Heliyon 8 (2022) e12594

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Clinical characteristics and severity of beta and delta variants of SARS-CoV-2 and the effect of vaccine on delta variants

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HIGHLIGHTS

- There were differences in viral shedding, IgG between the Delta and Beta VOC.
- The longer the vaccination period, the lower the content of IgG and IgM.
- Vaccines can reduce the severe illness rate of Delta VOC.
- Convalescent plasma therapy cannot have a better effect.

ARTICLE INFO

Keywords:
COVID-19
Delta variants
IgG
IgM
Virus shedding
Inactivated vaccines
Convalescent plasma

ABSTRACT

Background: The Delta variant of concern (VOC) is rapidly becoming the dominant strain globally. We report the clinical characteristics and severity of hospitalized patients infected with Delta and Beta VOCs during the local outbreak in Harbin, Heilongjiang Province, China, and the effect of vaccines on the Delta variant.

Methods: We collected a total of 735 COVID-19 patients from the First Affiliated Hospital of Harbin Medical University, including 96 cases infected with the Delta VOC and 639 cases infected with the Beta VOC. Demographic, clinical characteristic and laboratory findings were collected and compared.

Results: Differences in viral shedding, IgG and IgM levels, and the neutrophil-to-lymphocyte ratio were noted between the Delta and Beta VOCs ($p < 0.05$). Survival analysis of the two groups revealed longer viral shedding of the Delta VOC ($p < 0.05$). For the Delta VOC, the longer the vaccination period, the lower the IgG and IgM levels. IgM levels were higher in the convalescent plasma group, whereas lymphocyte counts were lower.

Conclusions: Delta VOC virus shedding was longer compared with Beta VOC shedding. Vaccination with inactivated vaccines can reduce the severe illness rate of the Delta VOC. IgG and IgM levels are reduced as the time period between the first and second vaccine doses increases.

1. Introduction

The coronavirus disease 2019 (COVID-19) outbreak occurred in December 2019 and was caused by the wild-type strain of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Currently, multiple SARS-CoV-2 variants have appeared worldwide (Harvey et al., 2021). Currently, four main lineages, including Alpha (B.1.1.7 strain), Beta (B.1.351 strain), Gamma (P.1 strain) and Delta (B.1.617.2 strain), have been identified by the World Health Organization (WHO) as variants of concern (VOCs). The Delta VOC was first discovered in India in October 2020 and quickly became the dominant strain in many countries (GISAID Initiative, 2021b) (https://www.gisaid.org/hcov19-variants/, accessed

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https://doi.org/10.1016/j.heliyon.2022.e12594
Received 24 April 2022; Received in revised form 14 October 2022; Accepted 15 December 2022

August 2021). At the end of October 2021, the SARS-CoV-2 Delta VOC accounted for greater than 90% of infections in most countries in the past 4 weeks (GISAID Initiative, 2021a) (https://www.gisaid.org/hcov19-variants/, accessed July 2021). Compared with wild-type strains, the transmission rate of the four SARS-CoV-2 VOCs has increased, and the transmission rate of the Delta VOC has increased by 97% (Campbell et al., 2021). However, the effect of the Delta VOC on disease severity and its difference compared with other SARS-CoV-2 strains need to be further studied.

The global prevalence and spread of COVID-19 has prompted the development of vaccines, including inactivated vaccines, recombinant protein vaccines, adenovirus vector vaccines, DNA vaccines and RNA vaccines. The vaccine efficacy (VE) of these vaccines against the wild-type strain is as high as 95% in clinical trials (Logunov et al., 2021; Palacios et al., 2020; Polack et al., 2020) However, with the spread of SARS-CoV-2 VOCs worldwide, potentially reductions in VE has also become a topic of concern. Compared with the wild-type strain, the Alpha VOC is associated with a higher hospitalization rate and mortality rate in the UK (Sander et al., 2021). The results of the third phase of the clinical trial showed that the VE of the Novavax vaccine against wild-type strains reached 95.6%, whereas the VE against the Alpha and Beta VOCs were 85.6% and 60%, respectively(Mahase, 2021). The VE of the ChAdOx1 nCoV-19 vaccine against the Beta VOC was 21.9% compared with 89.3% for the wild-type strain (Cook et al., 2019; Voysey et al., 2021) (Novavax, 2021) (https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates -893-efficacy-uk-phase-3, accessed January 2021). In another NVX-CoV2373 vaccine trial against Beta VOC, the VE was 49.4% (Mahase, 2021). These findings have confirmed the reduced VE of various vaccines against SARS-CoV-2 VOCs.

Two inactivated vaccines developed in China (the China National Biotec Group SARS-CoV-2 vaccine and the CoronaVac vaccine (Sinovac Biotech Ltd., China)) have been used to vaccinate individuals in mainland China. Animal experiments and phase 1 and 2 clinical trials have consistently shown a low incidence of adverse reactions (Gao et al., 2020; Wang et al., 2020; Xia et al., 2020; Zhang et al., 2021). COVID-19 outbreaks in Harbin, Heilongjiang Province in January and September 2021 were attributed to the Beta VOC and the Delta VOC, respectively. At the time of the COVID-19 outbreak in January 2021, the majority of residents of Heilongjiang Province had not yet been vaccinated. However, during the recent COVID-19 outbreak, most residents had already been vaccinated twice. A study showed robust effectiveness for both the BNT162b2 vaccine and mRNA-1273 vaccine in preventing Delta VOC hospitalization and death (Tang et al., 2021). Therefore, it is very important to understand the efficacy of the Chinese SARS-CoV-2 vaccine against the Delta VOC.

In this retrospective study, we compared the clinical characteristics and laboratory findings of patients infected with Beta and Delta VOCs with the aim of improving our understanding of virus variants and disease severity. We also analyzed the clinical characteristics of the Delta VOC after vaccination and the efficacy of convalescent plasma.

2. Methods

2.1. Study design and participants

A total of 735 COVID-19 patients from the COVID-19 treatment center of the First Affiliated Hospital of Harbin Medical University in Heilongjiang Province were included in this retrospective study. Ninety-six cases infected with the Delta VOC admitted from September 20, 2021 (the first officially confirmed case) to October 27, 2021 (the last case related to the first case) were included in the Delta VOC group. The Beta VOC group consisted of 639 cases infected from January to February 2021 (the first wave of epidemics) with complete medical records.

All patients were confirmed with disease and transferred to the First Affiliated Hospital of Harbin Medial University, the only official designated hospital to manage the SARS-CoV-2 patients in Heilongjiang Province. All patients were clinically classified according to the guidelines issued by the Chinese National Health Commission and the World Health Organization (National Health Commission & State Administration of Traditional Chinese Medicine, 2020) (https://http://www.nhc.gov.cn/cms-search/downFiles/a449a3e2e2c94d9a856d5faea2ff0f94.pdf, accessed August 2020). This study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University.

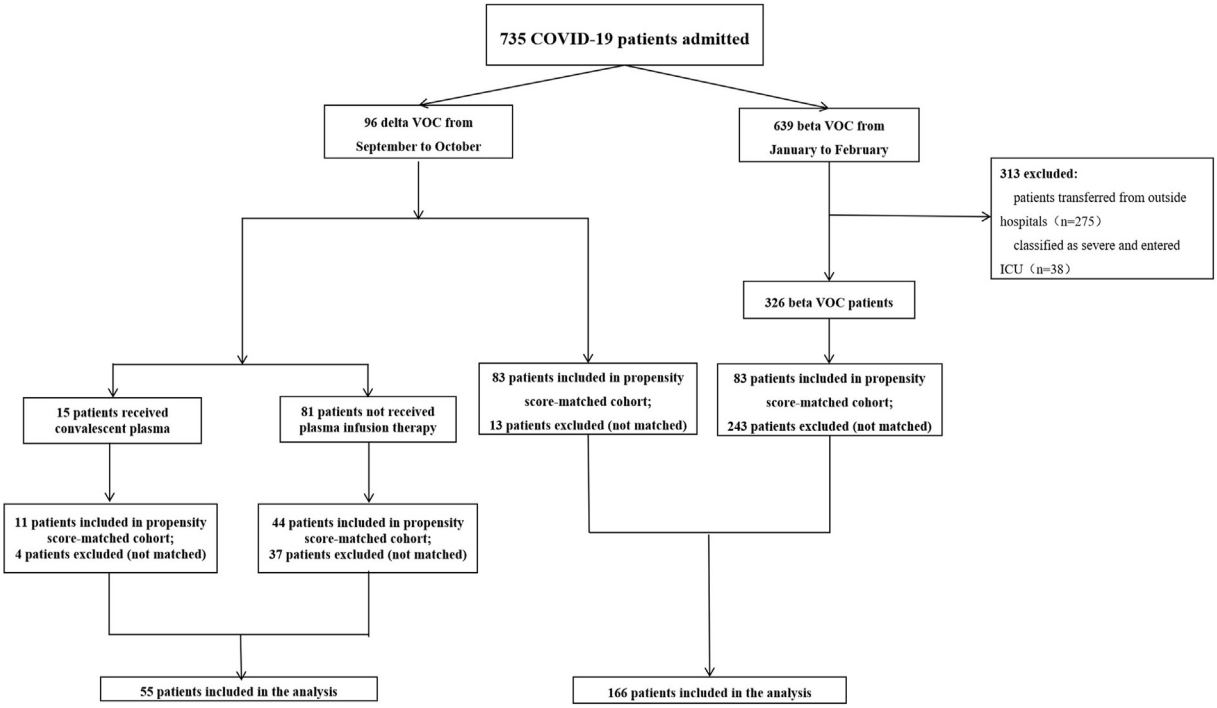

Figure 1. Flowchart of selection of study participants.

Table 1. Comparison between the beta group and the delta group.

Variable	Beta (n = 326)	Delta (n = 96)	Total (n = 422)	P
Baseline				
Age	52.500 (42.000, 64.000)	42.500 (28.000, 56.250)	51.000 (39.000, 63.000)	<0.001*
Sex				0.246
male	168 (51.5%)	43 (44.8%)	211 (50.0%)	
female	158 (48.5%)	53 (55.2%)	211 (50.0%)	
Classification				<0.001*
asymptomatic	102 (31.3%)	4 (4.2%)	106 (25.1%)	
mild	53 (16.3%)	48 (50.0%)	101 (23.9%)	
moderate	171 (52.5%)	43 (44.8%)	214 (50.7%)	
severe	0 (0.0%)	1 (1.0%)	1 (0.2%)	
Hematologic				
WBC, $\times10^9$/L	5.040 (4.050, 6.250)	6.180 (5.000, 7.285)	5.295 (4.145, 6.500)	<0.001*
PLT, $\times10^9$/L	191.000 (155.000, 238.000)	228.000 (194.000, 276.500)	200.000 (159.000, 250.000)	<0.001*
NEUT, $\times10^9$/L	2.890 (2.040, 3.840)	3.560 (2.580, 4.475)	3.020 (2.210, 4.002)	<0.001*
LYMPH, $\times10^9$/L	1.560 (1.190, 1.950)	1.690 (1.260, 2.170)	1.580 (1.205, 2.020)	0.023*
MONO, $\times10^9$/L	0.460 (0.360, 0.550)	0.610 (0.460, 0.705)	0.470 (0.380, 0.610)	<0.001*
Coagulation function				
PT, s	11.800 (11.300, 12.400)	11.800 (11.150, 12.500)	11.800 (11.300, 12.400)	0.205
FIB, g/L	2.930 (2.495, 3.910)	2.960 (2.480, 3.410)	2.930 (2.485, 3.700)	0.043*
APTT, s	29.600 (27.450, 33.050)	28.500 (26.400, 31.100)	29.300 (27.125, 32.700)	0.006*
TT, s	12.400 (11.800, 13.100)	14.100 (12.900, 15.200)	12.700 (12.000, 13.600)	<0.001*
Liver and renal function				
ALT, U/L	21.000 (12.600, 32.700)	20.750 (13.050, 32.050)	21.000 (12.650, 32.600)	0.232
AST, U/L	20.380 (16.000, 28.100)	18.250 (14.700, 24.550)	20.030 (15.850, 27.385)	0.961
AST/ALT	1.080 (0.770, 1.450)	0.940 (0.718, 1.237)	1.050 (0.750, 1.390)	0.008*
TBIL, umol/L	8.300 (6.000, 11.100)	9.350 (6.025, 12.400)	8.500 (6.000, 11.350)	0.006*
LDH, U/L	175.000 (144.000, 309.000)	143.500 (124.000, 168.000)	166.000 (139.000, 221.500)	<0.001*
BUN, mmol/L	5.260 (4.290, 6.340)	4.115 (3.532, 4.888)	4.950 (4.030, 6.120)	<0.001*
BUN/Cr	0.090 (0.070, 0.110)	0.060 (0.050, 0.070)	0.080 (0.060, 0.100)	<0.001*
UA, umol/L	268.000 (217.600, 325.400)	320.550 (267.675, 371.525)	278.400 (222.600, 337.300)	<0.001*
after matching				
	Delta (n = 83)	Beta (n = 83)	Total (n = 166)	P
Age	47.000 (33.000, 56.500)	47.000 (33.500, 58.000)	47.000 (33.000, 57.750)	0.992
Sex				0.531
male	34 (41.0%)	38 (45.8%)	72 (43.4%)	
female	49 (59.0%)	45 (54.2%)	94 (56.6%)	
Classification				0.712
asymptomatic	6 (7.2%)	4 (4.8%)	10 (6.0%)	
mild	32 (38.6%)	36 (43.4%)	68 (41.0%)	
moderate	45 (54.2%)	43 (51.8%)	88 (53.0%)	
Virus shedding time, day	10.000 (7.000, 13.396)	13.000 (9.500, 16.000)	11.000 (8.000, 14.573)	0.002*
Hospitalisation time, day	16.000 (14.000, 18.000)	16.000 (13.000, 19.000)	16.000 (13.000, 18.000)	0.415
IgG, AU/ml	1.030 (0.085, 7.085)	3.150 (0.725, 17.780)	2.175 (0.220, 11.820)	0.027*
IgM, AU/ml	1.870 (0.075, 9.185)	0.060 (0.030, 0.260)	0.205 (0.040, 2.725)	<0.001*
NLR	1.702 (1.314, 2.408)	2.013 (1.532, 3.379)	1.816 (1.425, 2.756)	0.025*
CRP, mg/L	0.250 (0.250, 3.380)	2.640 (0.500, 7.840)	1.310 (0.250, 6.820)	0.282
D-D, ug/mL	0.700 (0.560, 0.885)	0.490 (0.435, 0.580)	0.570 (0.470, 0.740)	0.277
CK, U/L	59.050 (45.625, 84.510)	79.495 (49.293, 123.963)	63.890 (47.410, 101.910)	0.030*
Cr, umol/L	59.100 (50.000, 69.050)	67.200 (57.600, 81.175)	63.200 (53.400, 75.400)	<0.001*

Note: "*" indicates that the difference between the two groups are statistically significant.

2.2. Clinical data collection

Demographic, clinical characteristic and laboratory findings were collected in both cohorts and recorded on the first day of admission. All diagnoses were made based on the Guidelines for the Diagnosis and Treatment of Novel Coronavirus Infection produced by the Chinese National Health Commission (Trial Version 8) (National Health Commission & State Administration of Traditional Chinese Medicine 19 August 2020) (https://http://www.nhc.gov.cn/cms-search/downFiles/a449a3e2e2c94d9a856d5faea2ff0f94.pdf, accessed August 2020). Data on hematologic, liver and renal function; coagulation function; and IgG, IgM, cytokine and lymphocyte levels were obtained on the first day of admission.

2.3. K nearest neighbors

We used the K nearest neighbors (KNN) matching method for analysis. Three baseline indicators of age, sex, and severity of the new variant

Table 2. Comparison of the conversion rate of severe illness between the two groups.

Variable	Beta group (n = 639)	Delta group (n = 96)	χ^2 Value	*P* Value
Severe	38 (5.95)	1 (1.04)	3.9966	0.0456*
Non-severe	601 (94.05)	95 (98.96)		

Note: "*" indicates that the difference between the two groups are statistically significant.

were defined as matching indicators. To control the confounding factors between the groups, the KNN method was used for 1:1 matching between the Beta and Delta groups. Then, we used 1:4 matching to match the plasma group and the control group of the Delta group. Finally, the clinical data were analyzed and compared before and after matching.

2.4. Statistical analysis

R version 4.0.5 and SAS 9.4 were used for statistical analyses. Quantitative data with a normal distribution are statistically described as the mean ± standard deviation ($\overline{x} \pm s$). Two independent sample t tests were used to compare the two groups (statistics are t values). Analysis of variance was used to compare the three groups (statistics were F values). The quantitative data with a skewed distribution were compared with the median, and the interquartile range [M(P25, P75)] was used for statistical description. The Wilcoxon rank sum test was used for comparison between two groups (statistics are Z values), and the Bonferroni method was used for pairwise comparison between multiple groups. The qualitative data frequency (percentage) was used for statistical description. The $\chi 2$ test or Fisher exact probability method was used to compare the composition of the two groups (the statistic is $\chi 2$ value), and the Scheff method was used for pairwise comparison between multiple groups. Correlation analysis of quantitative data was performed to calculate the Spearman rank correlation coefficient. Survival analysis was performed to generate a Kaplan–Meier curve, and data were assessed using the log-rank test based on $\alpha = 0.05$. Here, $P < 0.05$ indicates a statistically significant results.

3. Results

3.1. Study participant recruitment

A total of 735 patients suffering from COVID-19 in January and September 2021 were included in this study. In January, 639 patients were diagnosed with the Beta VOC. Those who were transferred from other hospitals (n = 275), and patients who entered the ICU (n = 38) as severe cases were excluded. In September, 96 patients were diagnosed with the Delta VOC. Fifteen patients were treated with convalescent plasma, and 81 patients received standard care. The trial profile is shown in Figure 1.

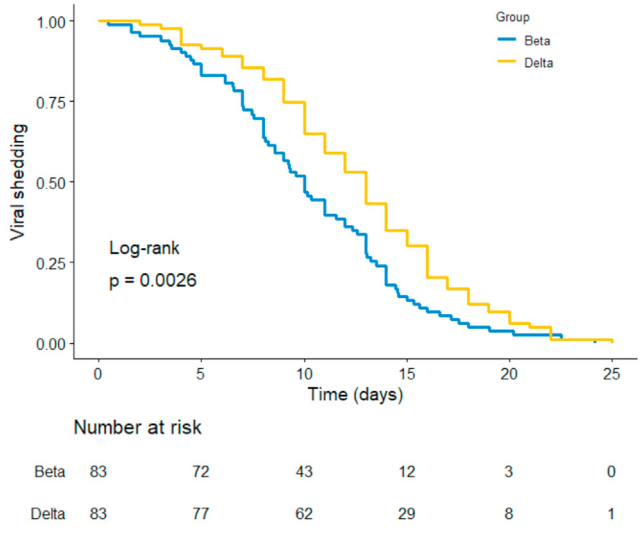

Figure 2. Survival analysis of the Beta VOC and Delta VOC of the viral shedding.

3.2. Clinical characteristics of patients infected with beta and delta VOCs

The clinical characteristics of 96 patients infected with the Delta VOC and 326 patients infected with the Beta VOC are shown in Table 1. The Beta VOC group was older than the Delta VOC group (median: 52.5 vs. 42.5 years, $P < 0.001$). The following features of the Beta VOC group were observed: 168 males (51.5%), 102 asymptomatic patients (31.3%), 53 patients with mild disease (16.3%), and 171 patients with moderate disease (52.5%). The Delta VOC group included 43 males (44.8%), 4 asymptomatic patients (4.2%), 43 patients with mild disease (50.0%), 48 patients with moderate disease (44.8%), and 1 patient with severe disease (1.04%). Differences in WBC (White blood cell), PLT (Platelets), NEUT (Neutrophil count), LYMPH (Lymphocyte count), MONO (Monocyte count), APTT (Activated partial thromboplastin time), FIB (Fibrinogen), TT (Thrombin time), TBIL (Total bilirubin), AST/ALT (Aspartate aminotransferase/Alanine aminotransferase), LDH (Lactate dehydrogenase), BUN (Blood urea nitrogen), BUN/Cr (Blood urea nitrogen/Creatinine) and UA (Uric acid) were noted between the two groups ($P < 0.05$). The severe illness rate was increased in the Beta VOC group (5.95%) compared with the Delta VOC group (1.04%), and the difference in the severe illness rate between the two groups was statistically significant ($p = 0.0456$) (Table 2).

To eliminate the interference of age and clinical classification on the results and make the baseline levels of the Delta VOC group and Beta VOC group consistent, we used age, sex and the clinical classification matching indicators for KNN matching of the two groups of patients. After matching, no differences in age or clinical classification were noted, and the baseline level remained the same. Differences in viral shedding, IgG, IgM, NLR, Ck, and Cr were noted between the two groups ($p < 0.05$). Longer viral shedding; higher IgG, NLR, Ck and Cr levels; and lower IgM levels were noted in the Delta VOC group. Survival analysis of the two groups revealed longer viral shedding in the Delta VOC group ($p < 0.05$) (Table 1 and Figure 2).

3.3. Clinical characteristics of vaccinated delta VOC patients

We divided Delta VOC patients into four groups: children, youth, middle-aged and elderly based on cutoff values of <18 years (n = 10), 19–44 years (n = 40), 45–64 years (n = 33), and >65 years old (n = 13), respectively. Differences in PLT, LYMPH, AST, LDH, Cr, BUN/Cr, IgG, IgM, CK, D-D, and lymphocytes were noted among the four groups ($p < 0.05$) (Table 3).

The results of the correlation analysis of the time interval from vaccination to onset revealed that the vaccination time interval was negatively correlated with IgG and IgM levels (Table 4). Specifically, IgG and IgM levels decrease as the vaccination interval increases(Figures 3a-3d). No correlations were noted between the vaccination interval and viral shedding, viral load (ORFlab gene CT value and N gene CT value), or cytokines.

3.4. Convalescent plasma therapy in delta VOC patients

We divided Delta VOC patients into two groups according to the treatment method: the convalescent plasma treatment group (n = 15) and the standard treatment group (n = 81) (Table 5). Patients in the convalescent plasma group were older than those in the standard treatment group (median: 58 vs. 39 years, $P < 0.001$). The convalescent plasma treatment group included 2 asymptomatic patients (13.3%), 4 patients with mild disease (26.7%), 8 patients with moderate disease

Table 3. Comparison results of baseline data for different age groups in delta group.

Variable	Age ≤18 years (n = 10)	Age 19–44 years (n = 40)	Age 45–64 years (n = 33)	Age ≥65 years (n = 13)	$F/H/\chi 2$	P
Sex					4.1568	0.2450
female	3 (30.00)	24 (60.00)	17 (51.52)	9 (69.23)		
male	7 (70.00)	16 (40.00)	16 (48.48)	4 (30.77)		
Classification						0.0076*
asymptomatic	1 (10.00)	0 (0.00)	2 (6.06)	1 (7.69)		
mild	7 (70.00)	25 (62.50)	14 (42.42)	2 (15.38)		
moderate	2 (20.00)	15 (37.50)[e]	17 (51.52)	9 (69.23)		
severe	0 (0.00)	0 (0.00)	0 (0.00)	1 (7.69)		
Vaccination						<0.0001*
No	7 (70.00)[abc]	1 (2.50)	3 (9.09)	0 (0.00)		
Yes	3 (30.00)	39 (97.50)	30 (90.91)	13 (100.00)		
Hematologic						
WBC, $\times 10^9$/L	7.2022 ± 2.9467	6.0068 ± 1.413	6.2688 ± 2.2544	6.5308 ± 2.6983	0.88	0.4571
PLT, $\times 10^9$/L	310.4444 ± 96.6309[bc]	250.9 ± 73.0963	224.4848 ± 61.2317	192.6154 ± 55.078	5.97	0.0009*
NEUT, $\times 10^9$/L	3.94(2.02–4.39)	3.615(2.75–4.46)	3.36(2.56–4.37)	3.9(2.36–5.21)	0.0144	0.9995
LYMPH, $\times 10^9$/L	2.3(2.18–2.65)[bc]	1.6(1.22–2.065)	1.58(1.27–2.08)	1.62(1–1.74)	11.8874	0.0078*
MONO, $\times 10^9$/L	0.7078 ± 0.1975	0.5823 ± 0.1726	0.6403 ± 0.2539	0.6377 ± 0.242	1.03	0.3841
Coagulation function						
PT, s	12.4444 ± 1.4689	12.0375 ± 1.0392	11.5939 ± 0.9401	11.7077 ± 0.697	2.25	0.0875
FIB, g/L	2.7378 ± 0.7957	3.0403 ± 0.6101	3.143 ± 1.0312	2.9962 ± 0.7096	0.61	0.6110
APTT, s	32.6(28.5–35)	28.65(26.4–31.4)	28.1(25.4–29.5)	28.9(28–30.5)	7.4570	0.0587
TT, s	15.2222 ± 1.8586	13.75 ± 1.3582	14.5394 ± 1.8985	14.1769 ± 2.1222	2.40	0.0731
Liver and renal function						
ALT, U/L	17.25(9.3–85.3)	18.75(11.5–34.35)	23(17.9–30.7)	21(17.7–25.6)	1.8720	0.5994
AST, U/L	24.9(17–64.65)	16.2(13.85–21.05)	18.9(16.1–26.5)	22.9(17.8–25.9)	9.8124	0.0202*
AST/ALT	1.475 ± 0.7998	0.9685 ± 0.3887	0.9485 ± 0.297	1.0962 ± 0.2495	5.7103	0.1266
TBIL, umol/L	5.25(4.55–9.25)	9.35(6.85–12.55)	10.3(7.6–13.4)	8.1(6–10.7)	6.7904	0.0789
LDH, U/L	167(133.5–212.5)	131.5(114–144.5)[e]	152(127–172)	169(151–191)	19.0113	0.0003*
BUN, mmol/L	3.95(3.47–5.375)	3.88(3.415–4.52)	4.34(3.71–5.27)	4.48(4.03–5.56)	5.5250	0.1372
Cr, umol/L	47.5(41–53.55)[ab]	63.55(58–81.65)	71.8(58.1–78.5)	64.4(53.4–76.8)	11.9213	0.0077*
BUN/Cr	0.08(0.07–0.12)[a]	0.05(0.04–0.07)[e]	0.07(0.05–0.07)	0.07(0.06–0.08)	17.4821	0.0006*
UA, umol/L	347.6875 ± 85.7932	330.835 ± 89.9001	334.8091 ± 99.0559	274.1385 ± 66.9378	1.72	0.1676
Virus shedding time, day	10.4 ± 3.5024	11.8 ± 4.7566	13.1212 ± 4.9671	15.2308 ± 4.0446	2.68	0.0515
Hospitalisation time, day	13.6 ± 3.2042	14.975 ± 3.9645	16.3333 ± 4.4418	17.6923 ± 3.521	2.68	0.0514
ORFlabCT	21.7713 ± 4.8978	21.8006 ± 5.4918	20.8736 ± 5.407	20.2515 ± 6.5323	0.31	0.8176
NCT	19.6038 ± 6.1546	19.1443 ± 6.1276	18.5566 ± 5.7653	17.2415 ± 5.9964	0.39	0.7622
IgG, AU/ml	0.09(0.03–7.13)	6.79(2.105–24.22)[d]	1.48(0.22–4.88)	2.76(0.72–30.13)	11.9656	0.0075*
IgM, AU/ml	0.04(0.04–0.06)	0.13(0.045–0.445)[d]	0.04(0.03–0.12)	0.05(0.04–0.31)	8.7886	0.0322*
NLR	1.8241(0.8783–2.125)	1.9958(1.5773–3.1924)	1.9234(1.4891–3.4932)	2.5843(1.5029–3.9)	3.9451	0.2675
CRP, mg/L	1.5(0.499–2.36)	2.275(0.499–7.93)	2.56(0.5–7.41)	6.93(2.44–9.07)	5.1480	0.1613
D-D, ug/mL	0.42(0.39–0.47)	0.48(0.43–0.535)	0.5(0.45–0.58)	0.56(0.5–0.64)	8.7015	0.0335*
CK, U/L	55.17(45.455–82.145)	60.295(45.075–99.63)[d]	89.92(69.84–161.53)	81.76(57.15–119.38)	8.9571	0.0299*
Cytokines						
IL-2, pg/ml	1.24(0.99–1.81)	0.95(0.675–1.875)	1.08(0.61–1.83)	0.55(0.4–1.05)	4.5442	0.2084
IL-4, pg/ml	2.17(1.92–2.67)	1.97(1.505–2.4)	1.76(1.29–2.38)	1.72(1.59–2.63)	2.1922	0.5335
IL-6, pg/ml	3.38(1.12–4.97)	2.06(0.9–4.32)	2.755(1.54–7.905)	4.5(2.8–7.95)	4.8745	0.1812
IL-10, pg/ml	4.13(3.02–4.75)	3.99(3.02–5.26)	4.58(2.79–6.6)	4.92(3.45–8.31)	2.1408	0.5437
TNF-α, pg/ml	4.42(3.5–4.62)	3.165(2.405–3.785)	2.71(2.15–3.71)	2.49(2.21–2.98)	6.9989	0.0719
IFN-γ, pg/ml	1.23(1.12–1.29)	1.09(0.84–1.725)	1.26(1.07–1.5)	1.6(1.11–1.64)	5.4030	0.1446
Lymphocytes						
Lymph, Cell/ul	2329.4444 ± 594.7926[abc]	1507.575 ± 522.4229	1513.697 ± 620.797	1334.25 ± 765.9797	5.69	0.0013*
T lymph, Cell/ul	1688.7778 ± 438.3742[abc]	1089.525 ± 417.9818	1050.0606 ± 468.1702	802.9167 ± 341.3584	7.69	0.0001*
T4 lymph, Cell/ul	777(655–847)[c]	615(437–762)	625(416–766)	457(236.5–627)	8.9977	0.0293*
T8 lymph, Cell/ul	603(529–735)[abc]	402(307.5–550)	337(262–487)	317.5(208.5–349.5)	17.2227	0.0006*
B lymph, Cell/ul	346(321–501)[abc]	207.5(133–267)	159(99–256)	137.5(53–216)	16.3686	0.0010*
NK lymph, Cell/ul	204(170–259)	182(115.5–264)	254(148–345)	262.5(156.5–486.5)	3.7573	0.2889
DPT, Cell/ul	22(17–25)	15.5(10.5–26)	19(15–40)	14(9.5–20.5)	6.6659	0.0833

Note: "a" indicates that the difference between the two groups of age≤18years and age 19–44 years are statistically significant; "b" indicates that the difference between the two groups of age≤18 years and age 45–64 years are statistically significant; "c" indicates that the difference between the two groups is age≤18 years and age ≥65 years old is statistically significant; "d" means the difference between the age 19–44 years old and age 45–64 years old groups is statistically significant; "e" means the age 19–44 years old and age ≥65 years old groups are between the two groups The difference is statistically significant; "f" indicates that the difference between the age 45–64 years and age ≥65 years old groups is statistically significant. "*" indicates that the difference in the four groups are statistically significant.

Table 4. The results of the correlation analysis of the time interval from vaccination to onset.

Variable	Time interval from first vaccination to onset		Time interval from second vaccination to onset	
	r_s	P	r_s	P
Virus shedding time, day	0.0541	0.6226	0.0299	0.7910
Hospitalisation time, day	0.0735	0.5038	0.0647	0.5658
ORFlabCT	-0.0366	0.7586	0.0124	0.9191
NCT	-0.0912	0.4365	-0.0519	0.6649
IgG, pg/ml	-0.2613	0.0157*	-0.2874	0.0093*
IgM, pg/ml	-0.3324	0.0019*	-0.2445	0.0279*
IL-2, pg/ml	-0.0034	0.9751	-0.0131	0.9073
IL-4, pg/ml	-0.0760	0.4895	-0.0951	0.3985
IL-6, pg/ml	-0.0558	0.6141	-0.0417	0.7134
IL-10, pg/ml	0.1603	0.1428	0.1440	0.1996
TNF-α, pg/ml	-0.0190	0.8628	-0.0199	0.8603
IFN-γ, pg/ml	0.0914	0.4052	0.0993	0.3777

Note: "*" indicates that the difference between the two groups are statistically significant.

(53.3%), and 1 patient with severe disease (6.7%). The standard treatment group included 2 asymptomatic patients (2.5%), 44 patients with mild disease (54.3%), and 35 patients with moderate disease (43.2%). The main laboratory test results before treatment are shown in Table 5. Differences in LDH and PT were noted between the two groups ($p < 0.05$).

Similarly, due to differences in age and clinical classification between the two groups, we matched the two groups of patients using the KNN method. After matching, IgM, CRP, CK, and IL-6 levels were higher in the convalescent plasma group, whereas lymphocytes, T lymph, T4 lymph, and T8 lymph levels were lower. Survival analysis of the two groups revealed that viral shedding and hospitalization time differed between the two groups before matching. Specifically, longer viral shedding and hospitalization times were noted in the convalescent plasma group (Figures 4a, 4b). After matching, no differences in viral shedding or hospitalization were noted (Figures 4c, 4d). Age and clinical classification had a greater impact on the comparisons between the two groups.

4. Discussion

In this retrospective study, we compared the clinical characteristics of Beta VOC and Delta VOC. We found that compared with the Beta VOC, the Delta VOC exhibits longer viral shedding, but the severe disease rate of Delta VOC patients after vaccination is lower than that of Beta VOC patients. These findings indicate that vaccination provides a protective effect for the Delta VOC. For the Delta VOC, convalescent plasma does not shorten the patient's viral shedding or hospitalization. The longer the vaccination period, the lower the IgG and IgM levels. Our research is of great significance to further understand the clinical characteristics of the Delta VOC.

Kaijin Xu et al. showed that viral shedding is related to sex and invasive mechanical ventilation (Xu et al., 2020). Other studies have suggested that viral shedding may be related to disease severity. SARS-CoV-2 in the respiratory tract of severe patients exhibits a longer duration, a higher viral load, and a later shedding peak compared with that noted for mild patients (Zheng et al., 2020). Therefore, in our study, to eliminate the interference of sex, clinical classification, and age, we matched the two groups of patients based on to sex, clinical classification,

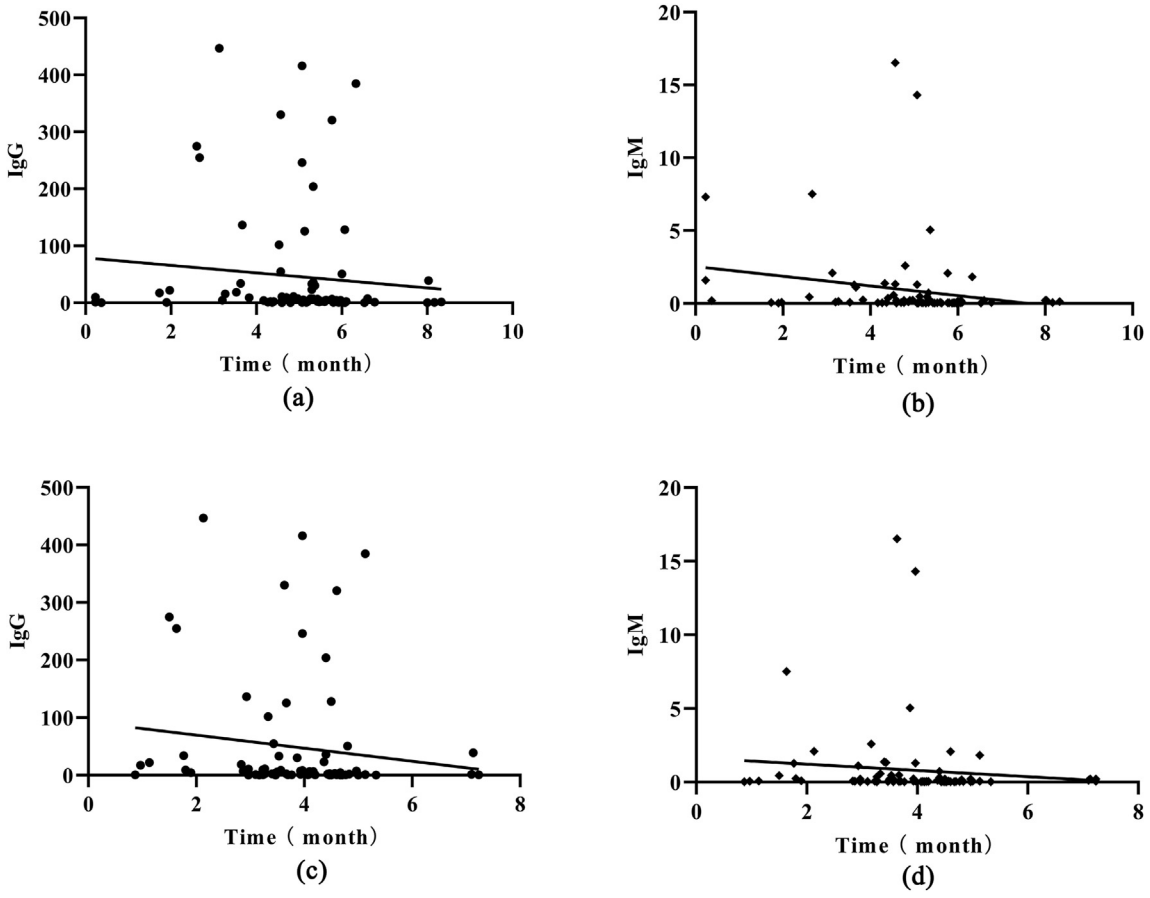

Figure 3. 3a and 3b is the correlation analysis of the IgG and IgM with time interval from first vaccination to onset, 3c and 3d is the correlation analysis of the IgG and IgM with time interval from second vaccination to onset.

Table 5. Comparison between convalescent plasma treatment group and standard treatment group.

Variable	Convalescent Plasma (n = 81)	Standard (n = 15)	Total(n = 96)	P
Baseline				
Age	39.000 (27.000, 53.000)	58.000 (46.500, 72.000)	42.500 (28.000, 56.250)	<0.001*
Sex				0.685
male	37 (45.7%)	6 (40.0%)	43 (44.8%)	
female	44 (54.3%)	9 (60.0%)	53 (55.2%)	
Classification				0.011*
asymptomatic	2 (2.5%)	2 (13.3%)	4 (4.2%)	
mild	44 (54.3%)	4 (26.7%)	48 (50.0%)	
moderate	35 (43.2%)	8 (53.3%)	43 (44.8%)	
severe	0 (0.0%)	1 (6.7%)	1 (1.0%)	
Hematologic				
WBC, $\times 10^9$/L	6.225 (5.225, 7.138)	5.040 (3.855, 7.655)	6.180 (5.000, 7.285)	0.396
PLT, $\times 10^9$/L	229.500 (195.750, 279.750)	215.000 (169.500, 241.000)	228.000 (194.000, 276.500)	0.214
NEUT, $\times 10^9$/L	3.745 (2.682, 4.460)	2.720 (2.425, 5.365)	3.560 (2.580, 4.475)	0.676
LYMPH, $\times 10^9$/L	1.740 (1.440, 2.185)	1.270 (0.810, 1.675)	1.690 (1.260, 2.170)	0.256
MONO, $\times 10^9$/L	0.600 (0.460, 0.702)	0.610 (0.430, 0.715)	0.610 (0.460, 0.705)	0.878
Coagulation function				
PT, s	11.850 (11.200, 12.700)	11.300 (11.050, 11.950)	11.800 (11.150, 12.500)	0.024*
FIB, g/L	2.960 (2.462, 3.410)	2.920 (2.530, 3.400)	2.960 (2.480, 3.410)	0.893
APTT, s	28.650 (26.575, 31.350)	27.800 (25.700, 29.150)	28.500 (26.400, 31.100)	0.135
TT, s	14.100 (12.900, 15.725)	13.900 (12.950, 14.550)	14.100 (12.900, 15.200)	0.212
Liver and renal function				
ALT, U/L	20.300 (12.600, 30.350)	21.500 (17.550, 44.000)	20.750 (13.050, 32.050)	0.227
AST, U/L	18.000 (14.650, 23.600)	23.000 (16.600, 47.700)	18.250 (14.700, 24.550)	0.061
AST/ALT	0.940 (0.700, 1.260)	0.930 (0.790, 1.160)	0.940 (0.718, 1.237)	0.679
TBIL, umol/L	9.300 (6.000, 12.400)	9.400 (7.050, 12.350)	9.350 (6.025, 12.400)	0.719
LDH, U/L	137.000 (120.500, 164.000)	159.000 (145.000, 177.500)	143.500 (124.000, 168.000)	0.006*
BUN, mmol/L	4.110 (3.535, 5.125)	4.160 (3.690, 4.585)	4.115 (3.532, 4.888)	0.517
Cr, umol/L	63.600 (55.300, 79.350)	70.000 (58.400, 75.900)	64.150 (55.250, 78.350)	0.905
BUN/Cr	0.060 (0.050, 0.070)	0.070 (0.050, 0.070)	0.060 (0.050, 0.070)	0.766
UA, umol/L	321.600 (274.600, 369.150)	285.600 (243.800, 389.700)	320.550 (267.675, 371.525)	0.518
After matching				
	Convalescent Plasma (n = 44)	Standard (n = 11)	Total(n = 55)	P
Age	50.500 (42.750, 61.000)	51.000 (44.000, 66.500)	51.000 (42.500, 61.500)	0.577
Sex				0.890
male	17 (38.6%)	4 (36.4%)	21 (38.2%)	
female	27 (61.4%)	7 (63.6%)	34 (61.8%)	
Classification				0.668
asymptomatic	2 (4.5%)	0 (0.0%)	2 (3.6%)	
mild	19 (43.2%)	4 (36.4%)	23 (41.8%)	
moderate	23 (52.3%)	7 (63.6%)	30 (54.5%)	
Virus shedding time, day	13.000 (9.000, 16.000)	15.000 (12.500, 17.000)	13.000 (10.000, 16.000)	0.118
Hospitalisation time, day	16.000 (12.000, 19.000)	18.000 (15.500, 19.000)	16.000 (13.000, 19.000)	0.106
ORFlabCT	27.650 (26.970, 29.200)	25.680 (24.822, 26.265)	27.470 (25.770, 29.150)	0.344
NCT	27.000 (25.975, 28.538)	23.700 (22.675, 24.827)	26.765 (24.257, 28.488)	0.245
IgG, AU/ml	264.690 (217.950, 374.560)	325.260 (50.765, 380.295)	265.005 (182.235, 374.615)	0.484
IgM, AU/ml	2.630 (0.960, 5.720)	6.780 (3.050, 13.800)	3.540 (1.078, 6.815)	0.012*
NLR	1.867 (1.499, 3.379)	2.433 (1.703, 4.248)	1.968 (1.521, 3.522)	0.654
CRP, mg/L	0.250 (0.250, 1.445)	22.470 (7.085, 40.130)	0.250 (0.250, 2.745)	<0.001*
D-D, ug/mL	0.510 (0.450, 0.610)	0.760 (0.675, 1.065)	0.540 (0.470, 0.677)	0.873
CK, U/L	57.260 (36.855, 81.320)	91.800 (69.900, 155.465)	63.935 (40.355, 90.093)	0.043*
Cytokines				
IL-2, pg/ml	1.065 (0.755, 1.647)	0.690 (0.395, 1.245)	1.020 (0.690, 1.500)	0.208
IL-4, pg/ml	1.820 (1.570, 2.287)	1.840 (1.420, 2.300)	1.840 (1.460, 2.340)	0.665
IL-6, pg/ml	0.000 (0.000, 1.460)	7.290 (3.755, 25.375)	0.300 (0.000, 3.500)	<0.001*
IL-10, pg/ml	2.595 (0.000, 3.600)	2.790 (1.480, 3.575)	2.660 (0.000, 3.650)	0.962
TNF-α, pg/ml	2.595 (1.925, 3.310)	2.980 (1.760, 3.635)	2.650 (1.910, 3.450)	0.739
IFN-γ, pg/ml	0.890 (0.790, 1.180)	1.040 (0.830, 1.305)	0.920 (0.798, 1.220)	0.764

(*continued on next page*)

Table 5 (*continued*)

Variable	Convalescent Plasma (n = 81)	Standard (n = 15)	Total(n = 96)	P
Lymphocytes				
Lymph, Cell/ul	1668.000 (1390.500, 2281.000)	1359.000 (1170.000, 1473.000)	1569.500 (1338.750, 2116.750)	0.007*
T lymph, Cell/ul	1270.000 (988.500, 1667.500)	910.000 (786.500, 1102.500)	1164.000 (931.000, 1553.500)	0.009*
T4 lymph, Cell/ul	715.000 (545.500, 976.500)	644.000 (453.500, 657.500)	684.000 (516.250, 890.000)	0.020*
T8 lymph, Cell/ul	501.000 (351.500, 599.000)	378.000 (298.000, 424.000)	448.000 (345.500, 577.750)	0.026*
B lymph, Cell/ul	236.000 (157.500, 313.500)	157.000 (96.500, 244.000)	219.000 (149.000, 309.500)	0.053
NK lymph, Cell/ul	223.000 (140.500, 313.000)	230.000 (136.500, 269.000)	223.000 (140.250, 299.500)	0.379
DPT, Cell/ul	26.000 (17.000, 39.000)	21.000 (10.500, 30.000)	25.500 (16.000, 36.750)	0.224

Note: "*" indicates that the difference between the two groups are statistically significant.

and age using the KNN method. The survival curves of the two matched groups revealed longer viral shedding of the Delta VOC. In addition, numerous studies have confirmed that the Delta VOC is more transmissible (Dougherty et al., 2021). The Delta VOC is 60% more infectious than the original wild-type strain and has a higher viral load (Zheng et al., 2020). Our research results are consistent with these findings.

However, the severe illness rate was higher in the Beta VOC group. This result appears contrary to the previous results (Lin et al., 2021). This finding may be related to the notion that most Delta VOC patients were vaccinated in our study. As reported, the BNT162b2 vaccine can reduce disease severity and mortality (Dagan et al., 2021). In addition, we also hypothesize that the vaccine can reduce the serious illness rate of Delta VOC, which is consistent with XiaoNing Li's research (Li et al., 2021). Their research results show that although two doses of the SARS-CoV-2 inactivated vaccine can only cause 59.0% of the VE upon infection with the Delta VOC, the SARS-CoV-2 inactivated vaccine effectively prevents severe COVID-19.

For the Delta VOC, the vaccination interval is negatively correlated with the two indicators of IgG and IgM. Specifically, IgG and IgM levels are reduced with the extension of the vaccination time. Given that the

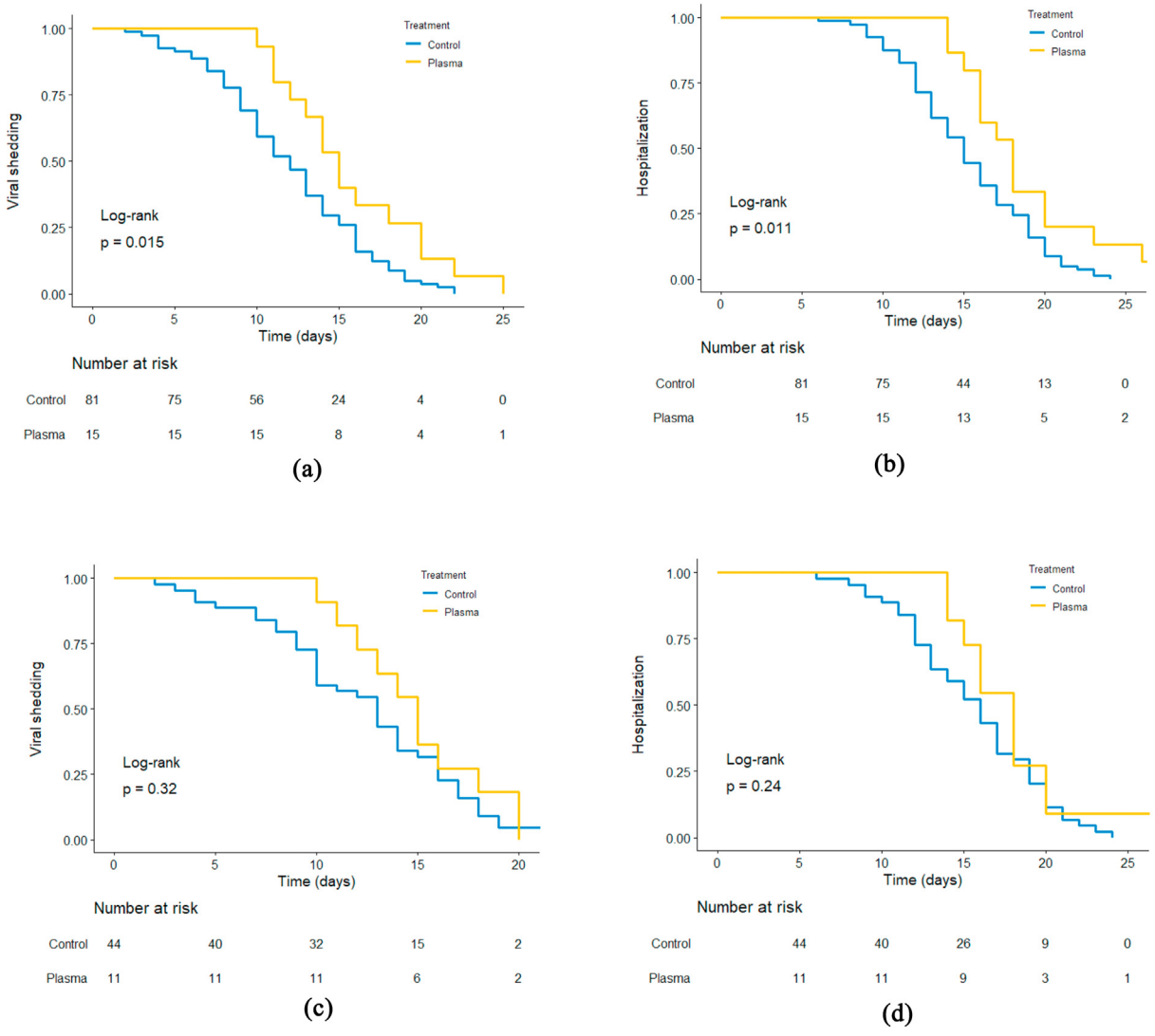

Figure 4. Survival analysis of the viral shedding and hospitalisation in Convalescent Plasma treatment and Standard treatment in Delta VOC. Figure 4a and b is before matching, 4c and 4d is after matching.

large number of plasmablasts induced by most vaccines cannot be maintained as long-lived memory plasma cells, a reduction in the immune response is typically expected (Baumgarth et al., 2020; Khodadadi et al., 2019; Quast and Tarlinton, 2021). In addition, IgG and IgM levels are also related to the patient's age at vaccination (Grupper et al., 2021). Ranzani et al. observed that the effectiveness of the vaccine decreased significantly with age in an elderly population (Ranzani et al., 2021). Another report showed that among 176 COVID-19 patients, the antibody level in elderly individuals was significantly lower than that in young individuals (Müller et al., 2021). In our results, Delta VOC patients exhibited differences in IgG and IgM levels based on age.

Convalescent plasma therapy is used in the treatment of COVID-19. Some studies have shown that convalescent plasma therapy can reduce mortality and the length of hospitalization in patients with moderate COVID-19 (Basheer et al., 2021). Convalescent plasma with a high IgG antibody titer at the early stage of disease is more effective for the treatment of patients with moderate COVID-19 in Convalescent plasma therapy(Fazeli et al., 2022).

However, our results are different from the results reported in some previous studies. We found that convalescent plasma therapy did not shorten viral shedding or hospitalization duration. After eliminating the interference of age and clinical classification factors, convalescent plasma therapy did not exhibit improved efficacy compared with standard treatment.

Our research also has some limitations. First, because Beta and Delta VOCs occur at different times and the nucleic acid detection methods are different, we did not collect the Ct value of Beta VOC. Thus, it is impossible to compare the viral load between the two variants. Second, after the Delta VOC outbreak, we quickly implemented prevention and control measures to inhibit rapid spread of the variant, so the number of people infected was limited. Third, after the beginning of the year, most people were vaccinated, so it is impossible to assess the effectiveness of the vaccine against the Delta VOC.

5. Conclusions

Compared with the Beta VOC, longer virus shedding was observed for the Delta VOC. Vaccination with inactivated vaccines can reduce the severe illness rate of the Delta VOC. IgG and IgM levels are reduced as the time between the first and second vaccine doses increases. Therefore, vaccination should be performed within a reasonable time frame.

Declarations

Author contribution statement

Changsong Wang, Kaijiang Yu: Conceived and designed the experiments; Performed the experiments.

Yahui Peng, Wei Yang, Yuxin Zhou, Dongsheng Fei, Kai Kang: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Xianglin Meng, Mingyan Zhao, Xiaomin Liu, Shihuan Yu, Feiyu Luan, Xiaohui Ma, Xiaonan Jia, Wenjing Mu: Analyzed and interpreted the data.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

None.

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