longer than that in the vaccinated group ($P < 0.05$). The differences between groups were statistically significant, but there was no significant difference between groups with different doses. There was no significant difference in BMI among the groups. According to the types of underlying diseases, the disease duration of the non-complications group was shorter than that of the complications group ($P > 0.05$), but there was no significant difference between the complications group. There was no significant difference in the duration of disease between the groups according to vaccine manufacturer. According to the interval from the last vaccination to infection, the duration of disease in the unvaccinated group was significantly longer than that in the other groups, and there was no significant difference between the duration of disease in patients with an interval of more than 1 year and the unvaccinated group. To conclude asymptomatic and mild symptoms are more common in young and middle-aged patients with normal weight or overweight. The number of days of nucleic acid turning negative in patients with underlying diseases was significantly longer than that in patients without underlying diseases, but it was not related to several underlying diseases. No matter how many doses of vaccine have been administered, and no matter what type of vaccine has been administered, the natural course of disease can be significantly shortened compared with the unvaccinated. The infection rate of novel coronavirus is lower within 3 months after vaccination. When the interval after the last vaccination was more than one year, the natural course of disease was prolonged, which was not significantly different from that of unvaccinated subjects.

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Chonglin Y and Cuiping Y presented the concept, designed the study analysed and interpreted data. Chonglin Y provided administrative support. JJ, HL and WX provided study materials or patients, collected and assembled data. All authors wrote the approved the manuscript.

Key words
COVID-19 vaccine, Natural course of COVID-19 disease, COVID-19 vaccine manufacturers

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INTRODUCTION

More than 100 years since the outbreak of the 1918 influenza pandemic, we now seem to face another pandemic. The outbreak of the new coronavirus (SARS-CoV-2) infection is spreading to every continent, forcing us to live with this virus for perhaps a long time. Since the outbreak of SARS-CoV-2 at the end of 2019 (short for

COVID-19), the pandemic has continued to spread around the world. So far, more than 500 million people have been confirmed with more than 6 million deaths (Rai *et al*., 2021). COVID-19 infection can be roughly divided into three stages: stage I, an asymptomatic incubation period with or without detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load (Wang *et al*., 2020). On 26th November 2021, the mutant B.1.1.529 was officially named Omicron by the World Health Organization (WHO) and identified as the fifth variant of concern (Umakanthan *et al*., 2020). At present, the Omicron strain has replaced the Delta strain as the dominant pandemic, and the subvariant of Omicron, the BA.2 strain, has replaced the BA.1 as the dominant novel coronavirus globally (Anwar *et al*., 2020). There was an outbreak of the mutant strain in Shanghai this spring (Meo *et al*., 2021; Saxena *et al*., 2022).

Asymptomatic and mild symptoms were predominant in those who had been vaccinated and those infected with Omicron strain. Patients with clinical symptoms are mainly manifested as moderate and low fever, dry pharynx, pharyngeal pain, nasal congestion, runny nose and other symptoms of upper respiratory tract infection, generally do not need too much treatment, just need the necessary supportive treatment. Novel coronavirus vaccine can reduce the infection and incidence, and is an effective means of reducing the incidence of severe illness and death, according to the COVID-19 Protocol (the ninth Trial Version) of China (Zhang *et al*., 2022). All eligible persons should be vaccinated and those eligible for enhanced immunization should be vaccinated. Booster immunization should be carried out in a timely manner.

There are some doubts that there are no clear answer about vaccination. For example, the relation of vaccine times and the infection, correlation between the time between the last vaccination and infection with COVID-19. The present study was undertaken to answer these questions.

MATERIALS AND METHODS

Subjects

This study included asymptomatic and mild COVID-19 patients treated by the temporary COVID-19 the fifth medical team in the Ruijin Hospital north affiliated to Shanghai Jiao Tong University School of Medicine from 21st March to 8th April 2022. The gender, age, Body mass index (BMI), symptoms, complications, vaccine manufacturer, interval time from the last vaccination to infection and disease course of all patients in each group were analyzed according to the doses and times of COVID-19 vaccine before infection.

Inclusion criteria: The patients who (i) were admitted to our hospital and admitted by our medical team. (ii) were novel coronavirus nucleic acid positive without any clinical symptoms and mild cases of confirmed cases according to the diagnostic criteria of the Ninth Edition of COVID-19 protocol of China (Zhang *et al*., 2022), (iii) received only general symptomatic nutritional support treatment and appropriate psychological intervention during hospitalization, and (iv) were not given any special treatment such as antiviral and immunity were included in this study.

Exclusion criteria: The patients (i) whose disease worsend to ordinary or severe during the course of disease, (ii) whose diseases complicated with severe basic respiratory diseases, SpO_2<93%, requiring oxygen therapy, and (iii) those with fracture, open injury, tumor, etc. requiring surgical treatment were excluded from this study.

Diagnostic criteria

Genomic analysis of Omicron mutant showed that the mutation site did not affect the sensitivity and specificity of the mainstream nucleic acid detection reagent in China. The mutation sites of the Omicron variant strain are mainly concentrated in the high variation region of S protein gene, and are not located in the primer and probe target region of nucleic acid detection reagent published in the Ninth Edition of COVID-19 Diagnosis and Treatment Protocol in China (*ORF1ab* gene and *N* gene published to the world by the Institute of Viral Disease, China CDC). SARS-COV-2 infection was detected in this study using PCR molecular test that is a nucleic acid test (Zhang *et al*., 2022). A positive test suggested the diagnostis of novel coronavirus infection (Umakanthan *et al*., 2020; Yuce *et al*., 2021).

Vaccination parameters

The vaccination time and the name of manufacturer of vaccines of all patients was checked by the patient health cloud or application (APP) and the last vaccination date was recorded. The novel coronavirus nucleic acid test results before admission were checked by the patient health Cloud APP, and the date of the first positive test was determined as the date of onset. After admission, all novel coronavirus nucleic acid tests were performed by PCR in the laboratory of our hospital. If the interval of sampling time was at least 24 h and the results of two consecutive nucleic acid tests were negative, the sampling date of the first negative nucleic acid test was considered as the cure date.

The following terminologies were adopted for this study. (i) Vaccination times (VT) was the actual number of doses of COVID-19 vaccine received by the patient, regardless of the vaccine manufacturer.

(ii) Time of last vaccination was the date of last vaccination against COVID-19.

(iii) Novel coronavirus nucleic acid test positive meant that the CT value of N gene or ORF1ab gene in Coronavirus nucleic acid test < 35.

(iv) Novel coronavirus nucleic acid test negative meant that the CT values of ORF1ab gene of N gene in Coronavirus nucleic acid test ≥ 35.

(v) For disisolation criteria fluorescence quantitative PCR method was adopted, and the sampling time interval was at least 24 h. CT values of N gene ORF1ab gene in two consecutive Coronavirus nucleic acid tests were all ≥ 35.

(vi) Days between last vaccination and infection (DLVI)is the difference between the date of the first novel coronavirus nucleic acid test positive and the date of the last vaccination against COVID-19.

(vii) Duration of disease (DD) meant the days between the negative date of the first coronavirus nucleic acid test negative and the positive date of the first coronavirus nucleic acid test.

Methodology adopted

COVID-19 patients were divided into asymptomatic patients and mild patients. They were divided into two groups according to times of vaccination and the interval time after the last vaccination. The basic information of patients in each group, especially the interval time from the last vaccine to the infection of COVID-19 and the duration of the disease were compared and analyzed so as to explore the impact of times and timing of vaccination on the natural outcome after infection.

Group by number of vaccinations implies that the number, age, BMI, symptoms and natural course of disease in each group were compared and analyzed, and the effect of vaccination times on the course of disease was analyzed. Then each group of asymptomatic and mild patients were further compared to analyze the difference in the course of disease.

Groups were divided according to whether there were complications and types of complications.

Groups were divided also according to the types of vaccines, and then the influence of different vaccines on the course of disease was compared.

The number, age, BMI, symptoms and natural course of disease of patients in each group were compared and analyzed according to the interval between the last vaccination and infection with COVID-19, and the influence of vaccination times on the course of disease was analyzed.

Statistical analysis

All the data are presented as the mean ± standard deviation. First, the global null hypothesis (i.e., that there were no differences between all groups) was tested using analysis of variance tests for DLVI and DD. If the level of significance was not reached, the parameter examined was excluded from the local tests. The local tests were then performed using the Kruskal-Wallis test to identify significant differences between all groups. The level of statistical significance was set at $P<0.05$. All statistical tests were two-sided. All the statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, Version 19.0; IBM Corp., Armonk, NY, USA).

RESULTS

General cases

210 patients were included, including 116 males and 94 females, with an average age of 46 years and BMI of 24.43±5.62 Kg/m^2. There were 181 asymptomatic and 29 mild cases. 166 novel inactivated vaccines were administered (90 inactivated vaccines produced by Sinopac Biobiology Institute in Beijing, 11 inactivated vaccines produced by Wuhan Institute and 65 inactivated vaccines produced by Beijing Sinovac life sciences), 2 adenovirus vector vaccines produced by CanSino Bio, and 3 recombinant subunit vaccines produced by Anhui Zhifei.

Patients who were asymptomatic or mild at the first diagnosis did not worsen to normal or severe in the natural course of disease, nor did they have severe respiratory diseases, nor did they have fractures, open injuries, tumors and other patients requiring surgical treatment. None of the patients received special treatment such as antiviral and immunity.

Correlation between different vaccination times and course of disease

They were divided into four groups based on the number of doses administered, regardless of the manufacturer. There were no vaccination contraindications and complications after vaccination.

Group 1: No vaccines had been administered (none), 39(18.6%), 23 male, 16 female, average age 59, BMI 23.22±3.11 Kg/m^2, asymptomatic 25, mild 14, duration of disease 14.49±6.59d.

Group 2: Only one dose of vaccine was given (once), 9(4.2%); 6 male, 3 female, average age 38, BMI 24.90±3.70 Kg/m^2, asymptomatic 3, mild 6, duration of disease 11.33±3.46 d.

Group 3: Two doses of vaccine was given (twice), 81(38.6%), 40 male, 41 female, average age 41, BMI 24.23±6.75 Kg/m^2, asymptomatic 53, mild 28, duration of disease 11.27±3.74 d.

Group 4: Three doses of vaccine was given (triple), 81(38.6%), 47 male, 34 female, average age 45, BMI 25.17±5.45 Kg/m^2, asymptomatic 45, mild 36, duration of disease 10.80±3.16 d, as shown in the Table I.

The comparison between groups showed that the average age of the first group was significantly higher than that of the other groups (F=11.84, $P < 0.05$), and there was no significant difference between the other groups ($P > 0.05$). There was no significant difference in BMI between groups (F=1.13, P=0.34). There was a significant difference in disease duration between the two groups (F=7.20, $P < 0.05$). Pairwise comparison between the first group and the other three groups showed a significant difference ($P < 0.05$), while there was no significant difference between the second, third and fourth groups ($P > 0.05$) (Table II, Fig. 1).

Table I. Cases grouped according to different inoculation times.

Vaccination times	None	Once	Twice	Triple	Total
All cases (%)	39 (18.6%)	9 (4.2%)	81 (38.6%)	81 (38.6%)	210 (100%)
Male	23	6	40	47	116
Female	16	3	41	34	94
Mean age (years)	59	38	41	45	46
BMI (kg/m^2)	23.22±3.11	24.90±3.70	24.23±6.75	25.17±5.45	24.43±5.62
Asymptomatic	25	3	53	45	126
Mild	14	6	28	36	84
Symptoms					
Cough, sputum, sore throat	14	6	28	36	84
Chest distress and chest pain	2	0	4	5	11
Palpitations, shortness of breath	0	1	3	3	7
Headache, dizziness	0	3	7	7	17
Nausea and vomiting	0	2	3	0	5
Abdominal pain and diarrhea	0	3	3	5	11
Vaccine manufacturers					
Beijing Institute of Biological Products	0	4	41	45	90
Beijing Sinovac Life Sciences	0	4	35	26	65
Wuhan Institute of Biological products	0	0	3	8	11
Anhui Zhifei	0	0	1	2	3
CanSino Bio	0	1	1	0	2
Complications					
Hypertension	16	2	8	5	31
Diabetes mellitus	10	1	4	5	20
Lung disease	2	1	1	1	5
Coronary heart disease	2	0	4	1	7
Malignant tumor	1	0	0	1	2
History of cerebral infarction	3	0	0	0	3
Chronic kidney disease	0	0	1	0	1
Gastrointestinal diseases	0	0	1	0	1
Hematological system diseases	0	0	0	1	1
Thyroid disease	0	0	0	2	2
DLVI	0	207.89±101.92	255.05±81.50	108.57±54.21	149.16±115.54
DD	14.49±6.59	11.33±3.46	11.27±3.74	10.80±3.16	11.69±4.40

DLVI, days between last vaccination and infection; DD, duration of disease.

Table II. Data of cases grouped according to the interval between the last vaccination and infection with COVID-19.

Group	A: < 3m	B:3m-6m	C:6m-9m	D:9m-1y	E: > 1y	F:Not vaccinated	Total
DLVI	64.59±20.93	130.85±25.37	236.34±26.69	305.76±19.09	410.50±23.87	0.00	149.16±115.54
All cases (%)	41(19.5%)	53(25.2%)	32(15.2%)	41(19.5%)	4(1.9%)	39(18.6%)	210(100%)
Male	26	29	20	16	2	23	116
Female	15	24	12	25	2	16	94
Mean age (years)	45	41	43	43	46	59	46
DD	10.59±3.38	11.25±3.14	11.16±4.38	11.07±3.12	12.25±4.19	14.49±6.59	11.69±4.40

For abbreviations see Table I.

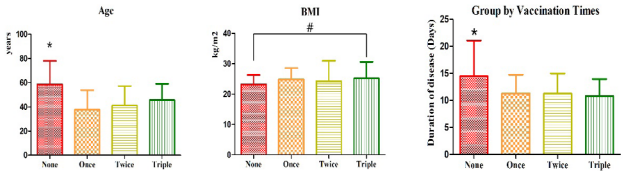

Fig. 1. The difference of each group average age, BMI and vaccination times. Compared with group None, *$P < 0.05$; # $P > 0.05$.

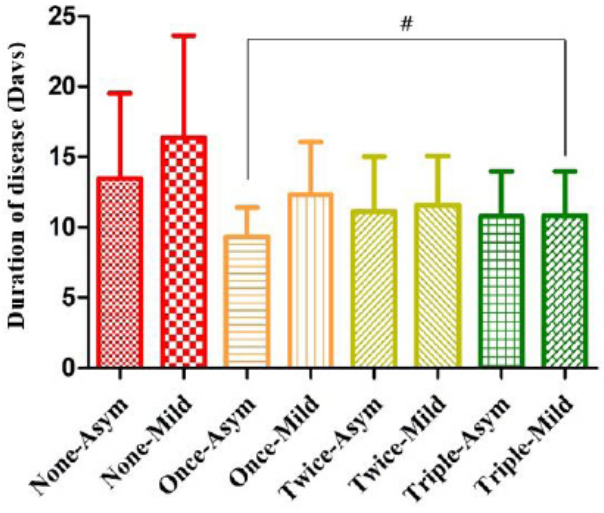

Fig. 2. Relationship between mild and asymptomatic disease duration. Compared with groups of None-Asym and None-Mild, # $P > 0.05$.

Relationship between mild and asymptomatic disease duration

The number of patients with mild disease was significantly less than that of asymptomatic patients. The three vaccinated groups were divided into six groups, and there was no significant difference in the time of turning negative between the three groups by ANOVA (F=0.385, P=0.819) (Fig. 2).

Relationship between complication and disease course

Grouped according to whether there were underlying disease or not, we found that 49 cases in the underlying disease group had 13.10±5.15 days of negative conversion, while 161 cases in the nonunderlying disease group had 11.26±4.07 days of negative conversion. Independent sample t-test showed that the difference was statistically significant (t = -2.60, $P = 0.01$).

According to the types of complications, from 1 to 4, the days of negative conversion were compared. ANOVA comparison showed no significant difference in the days of negative conversion between the groups (F = 0.18, P = 0.92) (Fig. 3).

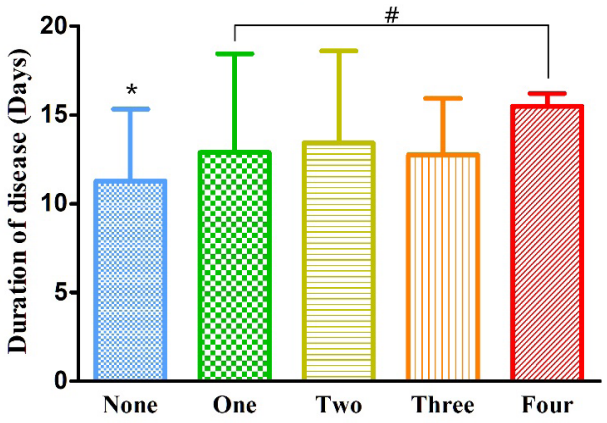

Fig. 3. Relationship between complication and disease course. Compared with group None, *$P < 0.05$; # $P > 0.05$.

Relationship between vaccine manufacturer and disease duration

Since the number of days to negative turning was not related to the times of vaccinations, we were grouped by Beijing Biologics, Wuhan Biologics, Sinovac Beijing, Anhui Zhifei and CanSino Bio vaccines, and there was no significant difference in the number of days to negative turning between the groups by ANOVA comparison (F = 0.195, $P = 0.940$) (Fig. 4).

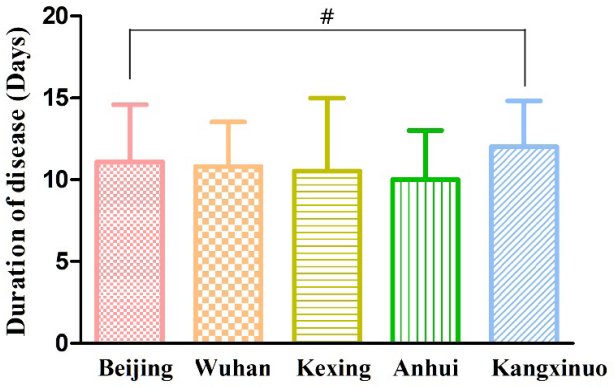

Fig. 4. Relationship between vaccine manufacturer and disease duration. Compared with group Beijing, # $P > 0.05$.

Relationship between the interval between the last inoculation and the onset of disease and the course of disease

They were divided into six groups based on the time between the last vaccination and infection.

Group A: the interval time was less than 3 months (64.59±20.93), 41 cases (19.5%), 26 males and 15 females, the average age was 45 years, the duration of disease was 10.59±3.38 days.

Group B: The interval was 3 months to 6 months, 53 cases (25.2%); There were 29 males and 24 females, with an average age of 41 years and a disease duration of 11.25±3.14 days.

Group C: The interval was 6 months to 9 months, 32 cases (15.2%), 20 males and 12 females, the average age was 43 years, the duration of disease was 11.11±3.70 days.

Group D: The interval was 9 months to 1 year, 41 cases (19.5%), 16 males and 25 females, the average age was 43 years, the duration of disease was 11.16±4.38 days.

Group E: There were 4 patients (1.9%) with an interval of more than 1 year, including 2 males and 2 females, with an average age of 46 years and a disease duration of 12.25±4.19.

Group F: 39 patients (18.6%) were not vaccinated with any vaccine, including 23 males and 16 females, with an average age of 59 years and a disease duration of 14.49±6.59 days.

The results of comparison between groups showed that the average age of patients in group F was significantly higher than that in other groups (F=4.371, $P < 0.05$), and there was no significant difference in pairwise comparison between other groups ($P > 0.05$). There was no significant difference in pairwise comparison between groups A, B, C and D ($P > 0.05$). There was no significant difference between group E and group F ($P = 0.31$), but there were significant differences between group F and groups A, B, C and D ($P < 0.05$) (Fig. 5).

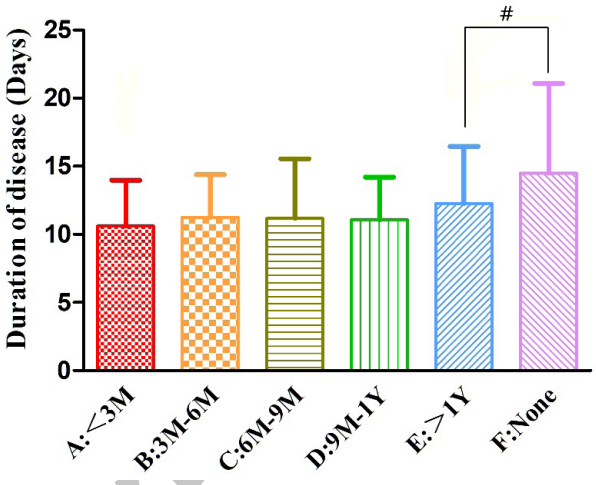

Fig. 5. Relationship between the interval between the last inoculation and the onset of disease and the course of disease. Compared with group None, # $P > 0.05$.

DISCUSSION

Compared with Delta, Omicron strain is more likely to infect the upper respiratory tract, which may be one of the reasons for the asymptomatic or mild infection of Omicron strain and the clinical symptoms of upper respiratory tract infection (Meo *et al*., 2021; Ochani *et al*., 2021; Kumar *et al*., 2022). In addition, viruses in the upper respiratory tract are relatively easy to spread into the air through coughing and sneezing, and relatively easy to spread from person to person through breathing, which could explain Omicron's rapid transmission. In addition, Omicron infection resulted in less low respiratory tract involvement and lower hospitalization rates, but an increased risk of sore throat and hoarseness.

Aerosol transmission in a relatively closed environment and contact with virus-contaminated items can also result in both routes of infection.

None of the patients included in this study received antiviral or immunotherapy. This study aimed to observe the natural course of disease outcome in asymptomatic and mild patients, and to analyze the effect of previous vaccination on disease outcome after infection.

Age and weight factors analysis

From the analysis of the study results, among the 210 asymptomatic or mild patients included in the study, 39 patients (18.6%) were not vaccinated, and 171 patients

(81.4%) were vaccinated. Studies have shown that K417N, E484A, or N501Y mutations in novel Coronuss protein indicate enhanced immune escape ability (Bhattacharya *et al*., 2022; Zhao *et al*., 2022). The Omicron variant also had the triple mutation "K417N+E484A+N501Y" (Bhattacharya *et al*., 2022; Aleem *et al*., 2022). In addition, the Omicron variant has several other mutations that may reduce the neutralizing activity of some MAbs. The superposition of mutations may reduce the protective efficacy of some antibody drugs against Omicron variants, and the immune escape ability of existing vaccines is not clear. However, the results of this study confirm that despite vaccination, patients can still get infected with the Omicron strain, but their symptoms tend to be mild. Studies have shown that routine COVID-19 vaccination is less effective in preventing Omicron infection, symptomatic infection and severe illness than four other Covid variants classified as "of concern," including the Alpha strain (Du *et al*., 2022; Fan *et al*., 2022; Rose *et al*., 2022). But in most studies, existing vaccines have been highly effective in preventing severe OMicRON. Just as we also found that unvaccinated patients are more likely to develop common or severe COVID-19 during clinical treatment. Therefore, the proportion of asymptomatic and mild patients is relatively low (Hastert *et al*., 2022).

Similar to the earlier Omicron subtype, BA.4, BA.5 and BA.2.12.1 showed the ability to escape antibodies generated by COVID-19 vaccines or earlier COVID-19 infections, but in most cases, immunity acquired through vaccination or natural infection can still prevent severe illness caused by the new subtype strain (Wang *et al*., 2022; Cao *et al*., 2022; Hachmann *et al*., 2022; Beheshti *et al*., 2022).

In addition, unvaccinated patients are often complicated with various underlying diseases or vaccination contraindications. The results of this study also show that the age of unvaccinated patients is significantly higher than that of vaccinated patients. Novel coronavirus population is generally susceptible. The BMI of asymptomatic and mild patients in this study was 24.43±5.62 Kg/m^2, and there was no significant difference in BMI among the groups. The results suggested that the asymptomatic and mild patients were mainly normal weight or overweight patients, that is to say, those who were underweight or overweight and infected with novel coronavirus Omicron strain may have more severe symptoms.

Analysis by number of vaccinations

In February 2021, Chile started vaccination against COVID-19 vaccine. Beginning in early August 2021, the Ministry of Health of Chile initiated booster immunization for persons fully vaccinated with CoronaVac inactivated vaccine. The study was conducted during the Delta epidemic, with 11.17 million subjects enrolled, of whom 4.12 million completed primary immunization with two doses of inactivated vaccine and received a booster shot during the study. The number of people who received three doses of inactivated vaccine was 186,946; The number of people who received two doses of inactivated vaccine and one dose of BNT62b2 mRNA vaccine was 2,019,260. The number of people who received two doses of inactivated vaccine and one dose of AZD1222 adenovirus vector vaccine was 1,921,340 (Jara *et al*., 2022; Tabilo *et al*., 2022; Schultz *et al*., 2022; Acevedo *et al*., 2022; Melo-Gonzalez *et al*., 2021). On 23 April 2022, data from a Chilean study published in The Lancet Global Health showed that after two doses of inactivated vaccine, compared with continuing with a third dose of inactivated vaccine (homologous booster), Heterologous vaccination with different technical routes of COVID-19 vaccine (sequential booster) can improve the protective efficacy of about 20% to 30%. Real-world data from Hong Kong also show that the protection rate of sequential booster vaccination is significantly higher than that of homologous booster vaccination. The importance of vaccination in preventing severe illness and death has been repeatedly mentioned during Hong Kong's previous Omicron outbreak (Jara *et al*., 2022).

In terms of booster effects, 36 studies involving multiple booster shots showed a significant increase in the prevention of severe omicron from 14 days to 3 months after a booster dose; In 34 assessments, the effectiveness in preventing severe illness was greater than 70% between 14 days and 3 months after a booster dose. In 18 of 20 more long-term evaluations of the efficacy of mRNA booster shots, the efficacy in preventing severe illness was greater than 70% for 3 to 6 months after a single dose of mRNA booster shot (Jahrsdorfer *et al*., 2022; Campos *et al*., 2022; Korves *et al*., 2022; Gerges *et al*., 2022; Herman-Edelstein *et al*., 2022; Nantanee *et al*., 2022; Adams *et al*., 2022; Munoz *et al*., 2022; Kim *et al*., 2022; Kawasuji *et al*., 2022; Wang *et al*., 2022).

The available evidence shows that the Omicron strain is more transmissible than the Delta strain, the virulence of the Omicron strain is reduced, the accuracy of the PCR test is not affected, but the effect of some monoclonal antibody drugs may be reduced.

In the WHO's weekly epidemic report, published on May 11, 10 countries including Brazil, Canada, the Czech Republic and Denmark were studied, evaluating marketed vaccines from Pfizer/BioNTech, Modena, AstraZeneca, Sinovac and Johnson and Johnson. Some of these studies assessed only the effect of completing routine vaccination, others assessed only the effect of receiving a single booster

dose, and still others assessed both conditions.

The results showed that the effectiveness of Sinovac inactivated vaccine in preventing symptomatic infection was 78.8%, BNT162b2 sequentially enhanced was 96.5%, AZD1222 sequentially enhanced was 93.2% compared with unvaccinated subjects. In terms of adjusted vaccine effectiveness in preventing COVID-19-related hospitalization, ICU and death, Sinovac inactivated vaccine homologous enhancement was 86.3%, 92.2% and 86.7%, respectively, and BNT162b2 sequential enhancement was 96.1%, 96.2% and 96.8%. The sequential enhancement of AZD1222 was 97.7%, 98.9% and 98.1% (Tawinprai *et al*., 2022; Assawasaksakul *et al*., 2022; Suah *et al*., 2022; Hassine, 2022).

However, among the 210 asymptomatic and mild patients included in this study, the number of patients who received two doses of vaccine was the same as the number of patients who received three doses of vaccine, which may be limited by the sample size and the statistical results may be biased.

In this study, we did not focus on the type of vaccine, only on the number of vaccinations. The average number of negative turning days in unvaccinated patients (14.49 days) was significantly longer than that in vaccinated patients (11.05 days). However, there was no significant difference in the number of days to negative nucleic acid in these asymptomatic or mild patients after vaccination. In other words, vaccination does not reduce the rate of infection, but it helps the infection turn negative more quickly.

There was also no significant difference in the number of days to negative between asymptomatic and mild patients who received the vaccine, regardless of how many times. For mild and asymptomatic patients, the number of days of nucleic acid turning negative in patients with underlying diseases was significantly higher than that in patients without underlying diseases. However, the combination of several basic diseases has no obvious effect on the time of turning negative. The type and brand of vaccine administered also had no effect on the time to negative in vaccinated patients.

Analysis by the interval between the last vaccination and infection

The interval between vaccination and infection reflects to some extent how long the vaccine protects the body, but it is also related to how long the population receives the virus, especially how long after vaccination the protection declines. This study result shows that the number of patients vaccinated is more than 1 year at least, it has to do with national comprehensive promotion vaccination time less than a year, so the last vaccination itself is more than 1 year a relatively small number of patients, and may also be vaccinated against the last more than a year later the vaccine protection down, people infected with the gram si strain after may show is normal or heavy, it was not included in this study.

Among the patients who received the last vaccine less than one year, the longer the interval was, the higher the incidence rate was. The interval was less than 3 months in 19.5% of the patients, and more than half a year in 34.8% of the patients. It also means that the longer you get vaccinated, the more likely you are to catch the virus. However, there was no significant difference in the mean duration of disease between the three groups. Patients with an interval of less than 1 year had an average of 11.02 days of negative conversion, which was shorter than that of unvaccinated patients (14.49 days). However, there was no significant difference in the average duration of disease between patients with an interval of more than 1 year after vaccination and those without vaccination. This result again indicates that the protective efficacy of the vaccine decreases after 1 year of receiving the last vaccine.

Recently, a study published on MedrXiv by the University of Hong Kong, HKU Shenzhen Hospital (Gadrey *et al*., 2019; Wu *et al*., 2021), and Imperial College London analyzed the protection and immune response of the three-shot vaccine against BA.2. The new HKU study, which focused on the difference in prevention of breakthrough infection between two doses versus three doses, involved more than 7,200 civil servants in Hong Kong, of whom 82.7% (5,995) had received two doses and 14% (1,012) had received three doses. During the Omicron BA.2 outbreak, 29.3% of those vaccinated were infected, and the study found that three shots of the vaccine provided more effective protection, with a lower incidence of breakthrough infections. However, we have seen a large number of unvaccinated patients and patients with different doses of vaccine, and their time from the last vaccination to COVID-19 infection and the duration of disease are different. There are still some unanswered questions about vaccination. If the number of vaccinations and infection is related? Is there a correlation between the number of vaccinations and the time between the last vaccination and COVID-19 infection? Is there a correlation between the number of vaccinations and the length of the natural course of disease? Is the time between the last vaccination and COVID-19 infection related to the natural course of disease? Therefore, we tried to group these patients according to different doses of vaccine and the interval after vaccination, and compared the interval time from the last vaccination to COVID-19 infection and the duration of disease. We suspect that patients who receive the third vaccine will heal faster, and the shorter the

interval between the last vaccine and COVID-19 infection, the lower the incidence and the shorter the cure time.

Limitations

This study did not consider differences between vaccines, which may potentially have an impact on the treatment of the disease. Therefore, only between-group comparisons were performed in this study to offset the susceptibility bias caused by vaccine characteristics.

Limited by the sample size, there may be some sample bias, and more samples need to be included in the later stage for further analysis. This study did not analyze the common and severe patients, which may reduce the proportion of unvaccinated patients to a certain extent.

There may be a time difference between the actual time of infection and the time of positive nucleic acid test, and there is a certain measurement bias. Therefore, DLVI may be larger than the actual results, but this study mainly compares the differences between groups, and this measurement bias will not affect the evaluation of the study results.

CONCLUSION

Asymptomatic and mild disease is more likely to occur in young and middle-aged patients with normal weight or overweight. Vaccination does not completely prevent infection with the Omicron strain, but it can reduce the rate of infection, and even if infected, patients usually show no symptoms or mild symptoms. For mild and asymptomatic patients, the number of days of nucleic acid turning negative in patients with underlying diseases was significantly longer than that in patients without underlying diseases, but it was not related to several underlying diseases.

No matter how many doses of the vaccine have been administered, and no matter what type of vaccine has been administered, the natural course of the disease can be significantly shortened compared with the unvaccinated.

The infection rate of the novel coronavirus was the lowest within 3 months after vaccination. When the interval after the last vaccination was more than one year, the natural course of disease was prolonged, which was not significantly different from that of unvaccinated subjects.

The mechanism of viral infection is complex. Immunization can effectively improve the ability to prevent disease and avoid infection. Further research is needed on various issues related to COVID-19 vaccination

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IRB approval and ethical statement

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee of Ruijin Hospital, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the individual participants included in the study.

Statement of conflict of interest

The authors have declared no conflict of interest.

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