Research Article

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Clinical and immune response characteristics among vaccinated persons infected with SARS-CoV-2 delta variant: a retrospective study

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Abstract: Objective: This study aimed to observe the clinical and immune response characteristics of vaccinated persons infected with the delta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Yangzhou, China. Methods: We extracted the medical data of 129 patients with delta-variant infection who were admitted to Northern Jiangsu People's Hospital (Yangzhou, China) between August and September, 2021. The patients were grouped according to the number of vaccine doses received into an unvaccinated group: a one-dose group and a two-dose group. The vaccine used was SARS-CoV-2-inactivated vaccine developed by Sinovac. We retrospectively analyzed the patients' epidemiological, clinical, laboratory, and imaging data. Results: Almost all patients with delta-variant infection in Yangzhou were elderly, and patients with severe/critical illness were over 70 years of age. The rates of severe/critical illness ($P=0.006$), fever ($P=0.025$), and dyspnea ($P=0.045$) were lower in the two-dose group than in the unvaccinated group. Compared to the unvaccinated group, the two-dose group showed significantly higher lymphocyte counts and significantly lower levels of C-reactive protein (CRP), interleukin-6 (IL-6), and D-dimer during hospitalization and a significantly higher positive rate of immunoglobulin G (IgG) antibodies at admission (all $P<0.05$). The cumulative probabilities of hospital discharge and negative virus conversion were also higher in the two-dose group than in the unvaccinated group ($P<0.05$). Conclusions: Two doses of the SARS-CoV-2-inactivated vaccine were highly effective at limiting symptomatic disease and reducing immune response, while a single dose did not seem to be effective.

Key words: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Delta variant; Vaccine; Hospitalization; Immune response

1 Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Shi HS et al., 2020), has spread to more than 210 countries and territories (Huang et al., 2020; Haileamlak, 2021). As of Nov. 8, 2021,

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the number of people infected worldwide exceeded 250 million and the number of deaths exceeded 5 million. SARS-CoV-2 is an RNA virus with a relatively stable genome, mainly due to its proofreading enzyme (Wu and McGoogan, 2020). However, the COVID-19 pandemic has led to large-scale replication events on a global scale, and thus far, approximately 800 SARS-CoV-2 subtypes have been reported (Lu et al., 2021). The World Health Organization (WHO) has designated the following five variants of SARS-CoV-2 as variants of concern: alpha, beta, gamma, delta, and omicron. These correspond to the Phylogenetic Assignment of Named Global Outbreak (PANGO) lineage designations B.1.1.7, B.1.351, P.1,

B.1.617.2, and B.1.1.529, respectively (Parums, 2021). During the second wave of global SARS-CoV-2 infection outbreak, the increase in SARS-CoV-2 cases was attributed to the high transmission potential of the delta variant, which was rapidly replacing the alpha variant as the dominant variant in most countries (Gupta et al., 2021). The delta variant was first discovered in India in December 2020, and the available evidence suggests that this variant is associated with increased transmissibility, secondary attack rate, hospitalization risk, and immune escape (Dhar et al., 2021; Novelli et al., 2021).

In August 2021, there was an outbreak of the delta variant in Yangzhou, China. This outbreak occurred in an urban area and involved the largest number of patients infected with the delta variant in China thus far. The accepted opinion is that the activities of the first few confirmed patients, such as attending crowded public chess and card rooms, led to the rapid spread of the delta-variant virus in China. To date, this outbreak has resulted in more than 500 cases, and most of the patients are over 50 years of age, which has made treatment challenging. In view of the global spread of delta-variant infection, research on the nature, treatment, and especially prevention of this infection is urgently required.

Vaccines have been found to be effective in preventing the symptoms of SARS-CoV-2 infection, and their safety and efficacy have been confirmed through clinical trials (Baden et al., 2021; Skowronski and de Serres, 2021; Voysey et al., 2021). Vaccines were found to be almost as effective against the alpha variant as against the previous virus strains and were found to provide additional protection in COVID-19 patients with severe/critical illness (Abu-Raddad et al., 2021; Hall et al., 2021; Jalkanen et al., 2021). A trial of the NVX-CoV2373 vaccine (Novavax) showed an effectiveness of 51.0% against the beta variant (Shinde et al., 2021). Serum samples from patients infected with the P.1 (gamma) variant and treated with the BNT162b2 vaccine (Pfizer BioNTech) were found to show high levels of neutralizing antibodies (Liu et al., 2021). However, limited data are available on the clinical effectiveness of SARS-CoV-2 vaccines against the delta variant. In this study, we aimed to evaluate the effectiveness of the SARS-CoV-2 vaccine against infections caused by the delta variant.

2 Patients and methods

2.1 Participants and study design

This single-center, retrospective study involved a group of patients with SARS-CoV-2 delta-variant infection who were treated at Northern Jiangsu People's Hospital, Yangzhou, China. The diagnosis of SARS-CoV-2 delta-variant infection was confirmed using real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR) assays of nasopharyngeal and oropharyngeal swabs, followed by sequence analysis. Details of the laboratory confirmation protocol for the delta variant have been described previously (Ghosh et al., 2021). The diagnosis of SARS-CoV-2 delta infection complied with WHO guidelines (National Health Commission of the People's Republic of China, 2020). In this retrospective study, we categorized patients infected with SARS-CoV-2 delta variant according to their vaccination status into an unvaccinated group, a one-dose group, and a two-dose group. We explored the effects of vaccination status on the patients' clinical symptoms, laboratory indicators, computed tomography (CT) findings, length of hospital stay, and time until negative conversion of SARS-CoV-2 delta-variant virus. The SARS-CoV-2-inactivated vaccine administered to the studied patients was made by Sinovac in Beijing, China.

2.2 Data collection

We queried our electronic medical record database to search for all patients with laboratory-confirmed SARS-CoV-2 delta-variant infection who had been discharged from our hospital on or before Sept. 15, 2021. We recorded the initial symptoms of the patients at admission to our hospital as well as the admission history and physical notes. Then, we collected data on medical history and any chronic diseases via medical records and medical history reviews.

Fever was defined as a forehead temperature of >38 °C, and hypoxemia was defined as a pulse oximetry reading of <90% from a finger oximeter. Hypertension was defined as systolic blood pressure of >140 mmHg and diastolic blood pressure of >90 mmHg; tachycardia was defined as heart rate of >100 beats/min. All laboratory values on the day of admission and during hospitalization were collected from the electronic medical record database. Laboratory values assessed in the study included white blood cell,

lymphocyte, and platelet counts. Blood chemistry profiles included levels of liver- and renal-function markers, C-reactive protein (CRP), interleukin-6 (IL-6), creatine kinase, creatine kinase-MB, and D-dimer. Details on nucleic acid test results, chest CT findings, and treatment methods were also extracted. Patients were deemed to have abnormal chest CT findings if this was mentioned in the report from the radiologist. All the data were entered into a computer database and cross-checked twice to ensure their accuracy.

2.3 Study outcomes

The primary composite endpoint was discharged from the hospital. According to the Chinese National Health Commission's SARS-CoV-2 treatment criteria, patients must meet the following three conditions for discharge: (1) body temperature returned to normal for >3 d and respiratory symptom improvement; (2) improvement of lung involvement demonstrated by chest CT; and (3) two consecutive negative qRT-PCR tests, with a sampling interval of >1 d. The secondary endpoint was a SARS-CoV-2 delta-variant virus test turning negative (seroconversion). Based on the National Health Commission's SARS-CoV-2 diagnostic criteria, negative virus conversion was defined as two consecutive negative qRT-PCR tests, with a sampling interval of >1 d (cycle threshold (C_T) value of <40 was defined as a SARS-CoV-2 virus-positive result).

2.4 Statistical analysis

Continuous data were presented as means and standard deviations (SDs); categorical data were presented as numbers and percentages, and missing data were not imputed. Our objective was to report the impact of vaccination on the epidemiological and clinical characteristics and outcomes of patients infected with SARS-CoV-2 delta variant. All data from the three study groups were verified for normality and homogeneity of variance using the Kolmogorov-Smirnov and Brown-Forsythe tests before analysis; then, one-way analysis of variance (ANOVA) followed by the Tukey's post-hoc test was performed for each group. The log-rank method was applied to estimate the change in hospital discharge rates and the probabilities of negative conversion of SARS-CoV-2 delta-variant virus tests. The proportional hazard Cox regression model was used to identify potential factors associated with discharge and negative virus conversion.

Hazards ratios (HRs) were calculated with 95% confidence intervals (CIs). Differences were considered statistically significant if $P<0.05$. All statistical analyses were performed using SPSS v19.0 (IBM, Beijing, China) and GraphPad Prism v7.0 software (GraphPad, San Diego, USA).

3 Results

3.1 Clinical presentation and epidemiological characteristics

As of Sept. 15, 2021, a total of 485 people had been infected with the delta virus in Yangzhou, China and no deaths had been reported. In this study, we retrospectively analyzed the chart data of the 129 patients who were diagnosed with SARS-CoV-2 delta-variant infection between Aug. 4, 2021 and Sept. 15, 2021 in Northern Jiangsu People's Hospital, Yangzhou, China (Fig. 1). The demographic and baseline characteristics of these 129 patients are summarized in Table 1, which shows the comparison between unvaccinated patients and patients who received one or two vaccine doses. Of the 129 patients, 63 were men and 66 were women. The average age was (60±15) years. The body mass index of all patients was within the normal range. The most common comorbidities were hypertension (60, 46.5%), diabetes (17, 13.2%), and coronary heart disease (10, 7.8%). The most common symptoms were cough (68, 52.7%), fever (35, 27.1%), sore throat (24, 18.6%), fatigue (22, 17.1%), and sputum production (17, 13.2%). Other symptoms such as difficulty breathing (8, 6.2%), headache (3, 2.3%),
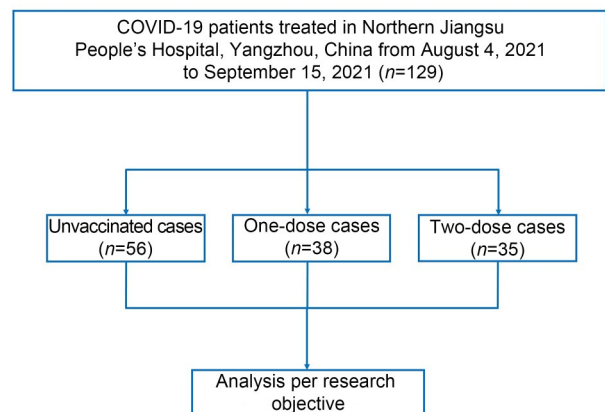

Fig. 1 Patients and flow chart. COVID-19: coronavirus disease 2019.

myalgia (4, 3.1%), diarrhea (6, 4.7%), anosmia (6, 4.7%), and loss of appetite (4, 3.1%) were less common. Age, gender, and complications did not significantly differ between unvaccinated patients and those who had received one or two doses of the vaccine. The incidence rates of fever (11.4% vs. 32.1%, P=0.025, χ^2 test), difficulty breathing (0% vs. 9.4%, P=0.045, χ^2 test), and severe/critical illness (2.4% vs. 25.0%, P=0.006, χ^2 test) were significantly lower in patients who received two vaccine doses than in unvaccinated patients (Table 1).

All patients with severe/critical illness were elderly (>70 years), including 14 unvaccinated patients, four patients who had received one vaccine dose, and one patient who had received two vaccine doses. We conducted a detailed dynamic evaluation of the clinical evolution of these 19 patients, and found that three patients had abnormal chest CT findings before diagnosis, with patchy shadow as the main CT manifestation. In all 19 of these patients, chest CT abnormality progressed through three stages: patchy shadow occurrence, patchy shadow progression, and patchy shadow absorption. For most patients, the nucleic acid test results during hospitalization underwent dynamic conversion between positive and negative, and ultimately stayed negative (Fig. S1). Analysis of all 129 SARS-CoV-2 delta variant-infected patients revealed similar probability density distributions of the time intervals from symptom onset to admission, symptom onset to diagnosis, and admission to diagnosis among unvaccinated patients and those with one or two vaccine doses (Figs. 2a–2c). The mean time

Table 1 Demographics and baseline characteristics of vaccinated and unvaccinated patients with SARS-CoV-2 delta-variant infection

Characteristics	Entire cohort (n=129)	Unvaccinated (n=56)	Vaccinated (n=73)			
			One-dose (n=38)	P value (one-dose vs. unvaccinated)	Two-dose (n=35)	P value (two-dose vs. unvaccinated)
Age (years)	60±15	60±18	60±16	0.802	60±6	0.490
Sex						
Male	63 (48.8%)	27 (48.2%)	22 (57.9%)	0.357	14 (40.0%)	0.444
Female	66 (51.2%)	29 (51.8%)	16 (42.1%)		21 (60.0%)	
Body mass index (kg/m²)	24.2±3.5	24.5±3.6	23.9±3.3	0.380	24.2±3.6	0.408
Comorbidities						
Hypertension	60 (46.5%)	30 (53.6%)	18 (47.4%)	0.555	12 (34.3%)	0.073
Hyperlipidemia	2 (1.6%)	1 (1.8%)	0 (0%)	0.408	1 (2.9%)	0.735
Diabetes	17 (13.2%)	11 (19.6%)	4 (10.5%)	0.236	2 (5.7%)	0.065
Chronic obstructive pulmonary disease	2 (1.6%)	0 (0%)	2 (5.3%)	0.083	0 (0%)	1.000
Coronary heart disease	10 (7.8%)	6 (10.7%)	2 (5.3%)	0.353	2 (5.7%)	0.413
Cerebrovascular disease	3 (2.3%)	3 (5.4%)	0 (0%)	0.147	0 (0%)	0.164
Liver disease	1 (0.8%)	1 (1.8%)	0 (0%)	0.408	0 (0%)	0.427
Renal disease	2 (1.6%)	1 (1.8%)	1 (2.6%)	0.780	0 (0%)	0.427
Malignancy	5 (3.9%)	1 (1.8%)	2 (5.3%)	0.347	2 (5.7%)	0.307
Symptoms/signs						
Cough	68 (52.7%)	32 (57.1%)	18 (47.4%)	0.351	18 (51.4%)	0.594
Fever	35 (27.1%)	18 (32.1%)	13 (34.2%)	0.834	4 (11.4%)	**0.025**
Difficulty breathing	8 (6.2%)	6 (9.4%)	2 (5.3%)	0.353	0 (0%)	**0.045**
Fatigue	22 (17.1%)	13 (23.2%)	6 (15.8%)	0.379	3 (8.6%)	0.074
Sputum production	17 (13.2%)	6 (10.7%)	8 (21.1%)	0.167	3 (8.6%)	0.739
Sore throat	24 (18.6%)	10 (17.9%)	5 (13.2%)	0.542	9 (25.7%)	0.370
Headache	3 (2.3%)	0 (0%)	2 (5.3%)	0.083	1 (2.9%)	0.203
Myalgia	4 (3.1%)	3 (5.4%)	1 (2.6%)	0.521	0 (0%)	0.164
Diarrhea	6 (4.7%)	4 (7.1%)	0 (0%)	0.092	2 (5.7%)	0.789
Anosmia	6 (4.7%)	2 (3.5%)	3 (7.9%)	0.359	1 (2.9%)	0.853
Loss of appetite	4 (3.1%)	1 (1.2%)	2 (5.3%)	0.347	1 (2.9%)	0.735
Severity						
Mild/moderate	110 (85.3%)	42 (75.0%)	34 (89.5%)	0.080	34 (97.6%)	**0.006**
Severe/critical	19 (14.7%)	14 (25.0%)	4 (10.5%)		1 (2.4%)	

Data are expressed as mean±SD or number (percentage). *P* values of <0.05 are in bold. SD: standard deviation; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

intervals from symptom onset to admission, symptom onset to diagnosis, and admission to diagnosis were also similar in the unvaccinated, one-dose, and two-dose groups (Figs. 2d–2f).

3.2 Laboratory findings

The laboratory findings for all patients are shown in Table 2. The total white blood cell count did not differ between the unvaccinated ($(5.59\pm2.13)\times10^9$ L^{-1}) and vaccinated groups (one-dose group: $(5.89\pm2.45)\times10^9$ L^{-1}, $P=0.569$; two-dose group: $(6.39\pm2.27)\times10^9$ L^{-1}, $P=0.273$). Similarly, the platelet count did not differ between the unvaccinated group and one-dose or two-dose group (all $P>0.05$). However, the lymphocyte count was significantly higher in the two-dose group than in the unvaccinated group ($(1.15\pm0.41)\times10^9$ L^{-1} vs. $(0.88\pm0.40)\times10^9$ L^{-1}, $P=0.010$, one-way ANOVA). The levels of CRP ((14.39 ± 15.61) mg/L vs. (32.41 ± 40.16) mg/L, $P=0.043$, one-way ANOVA) and IL-6 ((16.77 ± 13.43) pg/mL vs. (31.23 ± 34.21) pg/mL, $P=0.048$, one-way ANOVA) were significantly lower in the two-dose group than in the unvaccinated group. The D-dimer level at admission was significantly elevated in the unvaccinated group and almost normal in the two-dose group ((0.37 ± 0.21) mg/L vs. (1.26 ± 3.58) mg/L, $P=0.040$, one-way ANOVA). No significant differences among the three study groups were found in any of the other laboratory indices tested. Patients with SARS-CoV-2 delta-variant infection have been reported to have lymphocytopenia and elevated CRP, IL-6, and D-dimer levels (Zhang et al., 2020). Thus, the above changes in the 129 patients at admission are consistent with previous reports. Importantly, we found that completion of two doses of the vaccine limited the decrease in lymphocyte count, reduced the inflammatory response, and lowered the D-dimer level in infected patients. These findings suggest that completion of vaccination may limit the clinical progression of SARS-CoV-2 delta-variant infection.

Taking the above results into consideration, we further analyzed the lymphocyte count, as well as CRP, IL-6, and D-dimer levels, at 7 and 14 d after admission. At both time points, lymphocyte counts were significantly higher in the two-dose group than in the unvaccinated group (Day 7, $(1.36\pm0.39)\times10^9$ L^{-1} vs. $(1.11\pm0.40)\times10^9$ L^{-1}, $P=0.033$; Day 14, $(1.85\pm0.58)\times10^9$ L^{-1} vs. $(1.42\pm0.42)\times10^9$ L^{-1}, $P=0.002$; one-way ANOVA; Figs. 3a and 3e). D-Dimer levels were significantly lower in the two-dose group than in the unvaccinated group (Day 7, (0.43 ± 0.27) mg/L vs. (1.10 ± 0.82) mg/L, $P<0.001$; Day 14, (0.47 ± 0.32) mg/L vs. (0.85 ± 0.62) mg/L, $P=0.025$; one-way ANOVA; Figs. 3d and 3h). Similarly, the CRP and IL-6 levels were lower in the two-dose group than in the unvaccinated group
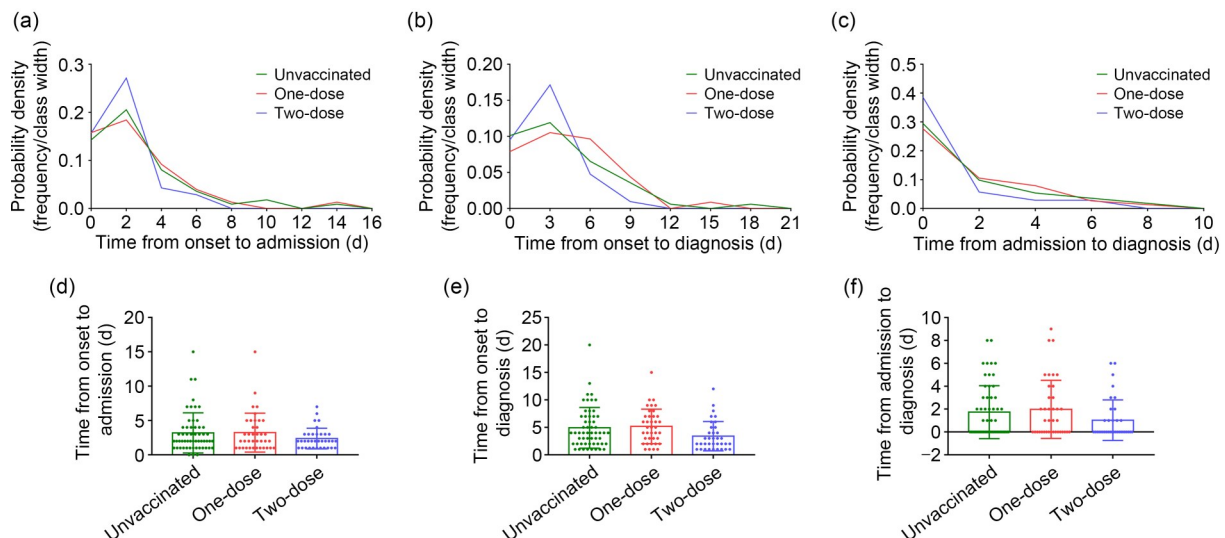

Fig. 2 Distribution of time intervals from onset to admission, onset to diagnosis, and admission to diagnosis. (a–c) Estimated distributions of the time intervals from onset to admission (a), onset to diagnosis (b), and admission to diagnosis (c) stratified by the number of vaccine doses. (d–f) Time from onset to admission (d), onset to diagnosis (e), and admission to diagnosis (f) in the unvaccinated, one-dose, and two-dose groups. Data are expressed as mean±SD. One-way ANOVA followed by post-hoc Tukey's test: $F_{(2, 126)}=1.96$ (d), $F_{(2, 126)}=1.04$ (e), $F_{(2, 126)}=1.75$ (f). Unvaccinated group, $n=56$; one-dose group, $n=38$; and two-dose group, $n=35$. SD: standard deviation; ANOVA: analysis of variance.

Table 2 Comparison of baseline laboratory test results between vaccinated and unvaccinated patients with SARS-CoV-2 delta-variant infection

Laboratory test	Normal range	Entire cohort (n=129)[*]	Unvaccinated (n=56)[*]	Vaccinated (n=73)			
				One-dose (n=38)[*]	P value (one-dose vs. unvaccinated)	Two-dose (n=35)[*]	P value (two-dose vs. unvaccinated)
White blood cell count (×10^9 L^{-1})	4.00–10.00	5.88±2.22	5.59±2.13	5.89±2.45	0.569	6.39±2.27	0.273
Lymphocytes (×10^9 L^{-1})	1.20–4.00	1.10±0.51	0.88±0.40	1.00±0.45	0.237	1.15±0.41	**0.010**
Platelets (×10^9 L^{-1})	115.00–350.00	167.83±60.94	152.93±53.70	162.55±65.74	0.427	183.29±53.59	0.057
Total bilirubin (μmol/L)	5.10–19.00	10.67±5.97	11.03±5.48	11.49±7.82	0.708	9.09±3.90	0.247
LDH (U/L)	109.00–245.00	234.74±92.44	239.66±90.67	232.03±75.52	0.947	229.83±112.22	0.947
Alanine aminotransferase (U/L)	5.00–35.00	27.41±24.45	30.69±22.39	23.88±17.72	0.161	22.25±11.46	0.108
Creatinine (μmol/L)	44.00–106.00	78.13±27.28	80.71±27.71	77.61±23.69	0.832	74.57±30.42	0.657
CRP (mg/L)	0–8.00	26.09±34.90	32.41±40.16	27.56±37.41	0.503	14.39±15.61	**0.043**
IL-6 (pg/mL)	0.10–2.90	26.45±28.18	31.23±34.21	25.83±26.13	0.354	16.77±13.43	**0.048**
CK (U/L)	26.00–140.00	231.05±835.73	173.78±198.11	179.24±269.49	0.904	137.97±168.13	0.798
CK-MB (ng/mL)	0.10–500.00	19.40±27.12	22.57±32.98	20.19±29.39	0.677	13.46±3.97	0.321
D-Dimer (mg/L)	0–0.50	0.95±2.50	1.26±3.58	0.71±0.73	0.808	0.37±0.21	**0.040**

[*] Data are expressed as mean±SD. P values of <0.05 are in bold. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; LDH: lactate dehydrogenase; CK: creatine kinase; CRP: C-reactive protein; IL-6: interleukin-6; SD: standard deviation.
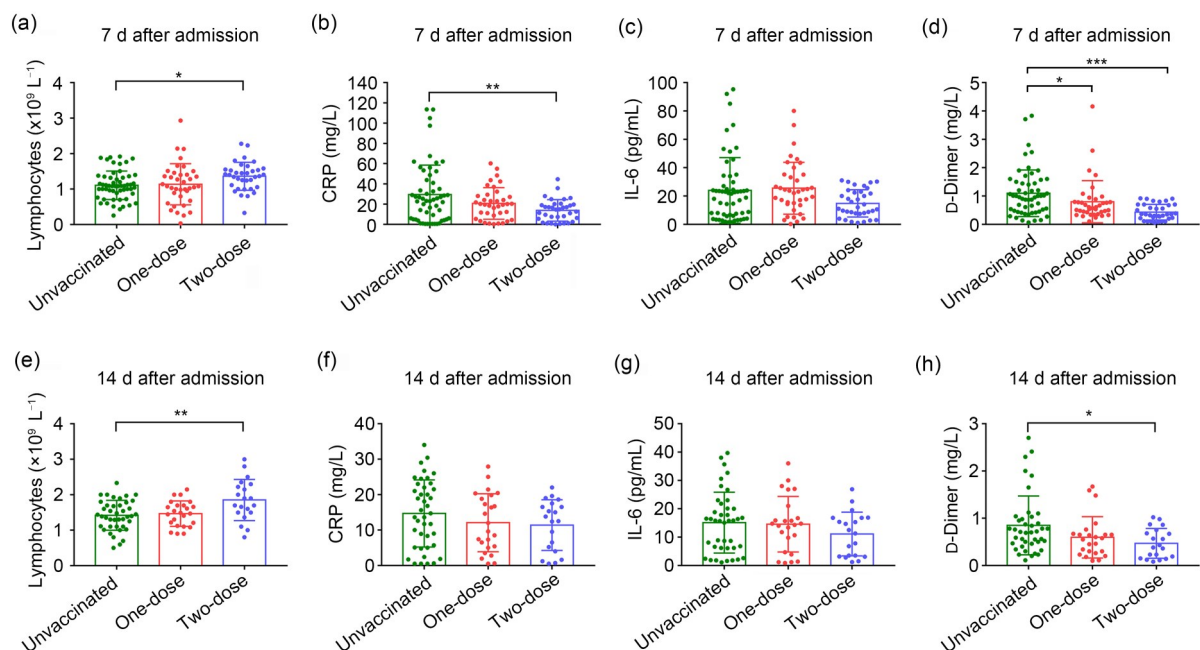

Fig. 3 Lymphocyte count and CRP, IL-6, and D-dimer levels in the unvaccinated, one-dose, and two-dose groups at 7 and 14 d after admission. (a) Lymphocyte counts on Day 7. Compared with the unvaccinated group, the two-dose group had a higher lymphocyte count. (b–d) Levels of CRP (b), IL-6 (c), and D-dimer (d) on Day 7. (e) Lymphocyte count remained higher in the two-dose group than in the unvaccinated group on Day 14. (f–h) Levels of CRP (f), IL-6 (g), and D-dimer (h) on Day 14. Data are expressed as mean±SD. [*] P<0.05, [**] P<0.01, and [***] P<0.001. One-way ANOVA followed by post-hoc Tukey's test: $F_{(2, 126)}$=2.40 (a), $F_{(2, 126)}$=8.34 (b), $F_{(2, 126)}$=8.34 (c), $F_{(2, 126)}$=5.06 (d), $F_{(2, 82)}$=2.42 (e), $F_{(2, 82)}$=1.55 (f), $F_{(2, 82)}$=0.73 (g), and $F_{(2, 82)}$=1.25 (h). At 7 d after admission: unvaccinated group, n=56; one-dose group, n=38; and two-dose group, n=35. At 14 d after admission: unvaccinated group, n=41; one-dose group, n=24; and two-dose group, n=20. CRP: C-reactive protein; IL-6: interleukin-6; SD: standard deviation; ANOVA: analysis of variance.

(Figs. 3b, 3c, 3f, and 3g), indicating a reduced inflammatory response in patients who contracted SARS-CoV-2 delta-variant infection after completion of vaccination. Although the CRP, IL-6, and D-dimer levels seemed to be correlated with disease severity, this result should be interpreted with caution. Therefore, we further investigated the correlations between levels of CRP, IL-6 and D-dimer (Fig. S2) and found that CRP and IL-6 levels were highly positively correlated with each other (r=0.51), while CRP (r=0.23) and IL-6 levels (r=0.29) were less strongly correlated with D-dimer level.

3.3 Antibody levels

To explore the changes in immune response after SARS-CoV-2 delta-variant infection, we analyzed the levels of immunoglobulin M (IgM) and IgG antibodies at different time points after admission. On the day of admission (Day 0), IgM antibodies were detected in 19.6%, 23.8%, and 20.0% of patients in the unvaccinated, one-dose, and two-dose groups, respectively; the corresponding detection rates for IgG antibodies were 41.1%, 29.0%, and 65.7%. Consistent with our observations, previous studies have found that the positive rate of IgG antibodies is higher than that of IgM antibodies in patients with SARS-CoV-2 infection

(Long et al., 2020; Xu X et al., 2020). Positive rates of IgM and IgG antibodies increased significantly at 7 d after admission, especially in the two-dose group, and reached 100% at 14 d after admission (Fig. 4). Furthermore, IgG antibody levels were significantly higher in the two-dose group than in the unvaccinated group on Day 0 ((47.30±95.85) vs. (12.39±31.35), P=0.030, one-way ANOVA; Fig. 5). The dynamic changes in antibody levels on Days 0, 7, and 14 in the 19 patients with severe/critical illness are shown in Fig. S3. The above results indicate that completion of vaccination may induce earlier production of antibodies against the SARS-CoV-2 delta-variant virus.

3.4 Radiological findings

According to recent data, almost all patients with SARS-CoV-2 delta-variant infection exhibit characteristic CT findings during the course of the disease, such as different degrees of ground-glass opacities with or without the crazy-paving sign, multifocal organizing pneumonia, and architectural distortion in a peripheral distribution (Hu et al., 2020, Lei et al., 2020). Therefore, chest CT is currently used as an important complement to qRT-PCR tests in the diagnosis of SARS-CoV-2 delta-variant infection. We analyzed the chest CT changes in the three study groups. The
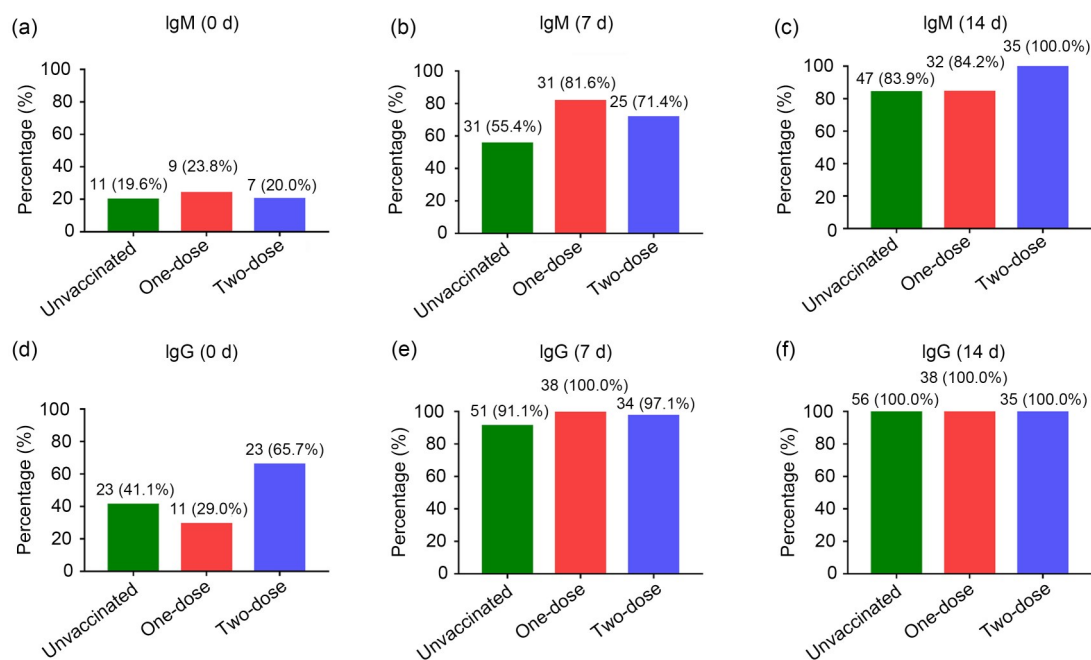

Fig. 4 Prevalences of immunoglobulin M (IgM) and IgG antibodies in the unvaccinated, one-dose, and two-dose groups after admission: (a–c) IgM antibodies at 0 (a), 7 (b), and 14 d (c) after admission; (d–f) IgG antibodies at 0 (d), 7 (e), and 14 d (f) after admission.
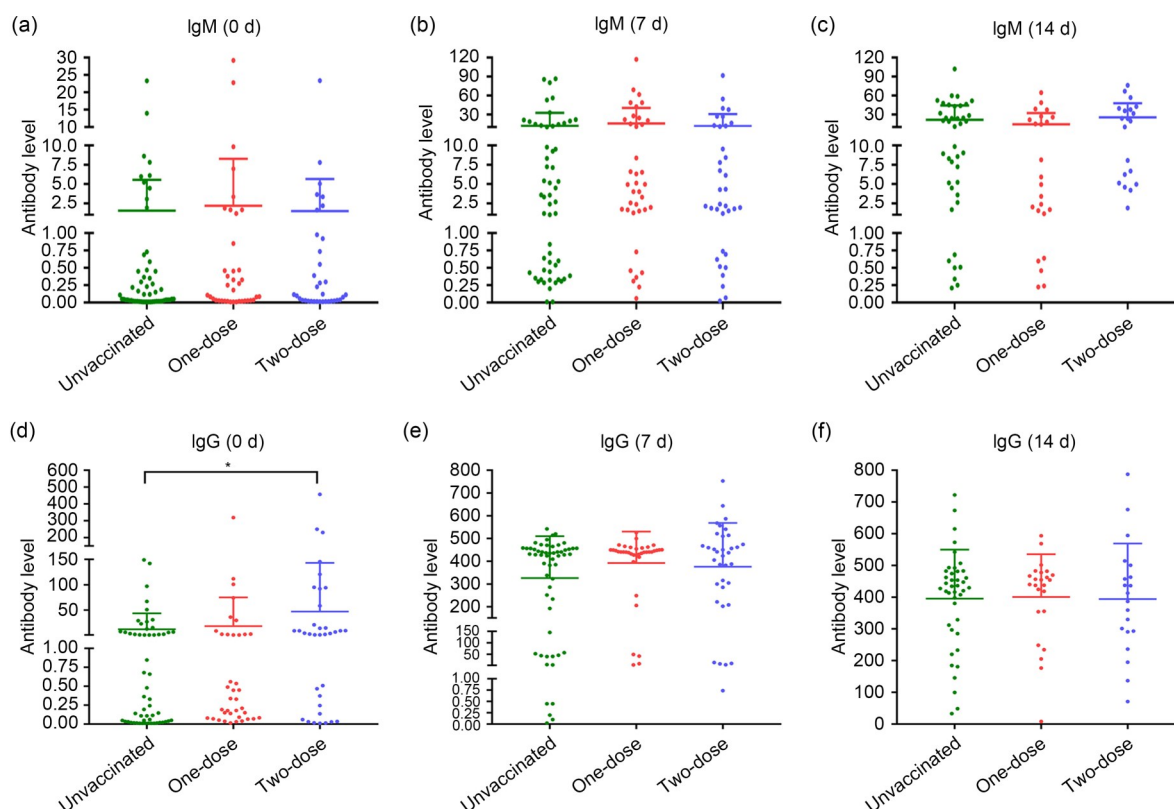
Fig. 5 Comparison of immunoglobulin M (IgM) and IgG antibody levels in the unvaccinated, one-dose, and two-dose groups after admission: (a–c) IgM levels at 0 (a), 7 (b), and 14 d (c) after admission; (d–f) IgG levels at 0 (d), 7 (e), and 14 d (f) after admission. Data are expressed as mean±SD. * $P<0.05$. One-way ANOVA followed by post-hoc Tukey's test: $F_{(2, 126)}=0.26$ (a), $F_{(2, 126)}=0.34$ (b), $F_{(2, 82)}=0.72$ (c), $F_{(2, 126)}=3.51$ (d), $F_{(2, 126)}=3.12$ (e), and $F_{(2, 82)}=0.90$ (f). At 0 and 7 d after admission: unvaccinated group, $n=56$; one-dose group, $n=38$; and two-dose group, $n=35$. At 14 d after admission: unvaccinated group, $n=41$; one-dose group, $n=24$; and two-dose group, $n=20$. SD: standard deviation; ANOVA: analysis of variance.

time interval from the onset of chest CT abnormalities to their progression was approximately 3 d in all three groups, and the probability density distributions of this interval were similar in all groups (Fig. 6a). The time interval from onset to complete absorption of chest CT abnormalities was approximately 15 d, and its probability density distribution was similar in the three groups (Figs. 6b and 6c).

3.5 Clinical outcomes

The primary composite endpoint was discharge from the hospital, and the secondary endpoint was a negative SARS-CoV-2 delta-variant virus test. According to the National Health Commission's SARS-CoV-2 diagnostic and treatment criteria (National Health Commission of the People's Republic of China and National Administration of Tranditional Chinese Medicine, 2022), a patient is considered to have turned

negative for the virus when two consecutive nucleic acid tests yield negative results. Once negative virus conversion occurs, doctors comprehensively evaluate the patients' condition to determine if they can be discharged from the hospital. In this study, we retrospectively analyzed the discharge rate and negative virus conversion rate in the three study groups.

By Sept. 15, 2021, all 129 patients had been discharged, and none had died. The discharge probabilities in the three groups are shown in Figs. 7a and 7b. According to the results of the log-rank (Mantel-Cox) test, the median discharge time was 15 d in the unvaccinated group, 14.5 d in the one-dose group, and 14 d in the two-dose group. The cumulative probability of hospital discharge was significantly higher ($P=$ 0.014, log-rank test; Fig. 7b) and the length of hospital stay was significantly lower ((14.3±3.4) d vs. (16.4±4.6) d, $P=0.038$, one-way ANOVA; Fig. S4a) in
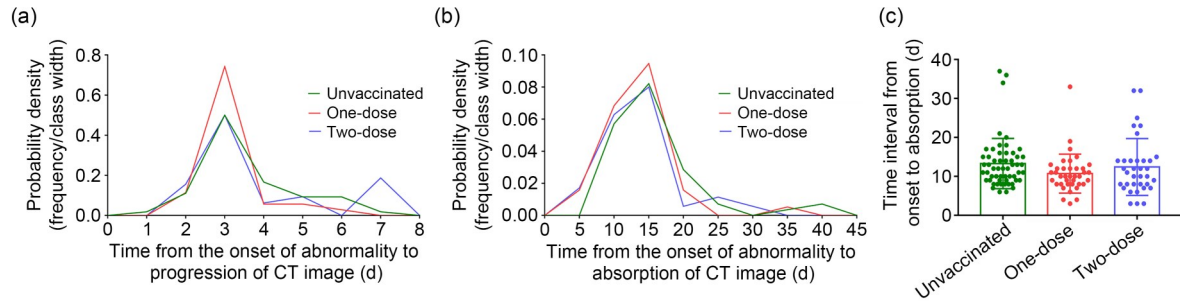
Fig. 6 Abnormal chest CT changes in the unvaccinated, one-dose, and two-dose groups. (a, b) Estimated distributions of time intervals from onset to progression (a) and onset to absorption (b) of chest CT abnormalities stratified by the number of vaccine doses. (c) Time interval from onset to absorption of CT abnormalities in the unvaccinated, one-dose, and two-dose groups. Data are expressed as mean±SD. One-way ANOVA followed by post-hoc Tukey's test: $F_{(2, 126)}$=1.76. Unvaccinated group, *n*=56; one-dose group, *n*=38; and two-dose group, *n*=35. CT: computed tomography; SD: standard deviation; ANOVA: analysis of variance.
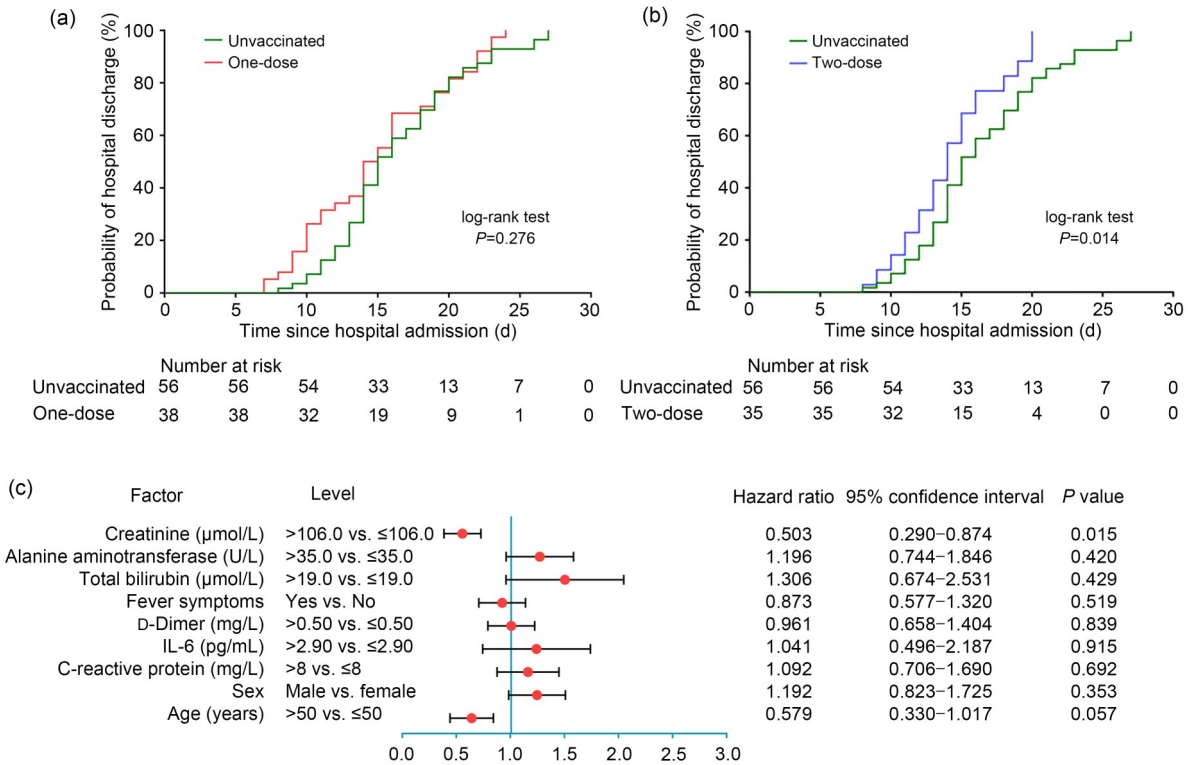

Fig. 7 Hospital discharge rates and factors associated with clinical outcomes in the unvaccinated, one-dose, and two-dose groups. (a, b) Probabilities of hospital discharge and length of hospitalization stratified by vaccine doses. (c) Results of proportional hazard Cox model. Hazard ratios and corresponding 95% confidence intervals are shown for the following factors: age, sex, fever, and levels of C-reactive protein, interleukin-6 (IL-6), D-dimer, total bilirubin, alanine aminotransferase, and creatinine.

the two-dose group than in the unvaccinated group. We used multivariable Cox regression analysis to investigate the associations of discharge rate with age, sex, fever, and levels of CRP, IL-6, D-dimer, total bilirubin, alanine aminotransferase, and creatinine. It was evident that an elevated creatinine level on admission

was an unfavorable factor for discharge (hazard ratio (HR)=0.503, 95% confidence interval (CI): 0.290–0.874, *P*=0.015; Fig. 7c).

The probabilities of negative conversion of the SARS-CoV-2 delta-variant virus in the three study groups are shown in Figs. 8a and 8b. According to the

results of the log-rank (Mantel-Cox) test, the median time until negative virus conversion was 12.5 d in the unvaccinated group, 13 d in the one-dose group, and 10 d in the two-dose group. The cumulative probability of a positive viral RNA test result (P=0.032, log-rank test; Fig. 8b) and the time until negative viral RNA conversion ((10.6 ± 4.2) d vs. (12.8 ± 4.9) d, P=0.039, one-way ANOVA; Fig. S4b) were significantly lower in the two-dose group than in the unvaccinated group. Multivariable Cox regression analysis was used to investigate associations of the negative virus conversion rate with age, sex, fever, and levels of CRP, IL-6, D-dimer, total bilirubin, alanine aminotransferase, and creatinine. We found no unfavorable factors for negative virus conversion rate (Fig. 8c). By observing the dynamic changes in viral RNA loads in the 19 patients with severe/critical illness, we found that many patients with SARS-CoV-2 delta-variant infection underwent dynamic virus transformation, which increased the difficulty of confirming negative virus conversion (Fig. S5).

3.6 Treatment measures

All patients were offered traditional Chinese medicine; 14 patients with severe/critical illness in the unvaccinated group were treated with neutralizing antibodies, and none of the patients were given empirical antiviral drugs, corticosteroids, thymosin, or other therapies. On the day of admission (Day 0), oxygen therapy was administered via nasal cannulas in 87 (67.4%) patients, nasal high-flow therapy in 7 (5.4%) patients, and non-invasive ventilation in 1 (0.8%) patient. No patient required endotracheal intubation on admission. On Day 7, the following methods were used for oxygen delivery: nasal cannula, 36 (27.9%) patients; nasal high-flow therapy, 7 (5.4%) patients; non-invasive ventilation, 3 (2.3%) patients; and endotracheal intubation, 2 (1.6%) patients. On Day 14, 26 (30.6%) patients used a nasal cannula, 6 (7.1%) patients received nasal high-flow therapy, 1 (1.2%) patient received non-invasive ventilation, and 2 (2.4%) patients required endotracheal intubation. The proportion of patients who did not require oxygen therapy
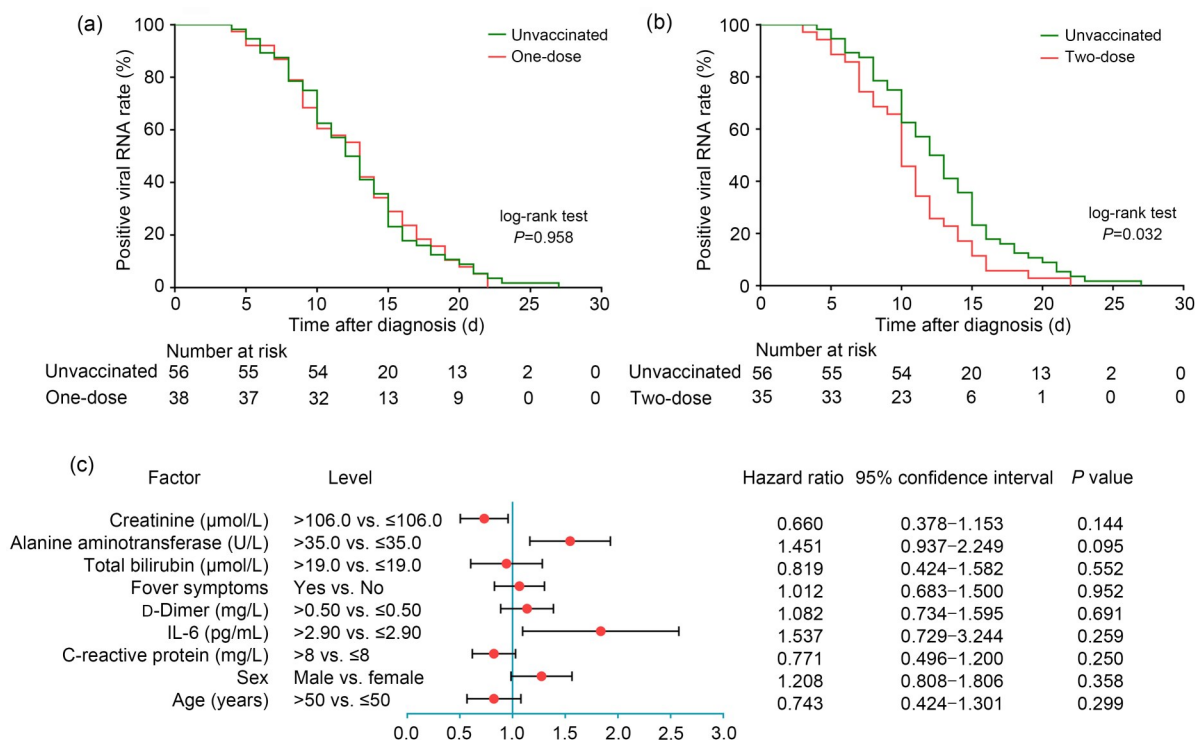

Fig. 8 Positive viral RNA rates and factors associated with negative virus conversion in the unvaccinated, one-dose, and two-dose groups. (a, b) Positive rate of viral RNA detection and time until negative virus conversion after diagnosis, stratified by vaccine doses. (c) Results of proportional hazard Cox model. Hazard ratios and corresponding 95% confidence intervals are shown for the following factors: age, sex, fever, and levels of C-reactive protein, interleukin-6 (IL-6), D-dimer, total bilirubin, alanine aminotransferase, and creatinine.

did not differ among the unvaccinated, one-dose, and two-dose groups on Day 0, 7, or 14; the selection of oxygen-delivery methods also did not differ among the three groups (Table 3).

4 Discussion

This retrospective study investigated the first outbreak of the delta variant in China. We enrolled a total of 129 patients with SARS-CoV-2 delta-variant infection who were admitted to our hospital for treatment. Our focus was on the impact of the SARS-CoV-2 vaccine on the immune response and clinical outcomes of patients infected with the delta variant. The principal findings of this study are threefold: (1) by analyzing the laboratory data of patients, we found that compared with unvaccinated patients, patients who completed two doses of vaccination showed higher lymphocyte counts and lower levels of CRP, IL-6, and D-dimer during hospitalization; (2) IgG levels were significantly higher in the two-dose group than in the unvaccinated group at admission, indicating that in patients who had completed vaccination, immune defenses were activated in the early stages of the infection; (3) Completion of two doses of the vaccine reduced the length of hospital stay and increased

the negative virus conversion rate of patients with delta-variant infection. Taken together, these findings suggested that the SARS-CoV-2 vaccine was effective against the delta variant in this Yangzhou outbreak, especially in patients who had completed two doses.

An epidemiological review showed that almost all patients with delta-variant infection in Yangzhou were elderly people, with an average age of 60 years, and all patients with severe/critical illness were over 70 years of age, which made treatment more challenging. The main reason for this is that the initial source of virus infection was frequent visits to chess and card rooms, which are public places where many older people gather. In addition, the elderly have less knowledge about the transmission routes of SARS-CoV-2 and poor personal protection practices, which led to the rapid spread of the delta variant. Therefore, training the elderly on SARS-CoV-2 transmission routes and personal protection will play an important role in the prevention and control of SARS-CoV-2 infections.

The delta variant consists of 41 different sublineages sharing additional T19R, del157/158, T478K, and D950N mutations in the Spike protein and the I82T mutation in M protein, as compared to B.1 (Baj et al., 2021). The SARS-CoV-2 Spike protein mutation of the delta variant is known to affect transmission and neutralization of the virus (Kemp et al., 2020). In

Table 3 Need for oxygen supplementation by means of non-invasive and invasive ventilation in vaccinated and unvaccinated patients with SARS-CoV-2 delta-variant infection

Time after admission (d)	Maximal need for oxygen	Entire cohort	Unvaccinated	Vaccinated			
				One-dose	*P* value (one-dose vs. unvaccinated)	Two-dose	*P* value (two-dose vs. unvaccinated)
0	No oxygen	34 (26.4%)	18 (32.1%)	6 (15.8%)	0.074	10 (28.6%)	0.720
	Nasal cannula	87 (67.4%)	33 (58.9%)	30 (78.9%)	0.521	24 (68.6%)	0.448
	Nasal high-flow therapy	7 (5.4%)	4 (7.1%)	2 (5.3%)		1 (2.9%)	
	Non-invasive ventilation	1 (0.8%)	1 (1.8%)	0 (0%)		0 (0%)	
	Endotracheal intubation	0 (0%)	0 (0%)	0 (0%)		0 (0%)	
7	No oxygen	81 (62.8%)	34 (60.7%)	24 (63.2%)	0.683	23 (65.7%)	0.620
	Nasal cannula	36 (27.9%)	14 (25.0%)	12 (31.6%)	0.288	10 (28.6%)	0.361
	Nasal high-flow therapy	7 (5.4%)	3 (5.4%)	2 (5.3%)		2 (5.7%)	
	Non-invasive ventilation	3 (2.3%)	3 (5.4%)	0 (0%)		0 (0%)	
	Endotracheal intubation	2 (1.6%)	2 (3.6%)	0 (0%)		0 (0%)	
14	No oxygen	50 (58.8%)	21 (51.2%)	15 (62.5%)	0.377	14 (70.0%)	0.164
	Nasal cannula	26 (30.6%)	13 (31.7%)	8 (33.3%)	0.547	5 (25.0%)	0.765
	Nasal high-flow therapy	6 (7.1%)	4 (9.8%)	1 (4.2%)		1 (5%)	
	Non-invasive ventilation	1 (1.2%)	1 (2.4%)	0 (0%)		0 (0%)	
	Endotracheal intubation	2 (2.4%)	2 (4.9%)	0 (0%)		0 (0%)	

At 0 and 7 d after admission: entire cohort, $n=129$; unvaccinated group, $n=56$; one-dose group, $n=38$; and two-dose group, $n=35$. At 14 d after admission: entire cohort, $n=85$; unvaccinated group, $n=41$; one-dose group, $n=24$; and two-dose group, $n=20$. Data are expressed as number (percentage). SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

addition, the secondary attack rate of the delta variant is higher than that of the alpha variant. At the time of writing, the delta variant was spreading rapidly around the world and had become the main variant in many countries, causing massive numbers of hospitalizations and deaths. According to our data, it took only 3 d, on average, from the onset of symptoms for patients to be diagnosed in the Yangzhou outbreak. Infection with the delta variant of SARS-CoV-2 caused changes in many biological indicators in the blood. By analyzing the laboratory data of the patients, we found that in the early stage of delta-variant infection, the peripheral lymphocyte count was decreased. Studies have confirmed that the main immune response to viral infection is a specific T-lymphocyte immune response (Beňová et al., 2020; Wan et al., 2020). The host's cellular immune response mostly produces a large number of CD8+ lymphocytes specific to the virus in approximately one week after the virus enters the human body (Wu et al., 2018). To determine why the lymphocyte count decreases in patients infected with the delta variant, we searched the literature. It has been reported that infection with SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, two viruses that are similar to SARS-CoV-2, also cause lymphocyte reduction (Liang et al., 2020). The mechanism of lymphopenia in COVID-19 patients is a matter of some debate. Both SARS-CoV and SARS-CoV-2 are known to infect host cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface (Lu et al., 2020; Xu XT et al., 2020). Immune cells, including T-lymphocytes, are negative for ACE2 receptors, which suggests that SARS-CoV-2 is unlikely to directly infect lymphocytes and cause their destruction (Hamming et al., 2004; Yan and Wu, 2021). Another prerequisite for SARS-CoV, SARS-CoV-2, and MERS-CoV to gain entry into host cells is the expression of transmembrane serine protease 2 (TMPRSS2), a cellular serine protease (Glowacka et al., 2011; Kleine-Weber et al., 2018; Hoffmann et al., 2020). It is unclear whether lymphocytes express TMPRSS2 or other similar proteases. Thus, the observed lymphopenia in COVID-19 patients is likely to be caused by the redistribution of leukocytes to other tissues due to the inflammatory response to the infection or by the apoptosis of lymphocytes triggered by the activation of the p53 signaling pathway (Xiong et al., 2020; Yan and Wu, 2021). Therefore, lymphocyte

reduction may be an important indicator of disease severity, and lymphocytopenia could be used as a reference index in the diagnosis of SARS-CoV-2 infections in the clinic (Huang et al., 2020).

Inflammatory response or cytokine storm also plays an important role in the progression of SARS-CoV-2 infection, and our findings confirm that delta-variant infection leads to increased levels of CRP and IL-6 (Li RF et al., 2020; Wang et al., 2020). Research has shown that levels of CRP and inflammatory cytokines may be related to and serve as an indicator of disease severity (Chen et al., 2020). Furthermore, infection-induced coagulation dysfunction and secondary hyperfibrinolysis have been found in severe cases of SARS-CoV-2 infection (Tang et al., 2020), and high levels of D-dimer at admission are associated with poor prognosis for SARS-CoV-2-infected patients (Wang et al., 2011). Therefore, we continuously monitored the changes in D-dimer levels after admission. We found that patients infected with the delta variant had high D-dimer levels at admission, which is consistent with previous reports (Wang et al., 2011; Tang et al., 2020). In addition, these patients had bilateral, subpleural, ground-glass opacities on chest CT images, which is consistent with recent radiological reports on SARS-CoV-2 (Kong and Agarwal, 2020; Pan et al., 2020; Shi Y et al., 2020). We also analyzed the progression of chest CT abnormalities from appearance to aggravation and ultimately absorption. Our results showed that in patients with SARS-CoV-2 delta-variant infection, chest CT abnormalities started to progress approximately 3 d after symptom onset and were completely absorbed by 15 d after symptom onset.

Studies have investigated the effectiveness of the SARS-CoV-2 vaccine against COVID-19, but few have investigated whether the vaccine is effective against delta-variant infection (Sultana et al., 2020; Malik et al., 2021). Upon comparing epidemiological data between unvaccinated patients and those with one or two vaccine doses, we found that the incidences of fever and difficulty breathing were significantly lower in patients who had completed two doses of vaccination than in those who were unvaccinated. Moreover, a high percentage of severe/critical cases occurred in the unvaccinated group. These findings suggested that the SARS-CoV-2 vaccine could reduce the incidence of severe symptoms after infection,

such as fever and breathing difficulty, and reduce the risk of patients developing severe/critical illness. In addition, it was clear that the completion of two vaccine doses limited SARS-CoV-2 infection-related lymphocytopenia, inflammation, and coagulation, which are all important indicators of the transformation of the infection into severe/critical disease.

It is generally believed that IgM antibodies provide the first line of defense against viral infection, and that production of IgG antibodies lags behind that of IgM antibodies, but provides long-term immunity and immune memory (Li ZT et al., 2020). Our observations showed that at admission, the total IgG level of anti-SARS-CoV-2 antibodies was already higher in the two-dose group than in the unvaccinated group. In our opinion, possible reasons for this are as follows: on the one hand, antibodies were generated after these patients completed two doses of vaccination, and a certain immune capacity was obtained; on the other hand, the patients in the two-dose group had mild symptoms, so they presented to the hospital later in the course of the disease, by which time some IgG antibodies had already been produced.

To further assess the impact of vaccination on the clinical outcomes of patients with delta-variant infection, we assessed the impact of vaccination on patient discharge rates and negative virus-conversion rates. We found that the cumulative probability of hospital discharge was higher in the two-dose group (log-rank test), and the length of hospital stay was significantly lower in the two-dose group than in the unvaccinated group. Predictors of hospital discharge among infected patients were identified using the Cox model. Creatinine levels of $>1\times10^6$ μmol/L were significantly associated with a lower likelihood of discharge. Studies have shown that acute kidney injury can occur in patients with critical SARS-CoV-2 infections (Gabarre et al., 2020; Hansrivijit et al., 2020), and patients with renal insufficiency have increased mortality (Mudatsir et al., 2020), which increases the length of hospital stay. It is important to understand which factors affect the condition of inpatients and their risks during hospitalization because we can use this knowledge to screen and identify high-risk patients at admission. Our study determined that the cumulative probability of positive viral RNA was lower in the two-dose group (log-rank test), and the time until negative viral RNA conversion was significantly lower in the two-dose group

than in the unvaccinated group. Thus, completion of two doses of vaccination had a positive effect on the outcomes of patients with SARS-CoV-2 infection.

Since most of the patients with delta-variant infection in Yangzhou had mild symptoms, symptomatic treatment, such as oxygen therapy, was administered, and hormone, plasma, or antiviral treatment was not used. Traditional Chinese medicine also played an important role, and all hospitalized patients were administered traditional Chinese medicine decoctions.

We acknowledge that our study has some limitations. First, the study included only 129 patients infected with the delta variant from a single hospital in Yangzhou. This limitation may have caused deviation of the epidemiological and clinical characteristics. Second, the retrospective study design may be a confounding factor. Although we performed multivariate analysis, residual bias and lack of adjustments for unmeasured confounding factors may still exist. Third, the time interval between vaccination and disease onset was not included in our admission information, so we could not analyze this factor or determine how it affected the changes in antibody levels in our patients. Fourth, although we found that vaccination status did not affect the timing of CT changes in our patients, we did not observe these changes over a prolonged period of time due to limited medical resources. However, the CT changes were not one of the main outcome measures of this study, and were used solely for the purpose of corroborating the clinical and laboratory findings. Finally, as the study was based on the experience of the delta variant outbreak in China, the results may not be fully applicable to future cases due to differences in race, vaccination rates, and treatments.

5 Conclusions

We retrospectively analyzed the cases of 129 patients who were treated for SARS-CoV-2 delta-variant infection in Northern Jiangsu People's Hospital, in order to explore the protective effect of the SARS-CoV-2 vaccine against the delta-variant infection. Overall, we found that two doses of the SARS-CoV-2 vaccine offered a high level of effectiveness against symptomatic disease and reduced the immune response, while one dose did not seem to be effective. Thus, our results support administering two doses of

the vaccine to populations vulnerable to the rapid spread of the delta variant.

Acknowledgments

Author contributions

Cunjin WANG, Yong LI, Yuchen PAN, and Luojing ZHOU contributed to data collection, analysis, interpretation, and writing of the manuscript. Xi ZHANG, Yan WEI, and Fang GUO contributed to figure preparation and manuscript editing. Yusheng SHU and Ju GAO contributed to the study concept and design, clinical and pathological analyses, study supervision, and critical revision of the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Cunjin WANG, Yong LI, Yuchen PAN, Luojing ZHOU, Xi ZHANG, Yan WEI, Fang GUO, Yusheng SHU, and Ju GAO declare that they have no conflict of interest.

This study was approved by the Research Ethics Committees of Northern Jiangsu People's Hospital (No. 2021ky284), and was performed in compliance with World Medical Association guidelines and the Helsinki Declaration of 1975, as revised in 2008 (5). The need for written informed consent was waived because this was a chart review, and the study protocol was approved under rapid review due to the urgent need to collect and report data. The data were collected and analyzed by three authors, who ensured the accuracy and integrity of the data and ensured that the data-collection process complied with the protocol.

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Supplementary information

Figs. S1–S5