Original Article

Effect of COVID-19 vaccine in adults infected with the Delta variant of SARS-CoV-2: a retrospective cohort study

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Background: Reducing mortality among those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains a critical challenge in clinic. The objective of this study was to analyze the effect of the coronavirus disease 2019 (COVID-19) vaccine on the prognosis of individuals infected with the Delta variant of SARS-CoV-2.

Methods: In a single-center, retrospective cohort study, all adult patients with COVID-19 from designated hospital in Xi'an, China, during the Delta outbreak from December 2021 to January 2022 were enrolled. The patients were divided into two groups according to whether they received the COVID-19 vaccine, and differences in clinical outcomes (pneumonia, oxygen therapy, severe disease, and mechanical ventilation or death), symptoms, and nucleic acid-negative time between the two groups were compared.

Results: A total of 651 adult patients with COVID-19 were included, among whom 578 were vaccinated and 73 were not vaccinated. Compared with the unvaccinated group, the vaccinated group had lower rates of pneumonia (49.8% *vs.* 67.1%; P=0.005), oxygen therapy (20.9% *vs.* 57.5%; P<0.001), severe illness (1.6% *vs.* 26.0%; P<0.001), and mechanical ventilation or mortality (0.3% *vs.* 13.7%; P<0.001). Multivariate logistic regression analysis showed that COVID-19 vaccination significantly reduced the risk of requiring oxygen therapy, severe illness, and mechanical ventilation or death. Compared with the unvaccinated group, the vaccinated group had a higher incidence of sore throat (31.8% *vs.* 17.8%; P=0.01) and a lower incidence of shortness of breath (3.1% *vs.* 20.5%; P<0.001), diarrhea (1.2% *vs.* 5.5%; P=0.03), and nausea or vomiting (1.4% *vs.* 6.8%; P=0.007). The median time of nucleic acid transition to negative was 14.0 [interquartile range (IQR), 10.0–17.0] and 15.0 (IQR, 11.0–18.0) days (P=0.18) in the vaccinated and unvaccinated groups, respectively.

Conclusions: Vaccination may reduce the risk of oxygen therapy, severe illness, and mechanical ventilation or death in patients with Delta variant COVID-19, as well as the incidence of pneumonia. Vaccinated patients had a higher incidence of sore throat and a lower incidence of shortness of breath, diarrhea, and nausea or vomiting compared to nonvaccinated patients. Vaccination did not shorten the time for the emergence of nucleic acid-negative status.

Keywords: Coronavirus disease 2019 vaccine (COVID-19 vaccine); pneumonia; oxygen therapy; mechanical ventilation; mortality

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Introduction

At present, the coronavirus disease 2019 (COVID-19) is still spreading and prevalent in the world, and the means to effectively reducing COVID-19-related adverse outcomes such as severe disease or even death after infection has attracted considerable attention. In addition to antiviral drugs, the impact of the COVID-19 vaccine on the adverse prognosis of COVID-19 has also been a focus of research in recent years. Previous studies have shown that vaccination against COVID-19 can reduce adverse outcomes such as severe illness or death (1-4). In China, the number of patients with COVID-19 infected with the Delta variant is low due to the strong pandemic control policy. From December 2021 to January 2022, a wave of Delta variant COVID-19 outbreaks occurred in Xi'an, China. At that time, antiviral drugs were not marketed or used in China, thus providing a unique opportunity to evaluate the effect of the vaccine on the prognosis of patients with the Delta variant of COVID-19. We collected clinical data from adult patients with COVID-19 during this outbreak to compare the clinical outcomes between vaccinated and unvaccinated populations. The objective was to analyze the effect of COVID-19 vaccine on the prognosis of those infected with the Delta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1351/rc).

Highlight box

Key findings

- Compared with the unvaccinated group of adult patients with the coronavirus disease 2019 (COVID-19) Delta variant, the vaccinated group had lower rates of pneumonia, oxygen therapy, severe illness, and mechanical ventilation or mortality. After adjustments were made for confounders, it was found that COVID-19 vaccination was associated with a significantly reduced the risk of oxygen therapy, severe illness, and mechanical ventilation or death but not a significant reduction in the risk of pneumonia. In addition, we found that vaccinated patients had a high incidence of sore throat and low incidence of shortness of breath, diarrhea, and nausea or vomiting. Moreover, vaccination against COVID-19 did not shorten the negative transition time of nucleic acids.

What is known and what is new?

- Vaccination against COVID-19 can reduce adverse outcomes such as severe illness or death. However, there are few reports on the Delta variant in China.
- During the Delta outbreak in Xi'an, China, vaccination reduced the incidence of adverse outcomes in adults infected with severe acute respiratory syndrome coronavirus 2.

What is the implication, and what should change now?

- We recommend that unvaccinated individuals be vaccinated in timely fashion to prevent adverse outcomes due to the prevalence of COVID-19.

Methods

Research design and ethics

This single-center, retrospective, cohort study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Air Force Medical University (also known as Xijing Hospital) (approval No. KY20222118-F-1). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The requirement for individual consent was waived due to the retrospective nature of the analysis.

Inclusion and exclusion criteria

During the COVID-19 pandemic period in Xi'an from December 2021 to January 2022, all people infected with SARS-CoV-2 in Xi'an were admitted to the designated hospital for isolation treatment. According to the testing results of the Shanxi Provincial Center for Disease Control and Prevention, the strain of the SARS-CoV-2 outbreak was the Delta variant. The sample was derived from all adult patients with COVID-19 admitted to the designated hospital between December 2021 and January 2022. Inclusion criteria were as follows: (I) the hospitalized COVID-19 patients confirmed by positive oral/nasopharyngeal swab nucleic acid tests; (II) aged 18 years or older. Exclusion criteria: patients with missing clinical data were excluded. According to the World Health Organization (WHO) guidelines (5), cases of COVID-19 can be classified as clinically non-severe, severe, or critical (Table S1). In this study, the severe and critical COVID-19 categories were combined into a single severe category.

Data collection

The following clinical data of adult patients with COVID-19 were collected: (I) basic information of patients, including sex, age, smoking history, comorbidities

(chronic obstructive pulmonary disease, bronchial asthma, hypertension, coronary atherosclerotic heart disease, chronic liver disease, chronic kidney disease, diabetes, cerebrovascular disease, tumor, etc.); (II) COVID-19 vaccination history, including number of doses, type of vaccine, and time of vaccination; (III) the time from onset to hospitalization; (IV) vital signs on admission, including temperature, pulse, respiration, and blood pressure; (V) first laboratory tests after admission, including blood routine [white blood cell count, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, red blood cell (RBC) count, hemoglobin level, platelet count], liver function indicators [total bilirubin level, alanine aminotransferase level, aspartate aminotransferase (AST) level, albumin level, globulin level] and renal function indicators (urea and creatinine levels); (VI) COVID-19-related symptoms; (VII) oxygen treatment methods received during hospitalization, including use of a nasal oxygen catheter, use of an oxygen mask, high-flow nasal oxygen therapy, noninvasive mechanical ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation; (VIII) time of negative nucleic acid transition of SARS-CoV-2. Nucleic acid conversion to a negative status was defined as two consecutive oral or nasopharyngeal swabs with negative nucleic acid tests for SARS-CoV-2, and the time of the first negative test was defined as the time of nucleic acid conversion to negative [the sampling times were at least 24 hours apart, fluorescence quantitative polymerase chain reaction detection was adopted, with a cycle threshold value >40 being considered negative]. Routine blood examinations, liver function index, and renal function index were completed via the collection of venous blood from patients. Routine blood tests were executed with a whole blood cell analyzer (XN-3000, Sysmex, Kobe, Japan), while liver function and renal function indexes were tested with a dry biochemical analyzer (FS5.1, Johnson & Johnson Medtech, Warsaw, IN, USA).

Clinical outcomes

Whether pneumonia was indicated on imaging (typical manifestations of COVID-19 pneumonia on imaging, such as multiple ground-glass opacities and consolidation opacities distributed in the periphery of both lungs), whether oxygen therapy was administered (including use of a nasal oxygen catheter, use of an oxygen mask, high-flow nasal oxygen therapy, noninvasive mechanical ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation), whether there was severe disease, and whether mechanical ventilation was administered (including noninvasive mechanical ventilation and invasive mechanical ventilation) or death occurred. We included mechanical ventilation and death as a combined outcome because these patients tend to require significant medical input and have poor prognosis.

Procedure

In this study, the exposure was vaccination before the onset of the disease. Patients were divided into a vaccinated group (exposed group) and an unvaccinated group (nonexposed group) according to whether they had been vaccinated against COVID-19. The demographic characteristics, days from onset to hospitalization, vital signs at admission, laboratory examination at admission, clinical symptoms, time of negative nucleic acid transition of SARS-CoV-2, and clinical outcomes were compared between the two groups. Multivariate regression analysis was used to control for confounding factors and analyze the effect of the vaccine on clinical outcomes of patients with COVID-19. In order to further examine the protective effect of COVID-19 vaccine on different populations, we also conducted subgroup analyses.

Statistical analysis

The measurement data were tested for normality via the Shapiro-Wilk test. Measurement data conforming to a normal distribution are represented by the mean ± standard deviation, and the independent samples *t*-test was used for comparisons between groups. Measurements with a skewed distribution are expressed as the median and interquartile range (IQR), and the Mann-Whitney test was used for intergroup comparisons. Count data are expressed as the frequency (percentage), with an intergroup ratio compared with the Pearson χ^2 test or Fisher exact test. The variables with $P<0.05$ in univariate logistic regression analysis were covariates and included in multivariate regression analysis. Multivariate logistic regression models were used to analyze the association between vaccine and clinical outcomes (pneumonia, oxygen therapy, severe disease, and mechanical ventilation or death), with the main independent variable being whether the COVID-19 vaccine was administered. All statistical analyses were performed in SPSS version 27.0 software (IBM Corp., Armonk, NY, USA), and forest plots were drawn using R version 4.3.2 software (The R

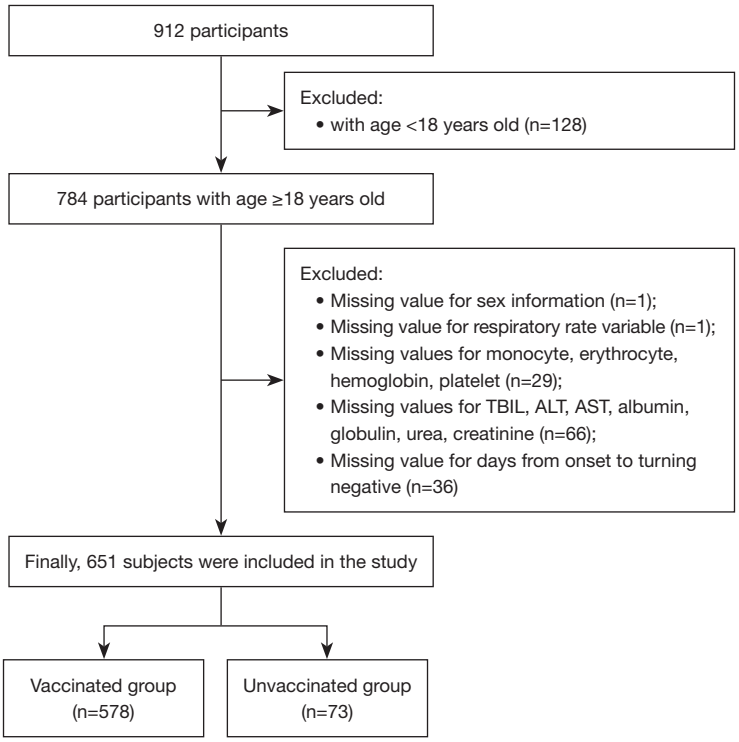

Figure 1 The flowchart of participant selection in this study. TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Foundation for Statistical Computing, Vienna, Austria). A two-sided P value <0.05 was considered statistically significant.

To control for selection bias, we included all patients with COVID-19 admitted to the designated hospital in Xi'an during the COVID-19 outbreak. All data were collected at short intervals during the patient's hospital stay to limit recall bias. In addition, multivariate logistic regression analysis was used to control for confounding bias.

Results

Baseline data

From December 2021 to January 2022, the designated hospital in Xi'an treated 912 patients with COVID-19, 128 of whom were under the age of 18 years. Of the 784 adult patients, 133 were excluded due to lack of relevant data. A total of 651 adults with complete clinical data were ultimately included in the study. Of these, 578 were vaccinated and 73 were unvaccinated (*Figure 1*). The comparison of baseline characteristics between the two groups is shown in *Table 1*. There were differences in age, comorbidities, systolic blood pressure, absolute lymphocyte count, hemoglobin level, platelet count, AST level, albumin level, and urea level between the vaccinated and unvaccinated groups. The median ages in the vaccinated and unvaccinated groups were 36.00 (IQR, 26.00–51.00) and 48.00 (IQR, 31.00–67.00) years, respectively (P<0.001), while the comorbidity rates were 12.3% and 50.7% (P<0.001), respectively. At admission, for the vaccinated and unvaccinated groups, median systolic blood pressure was 124.00 (IQR, 115.00–132.25) and 129.00 (IQR, 118.50–140.00) mmHg (P=0.01), the median absolute lymphocyte count was 1.44 (IQR, 1.05–1.92) and 1.21 (IQR, 0.97–1.73) $\times 10^9$/L (P=0.04), the median hemoglobin level was 141.00 (IQR, 128.00–154.25) and 137.00 (IQR, 122.00–152.00) g/L (P=0.047), the median platelet count was 194.00 (IQR, 152.00–233.00) and 175.00 (IQR, 135.00–225.50) $\times 10^9$/L (P=0.04), the median AST level was 20.00 (IQR, 16.00–27.25) and 24.00 (IQR, 18.00–35.50) IU/L (P=0.02), the median albumin level was 40.00 (IQR, 37.00–42.00) and 39.00 (IQR, 36.00–42.00) g/L (P=0.04), and the median urea level was 3.90 (IQR, 3.20–4.72) and 4.30 (IQR, 3.50–5.40) mmol/L (P=0.003), respectively.

Table 1 Comparison of baseline data between the vaccinated group and unvaccinated group

Characteristics	Total (N=651)	Vaccinated group (n=578)	Unvaccinated group (n=73)	P value
Age (years)	37.00 (27.00–52.00)	36.00 (26.00–51.00)	48.00 (31.00–67.00)	<0.001
Sex				0.09
Male	363 (55.8)	329 (56.9)	34 (46.6)	
Female	288 (44.2)	249 (43.1)	39 (53.4)	
Smoking history	21 (3.2)	18 (3.1)	3 (4.1)	0.92
Comorbidities	108 (16.6)	71 (12.3)	37 (50.7)	<0.001
Chronic obstructive pulmonary disease	3 (0.5)	2 (0.3)	1 (1.4)	0.30
Asthma	3 (0.5)	3 (0.5)	0	>0.99
Hypertension	66 (10.1)	45 (7.8)	21 (28.8)	<0.001
Coronary heart disease	19 (2.9)	7 (1.2)	12 (16.4)	<0.001
Chronic liver disease	10 (1.5)	9 (1.6)	1 (1.4)	>0.99
Chronic renal disease	5 (0.8)	3 (0.5)	2 (2.7)	0.10
Diabetes	27 (4.1)	17 (2.9)	10 (13.7)	<0.001
Cerebrovascular disease	7 (1.1)	2 (0.3)	5 (6.8)	<0.001
Hospitalization within 1 week of onset				0.33
No	126 (19.4)	115 (19.9)	11 (15.1)	
Yes	525 (80.6)	463 (80.1)	62 (84.9)	
Vital signs upon admission				
Temperature (℃)	36.60 (36.40–37.00)	36.60 (36.40–37.00)	36.60 (36.40–37.00)	0.90
Pulse (beats/min)	82.00 (78.00–92.00)	82.00 (78.00–92.00)	81.00 (77.50–91.00)	0.90
Respiratory rate (breaths/min)	20.00 (18.00–20.00)	20.00 (18.00–20.00)	20.00 (18.00–20.00)	0.52
Systolic pressure (mmHg)	124.00 (116.00–134.00)	124.00 (115.00–132.25)	129.00 (118.50–140.00)	0.01
Diastolic pressure (mmHg)	80.00 (72.00–88.00)	80.00 (72.00–88.00)	80.00 (71.00–89.50)	0.48
Laboratory tests upon admission				
WBC ($\times10^9$/L)	5.14 (4.11–6.38)	5.17 (4.11–6.38)	4.81 (3.90–6.36)	0.52
Neutrophil ($\times10^9$/L)	3.07 (2.23–4.07)	3.08 (2.20–4.07)	2.97 (2.29–4.05)	0.89
Lymphocyte ($\times10^9$/L)	1.42 (1.03–1.92)	1.44 (1.05–1.92)	1.21 (0.97–1.73)	0.04
Monocyte ($\times10^9$/L)	0.43 (0.34–0.55)	0.43 (0.34–0.55)	0.41 (0.31–0.57)	0.65
RBC ($\times10^{12}$/L)	4.52±0.54	4.53±0.53	4.44±0.59	0.18
Hemoglobin (g/L)	141.00 (127.00–154.00)	141.00 (128.00–154.25)	137.00 (122.00–152.00)	0.047
Platelet ($\times10^9$/L)	191.00 (150.00–232.00)	194.00 (152.00–233.00)	175.00 (135.00–225.50)	0.04
TBIL (μmol/L)	11.10 (8.30–14.40)	11.20 (8.30–14.50)	10.80 (8.15–14.25)	0.53
ALT (IU/L)	19.00 (13.00–34.00)	19.00 (13.00–34.00)	22.00 (13.50–39.00)	0.33
AST (IU/L)	20.00 (16.00–28.00)	20.00 (16.00–27.25)	24.00 (18.00–35.50)	0.02

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (N=651)	Vaccinated group (n=578)	Unvaccinated group (n=73)	P value
Albumin (g/L)	40.00 (37.00–42.00)	40.00 (37.00–42.00)	39.00 (36.00–42.00)	0.04
Globulin (g/L)	29.00 (26.00–31.00)	29.00 (26.00–31.00)	28.00 (25.00–31.00)	0.65
Urea (mmol/L)	3.90 (3.30–4.80)	3.90 (3.20–4.72)	4.30 (3.50–5.40)	0.003
Creatinine (μmol/L)	66.63 (59.41–74.62)	66.82 (59.54–74.71)	64.05 (58.82–73.85)	0.39

Data are presented as median (IQR), n (%), or mean ± SD. WBC, white blood cell; RBC, red blood cell; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; SD, standard deviation.

Table 2 Comparison of symptoms and days from symptom onset to nucleic acid negative status between the vaccinated group and unvaccinated group

Variables	Total (N=651)	Vaccinated group (n=578)	Unvaccinated group (n=73)	P value
Symptoms				
Fever	262 (40.2)	230 (39.8)	32 (43.8)	0.51
Fatigue	139 (21.4)	122 (21.1)	17 (23.3)	0.67
Nasal congestion or runny nose	130 (20.0)	121 (20.9)	9 (12.3)	0.08
Sore throat	197 (30.3)	184 (31.8)	13 (17.8)	0.01
Cough	324 (49.8)	291 (50.3)	33 (45.2)	0.41
Sputum production	124 (19.0)	113 (19.6)	11 (15.1)	0.36
Shortness of breath	33 (5.1)	18 (3.1)	15 (20.5)	<0.001
Headache	46 (7.1)	40 (6.9)	6 (8.2)	0.68
Dizziness	13 (2.0)	12 (2.1)	1 (1.4)	>0.99
Loss of smell or taste	76 (11.7)	68 (11.8)	8 (11.0)	0.84
Nausea or vomiting	13 (2.0)	8 (1.4)	5 (6.8)	0.007
Abdominal pain	4 (0.6)	3 (0.5)	1 (1.4)	0.38
Diarrhea	11 (1.7)	7 (1.2)	4 (5.5)	0.03
Days from symptom onset to nucleic acid negative status	14.0 (10.0–18.0)	14.0 (10.0–17.0)	15.0 (11.0–18.0)	0.18

Data are presented as n (%) or median (IQR). IQR, interquartile range.

COVID-19 symptoms and time to viral nucleic acid-negative status

Several symptoms were different between the two groups (*Table 2*). The percentage of patients with sore throat in the vaccinated group was higher than that in the unvaccinated vaccine group (31.8% *vs.* 17.8%; P=0.01), while the percentage of patients with shortness of breath was lower than that in the unvaccinated group (3.1% *vs.* 20.5%; P<0.001). In addition, compared with the unvaccinated group, the vaccinated group had a lower percentage of patients with diarrhea (1.2% *vs.* 5.5%; P=0.03) and nausea or vomiting (1.4% *vs.* 6.8%; P=0.007). The median time for viral nucleic acid to turn negative was 14.0 (IQR, 10.0–17.0) days in the vaccinated group and 15.0 (IQR, 11.0–18.0) days in the unvaccinated group, with no significant difference between the two groups (P=0.18).

Table 3 Comparison of clinical outcomes between the vaccinated group and unvaccinated group

Clinical outcomes	Total (N=651)	Vaccinated group (n=578)	Unvaccinated group (n=73)	P value
Pneumonia	337 (51.8)	288 (49.8)	49 (67.1)	0.005
Oxygen therapy	163 (25.0)	121 (20.9)	42 (57.5)	<0.001
Severe/critical COVID-19	28 (4.3)	9 (1.6)	19 (26.0)	<0.001
Mechanical ventilation or death	12 (1.8)	2 (0.3)	10 (13.7)	<0.001

Data are presented as n (%). COVID-19, coronavirus disease 2019.

Clinical outcomes

There were significant differences in clinical outcomes between the two groups (*Table 3*). Compared with unvaccinated group, the vaccinated group had lower incidences of pneumonia (49.8% *vs.* 67.1%; P=0.005), oxygen therapy (20.9% *vs.* 57.5%; P<0.001), severe disease (1.6% *vs.* 26.0%; P<0.001), and mechanical ventilation or mortality (0.3% *vs.* 13.7%; P<0.001).

The results of univariate logistic regression analysis are shown in *Table 4*. Independent variables with P<0.05 in univariate logistic regression analysis were included as covariables in multivariate logistic regression analysis. Different multifactor logistic regression models were constructed via the gradual addition of covariables, the results of which are shown in *Table 5*.

When other factors were not adjusted for, the effect of vaccination on pneumonia was statistically significant [odds ratio (OR) =0.486; 95% confidence interval (CI): 0.291–0.814; P=0.006]. However, after factors of age, sex, comorbidities, and time from onset to hospitalization were adjusted for, vaccination had no statistically significant association with pneumonia [adjusted OR (aOR) =0.798; 95% CI: 0.43–1.438; P=0.45]. On this basis, laboratory tests were adjusted at admission (white blood cell count, absolute lymphocyte count, RBC count, hemoglobin, total bilirubin, alanine aminotransferase level, AST level, albumin level), and the association of vaccination with pneumonia was still not statistically significant (aOR =0.797; 95% CI: 0.436–1.455; P=0.46).

When other factors were not adjusted for, the effect of vaccination on oxygen therapy was statistically significant (OR =0.195; 95% CI: 0.118–0.324; P<0.001). After factors of age, comorbidities, and time from onset to hospitalization were adjusted for, vaccination had a statistically significant association with receiving oxygen therapy (aOR =0.324; 95% CI: 0.182–0.578; P<0.001). After the factors of age, comorbidities, time from onset to hospitalization, and vital signs (body temperature and systolic blood pressure) were adjusted for, the association of vaccination with receiving oxygen therapy remained statistically significant (aOR =0.315; 95% CI: 0.175–0.567; P<0.001). On this basis, after adjustments were made for laboratory tests on admission (absolute lymphocyte value, hemoglobin level, platelet count, albumin level, globulin level, and urea level), the association of vaccination with oxygen therapy remained statistically significant (aOR =0.317; 95% CI: 0.175–0.573; P<0.001).

When other factors were not adjusted for, the association of vaccination with severe disease was statistically significant (OR =0.045; 95% CI: 0.019–0.104; P<0.001). After factors of age and comorbidities were adjusted for, the association of vaccination with severe disease was statistically significant (aOR =0.122; 95% CI: 0.047–0.317; P<0.001). After adjustments were made for age, comorbidities, and systolic blood pressure at admission, vaccination had a statistically significant association with severe disease (aOR =0.122; 95% CI: 0.047–0.317; P<0.001). On this basis, after adjustments were made for laboratory tests on admission (absolute lymphocyte count, absolute monocyte count, hemoglobin level, platelet count, albumin level, and urea level), the association of vaccination with severe disease remained statistically significant (aOR =0.122; 95% CI: 0.045–0.331; P<0.001).

When other factors were not adjusted for, the association of vaccination with mechanical ventilation or death was statistically significant (OR =0.022, 95% CI: 0.005–0.102; P<0.001). After adjustments were made for age and comorbidities, the association of vaccination with mechanical ventilation or death was statistically significant (aOR =0.113; 95% CI: 0.020–0.639; P=0.01). After adjustments were made for age, comorbidities, and systolic blood pressure at hospital admission, vaccination had a statistically significant association with mechanical

Table 4 Univariate logistic regression

Variables	Pneumonia		Oxygen therapy		Severe/critical COVID-19		Mechanical ventilation or death	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	1.053 (1.040–1.065)	<0.001	1.052 (1.039–1.065)	<0.001	1.091 (1.062–1.121)	<0.001	1.156 (1.095–1.220)	<0.001
Sex, female	1.381 (1.012–1.885)	0.04	1.100 (0.771–1.571)	0.60	1.097 (0.513–2.344)	0.81	1.266 (0.404–3.968)	0.69
Smoking history	0.563 (0.230–1.377)	0.21	1.205 (0.460–3.159)	0.70	2.445 (0.541–11.058)	0.25	2.814 (0.346–22.862)	0.33
Comorbidities	3.777 (2.342–6.092)	<0.001	4.839 (3.135–7.469)	<0.001	22.895 (9.025–58.084)	<0.001	61.464 (7.846–481.515)	<0.001
Hospitalization within 1 week of onset	0.507 (0.338–0.759)	<0.001	2.128 (1.260–3.595)	0.005	2.050 (0.609–6.900)	0.25	2.675 (0.342–20.914)	0.35
Vaccinated	0.486 (0.291–0.814)	0.006	0.195 (0.118–0.324)	<0.001	0.045 (0.019–0.104)	<0.001	0.022 (0.005–0.102)	<0.001
Temperature (℃)	1.305 (0.986–1.726)	0.06	1.521 (1.123–2.059)	0.007	1.766 (0.997–3.128)	0.05	2.012 (0.889–4.553)	0.09
Pulse (beats/min)	0.991 (0.980–1.003)	0.15	1.010 (0.996–1.023)	0.15	1.017 (0.990–1.045)	0.22	1.000 (0.957–1.045)	>0.99
Respiratory rate (breaths/min)	1.020 (0.932–1.116)	0.67	1.030 (0.928–1.143)	0.58	1.075 (0.861–1.342)	0.52	0.975 (0.697–1.362)	0.88
Systolic pressure (mmHg)	1.001 (0.991–1.010)	0.91	1.014 (1.003–1.025)	0.01	1.034 (1.015–1.054)	<0.001	1.041 (1.015–1.068)	0.002
Diastolic pressure (mmHg)	1.000 (0.987–1.013)	0.96	1.010 (0.995–1.025)	0.20	1.010 (0.980–1.041)	0.53	1.006 (0.960–1.054)	0.80
WBC ($\times10^9$/L)	0.899 (0.825–0.981)	0.02	0.969 (0.877–1.070)	0.53	0.950 (0.763–1.183)	0.65	0.781 (0.532–1.146)	0.21
Neutrophil ($\times10^9$/L)	0.932 (0.844–1.030)	0.17	1.074 (0.961–1.200)	0.21	1.065 (0.847–1.339)	0.59	0.971 (0.665–1.417)	0.88
Lymphocyte ($\times10^9$/L)	0.707 (0.547–0.913)	0.008	0.459 (0.329–0.641)	<0.001	0.275 (0.121–0.624)	0.002	0.092 (0.020–0.431)	0.002
Monocyte ($\times10^9$/L)	0.647 (0.259–1.616)	0.35	1.730 (0.613–4.878)	0.30	14.069 (2.058–96.197)	0.007	2.414 (0.100–58.367)	0.59
RBC ($\times10^{12}$/L)	0.506 (0.375–0.684)	<0.001	0.829 (0.596–1.154)	0.27	0.633 (0.313–1.278)	0.20	0.205 (0.070–0.595)	0.004
Hemoglobin (g/L)	0.980 (0.972–0.989)	<0.001	0.990 (0.981–0.999)	0.03	0.981 (0.964–0.998)	0.03	0.974 (0.950–0.998)	0.04
Platelet ($\times10^9$/L)	0.999 (0.997–1.002)	0.51	0.995 (0.992–0.998)	<0.001	0.990 (0.983–0.997)	0.004	0.983 (0.973–0.994)	0.002
TBIL (μmol/L)	0.969 (0.943–0.996)	0.03	0.995 (0.965–1.027)	0.77	1.022 (0.962–1.085)	0.49	1.024 (0.937–1.120)	0.60
ALT (IU/L)	1.007 (1.002–1.011)	0.003	0.999 (0.995–1.003)	0.68	1.005 (0.999–1.012)	0.08	0.999 (0.984–1.014)	0.89
AST (IU/L)	1.010 (1.003–1.017)	0.004	1.003 (0.997–1.010)	0.31	1.008 (0.998–1.018)	0.13	1.003 (0.985–1.022)	0.75
Albumin (g/L)	0.884 (0.848–0.921)	<0.001	0.942 (0.902–0.983)	0.007	0.819 (0.748–0.896)	<0.001	0.918 (0.803–1.050)	0.21
Globulin (g/L)	1.029 (0.989–1.070)	0.16	1.063 (1.015–1.112)	0.009	1.024 (0.930–1.128)	0.63	0.989 (0.854–1.146)	0.89
Urea (mmol/L)	1.060 (0.957–1.175)	0.27	1.173 (1.030–1.335)	0.02	1.284 (1.018–1.620)	0.03	1.420 (1.013–1.989)	0.04
Creatinine (μmol/L)	1.001 (0.997–1.004)	0.69	1.004 (0.997–1.012)	0.27	1.006 (0.998–1.013)	0.15	1.011 (0.987–1.035)	0.37

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; WBC, white blood cell; RBC, red blood cell; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

ventilation or death (aOR =0.110; 95% CI: 0.019–0.631; P=0.01). On this basis, after adjustments were made for laboratory tests on admission (absolute lymphocyte count, RBC count, hemoglobin level, platelet count, and urea level), the association of vaccination with mechanical ventilation or death remained statistically significant (aOR =0.042; 95% CI: 0.004–0.406; P=0.006).

Subgroup analysis

We divided the significant variables in the univariate logistic regression analysis into subgroups for analysis. For pneumonia, there was an interaction between vaccination and AST level at admission (*Figure 2*). There was no interaction between the vaccination and other subgroups.

Table 5 Odds ratios (95% CI) for clinical outcomes of the vaccinated and unvaccinated groups

Clinical outcome	Models	Vaccinated group (n=578)	Unvaccinated group (n=73)	P value
Pneumonia	Unadjusted	0.486 (0.291–0.814)	1 (ref)	0.006
	Multivariable adjusted for age, sex, comorbidities, and hospitalization within 1 week of onset	0.798 (0.443–1.438)	1 (ref)	0.45
	Multivariable adjusted for age, sex, comorbidities, hospitalization within 1 week of onset, WBC count, lymphocyte, RBC count, hemoglobin, TBIL, ALT, AST, and albumin	0.797 (0.436–1.455)	1 (ref)	0.46
Oxygen therapy	Unadjusted	0.195 (0.118–0.324)	1 (ref)	<0.001
	Multivariable adjustment for age, comorbidities, and hospitalization within 1 week of onset	0.324 (0.182–0.578)	1 (ref)	<0.001
	Multivariable adjustment for age, comorbidities, hospitalization within 1 week of onset, temperature, and systolic pressure	0.315 (0.175–0.567)	1 (ref)	<0.001
	Multivariable adjustment for age, comorbidities, hospitalization within 1 week of onset, temperature, systolic pressure, lymphocyte, hemoglobin, platelet, albumin, globulin, and urea	0.317 (0.175–0.573)	1 (ref)	<0.001
Severe/ critical COVID-19	Unadjusted	0.045 (0.019–0.104)	1 (ref)	<0.001
	Multivariable adjustment for age and comorbidities	0.122 (0.047–0.317)	1 (ref)	<0.001
	Multivariable adjustment for age, comorbidities, and systolic pressure	0.122 (0.047–0.317)	1 (ref)	<0.001
	Multivariable adjustment for age, comorbidities, systolic pressure, lymphocyte, monocyte, hemoglobin, platelet, albumin, and urea	0.122 (0.045–0.331)	1 (ref)	<0.001
Mechanical ventilation or death	Unadjusted	0.022 (0.005–0.102)	1 (ref)	<0.001
	Multivariable adjustment for age and comorbidities	0.113 (0.020–0.639)	1 (ref)	0.01
	Multivariable adjustment for age, comorbidities, and systolic pressure	0.110 (0.019–0.631)	1 (ref)	0.01
	Multivariable adjustment for age, comorbidities, systolic pressure, lymphocyte, RBC count, hemoglobin, platelet, and urea	0.042 (0.004–0.406)	1 (ref)	0.006

Continuous variables: age, temperature, systolic pressure, WBC, lymphocyte, monocyte, RBC, hemoglobin, platelet, TBIL, ALT, AST, albumin, globulin, and urea. Categorical variables: sex (male or female), comorbidities (yes or no), hospitalization within 1 week of onset (yes or no). CI, confidence interval; WBC, white blood cell; RBC, red blood cell; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019.

The effects of vaccination on oxygen therapy, severe illness, and mechanical ventilation or death were not heterogeneous among subgroups, and there were no interactions among the subgroups (*Figures 3-5*).

Discussion

The results of this study suggest that COVID-19 vaccination can reduce the incidence of pneumonia, oxygen therapy rate, severe disease rate, and mechanical ventilation or mortality in adults with the COVID-19 Delta variant. After adjustments were made for confounders, COVID-19 vaccination was found to be significantly associated with a lower risk of receiving oxygen therapy, severe illness, and mechanical ventilation or death but not with a reduction in the risk of pneumonia. In addition, we found that vaccinated patients had a high incidence of sore throat and low incidence of shortness of breath, diarrhea, and nausea or vomiting, but vaccination against COVID-19 was not found to be associated with a shortened negative transition time of viral nucleic acids.

This study found evidence indicating that vaccination with COVID-19 reduces the risk of oxygen therapy, severe illness, and mechanical ventilation or death, which is

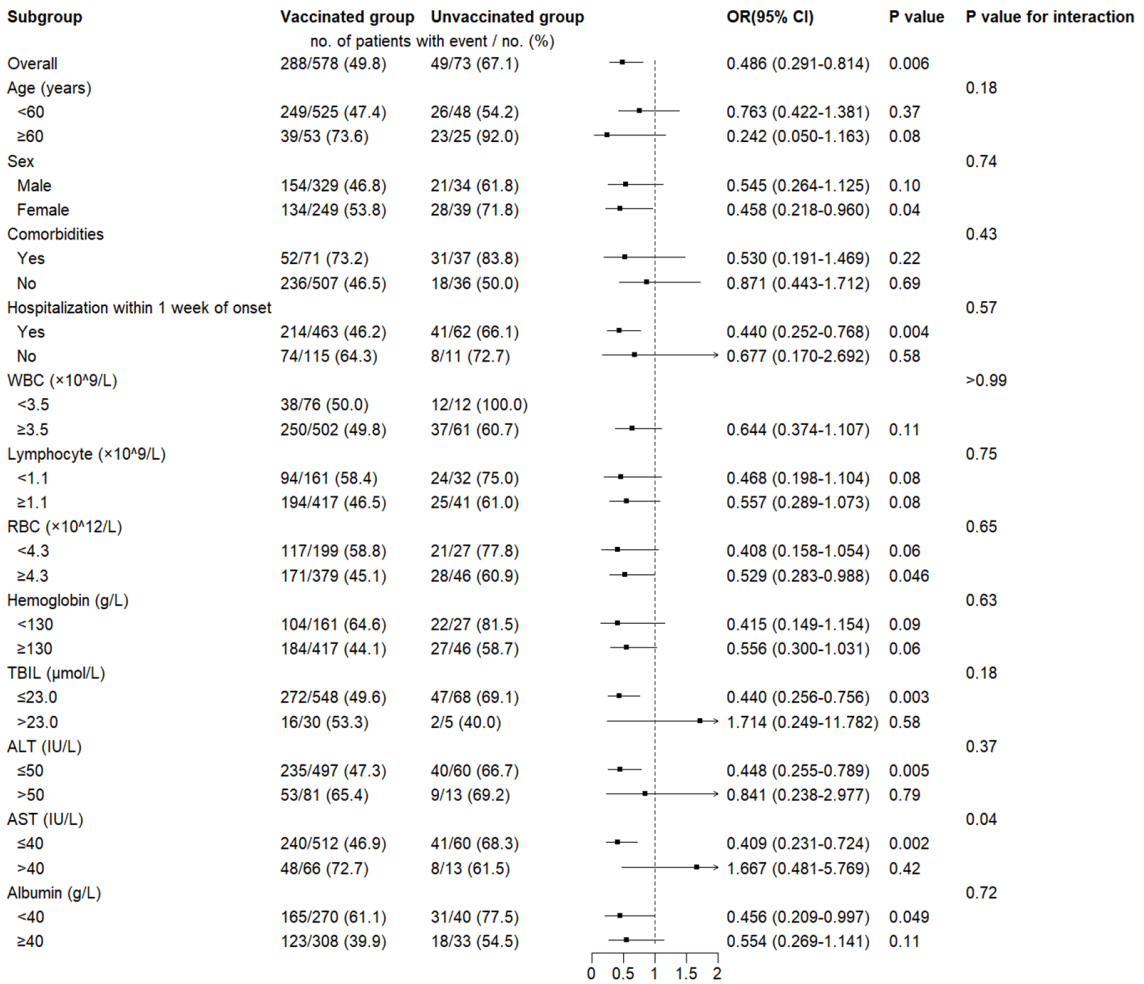

Figure 2 The subgroup analyses on the associations of vaccination and pneumonia. OR, odds ratio; CI, confidence interval; WBC, white blood cell; RBC, red blood cell; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

basically consistent with the conclusion of other studies on vaccine efficacy. Hu *et al.* found that the risk of severe illness was reduced by 88% in people infected with the Delta variant that had been fully vaccinated with the inactivated vaccine (6). A hospital-based, multicenter, case-control study in Japan reported that two doses of COVID-19 vaccine during the Delta outbreak and three doses during the Omicron outbreak were protective against the need for oxygen therapy, invasive mechanical ventilation, severe illness, and death (7). A study based on a nationwide population in South Korea found that vaccination against COVID-19 reduced the risk of severe illness and death (8). Haas *et al.* conducted a study based on the entire population of Israel and found that two doses of COVID-19 vaccine could effectively reduce COVID-19-related hospitalizations, severe cases, and death (3). A plethora of other studies have also supported the protective effect of vaccines against these adverse outcomes (2,9-11).

In this study, the incidence of pneumonia after infection with SARS-CoV-2 in the vaccinated group was lower than that in unvaccinated group. During the outbreak caused by infection with the Delta mutation in Yunnan, China in 2021, the efficacy of a completely inactivated vaccine in protecting against pneumonia was 76.7% (95% CI: 19.3–93.3%) and that of adenovirus vector vaccine was 67.9% (95% CI: 1.7–89.9%) (12). Vicini *et al.*'s study of that the frequency of pneumonia-free patients with COVID-19 who were fully vaccinated with the messenger RNA vaccine and

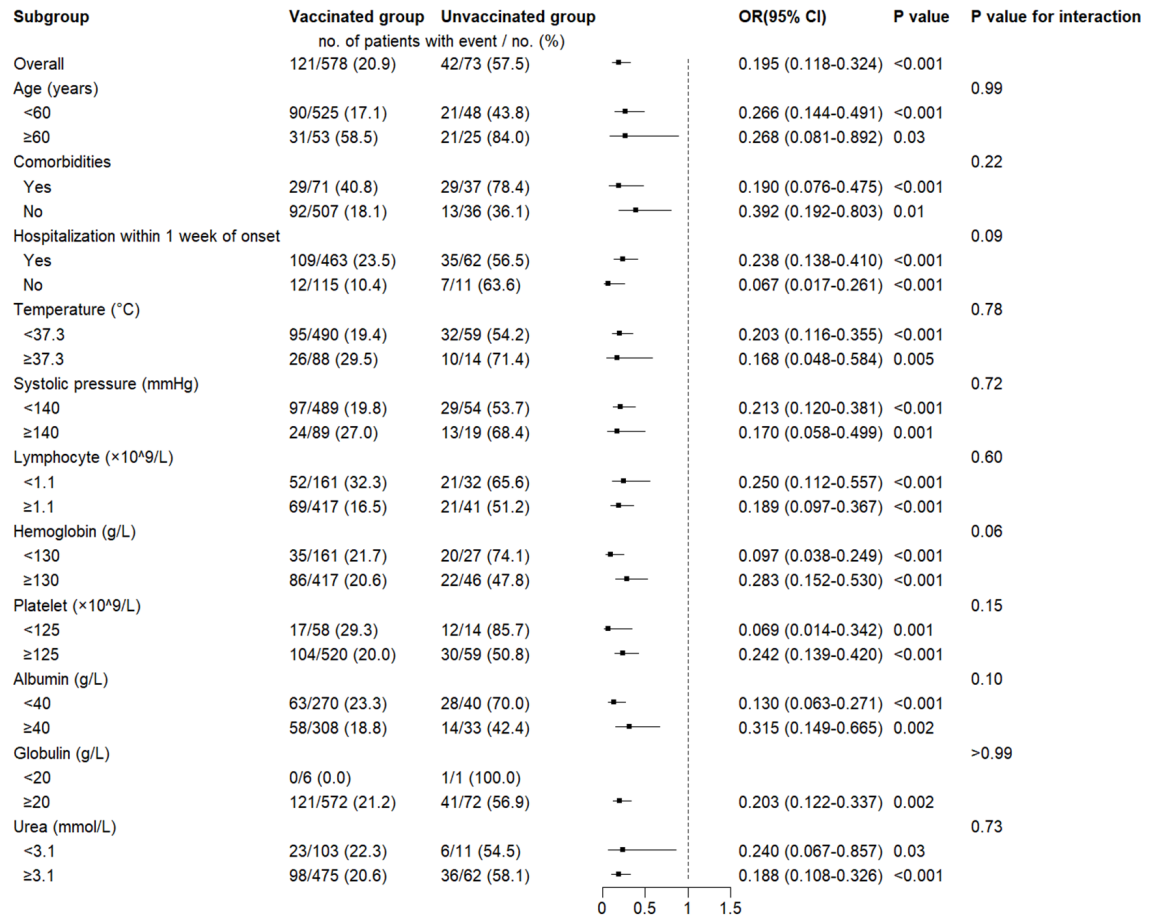

Figure 3 The subgroup analyses on the associations of vaccination and oxygen therapy. OR, odds ratio; CI, confidence interval.

adenovirus vector vaccine were 51% and 29%, respectively, both of which were higher than the 15% in those who were not vaccinated (13). During the 2021 Delta variant outbreak in Zhengzhou, China, the efficacy of a partial and full vaccination against pneumonia was 45.92% (95% CI: −15.82% to 74.75%) and 61.40% (95% CI: 36.05–76.70%), respectively (14). Several studies have confirmed the protective effect of vaccination against pneumonia (15,16). However, in our study, we found no statistically significant association of the vaccine with pneumonia after adjusting for confounders. This is inconsistent with the conclusions of the above-mentioned studies, which may be explained by the large difference in the number of people in the two groups in this study.

Among the subgroups related to age (<60 and ≥60 years) and comorbidities (with comorbidities and without comorbidities), the incidence of pneumonia, severe disease, oxygen therapy, and mechanical ventilation or mortality was higher in the unvaccinated patients than in the vaccinated patients (*Figures 2-5*). In addition, we found that the incidence of these four outcomes was higher in patients over 60 years of age than in those under 60 years of age and higher in those with comorbidities than in those without comorbidities regardless of whether they had been vaccinated against COVID-19. Pezzuto *et al.* have confirmed that COVID-19 patients with comorbidities have a worse prognosis (17,18). The proportion of pneumonia in patients hospitalized after 1 week of onset was higher than that in patients hospitalized within 1 week of onset. Therefore, we recommend that older adults and those with comorbidities should be vaccinated against COVID-19 at the appropriate time according to the prevalence of COVID-19. Once infected with SARS-CoV-2, individuals should proceed to the hospital as soon as possible to receive

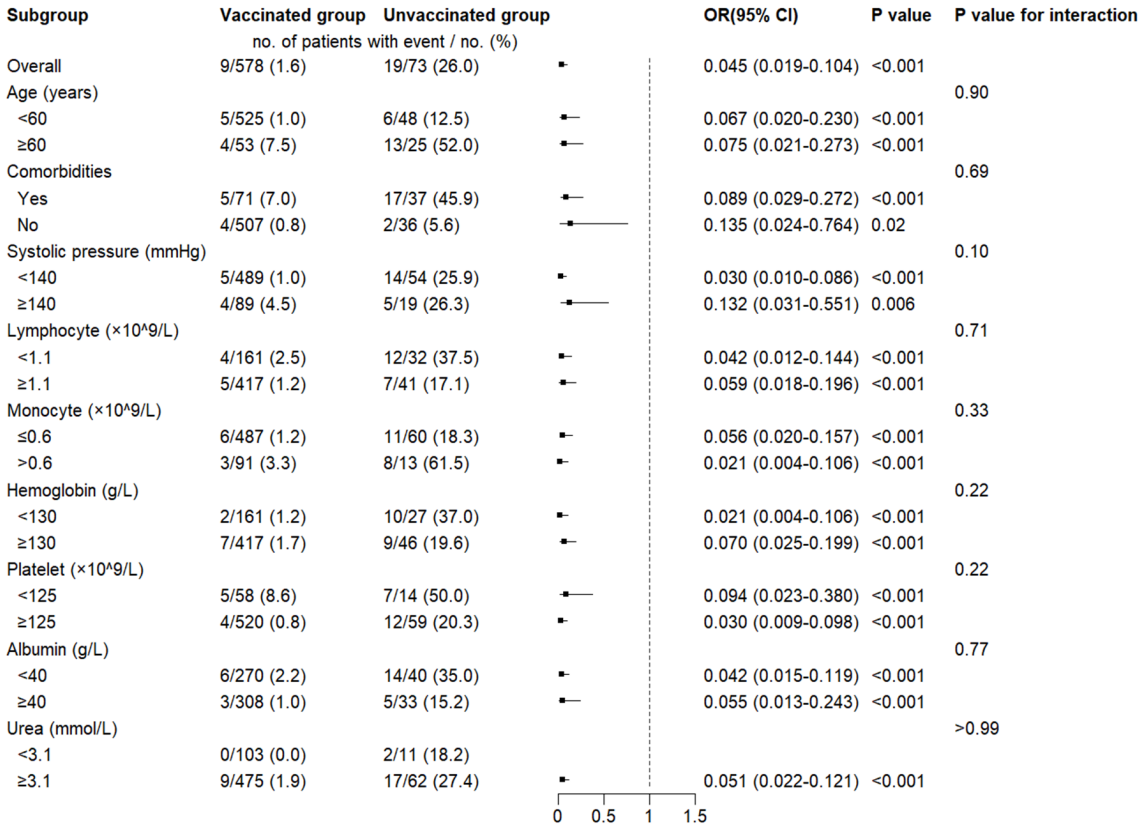

Figure 4 The subgroup analyses on the associations of vaccination and severe/critical COVID-19. OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019.

treatment in order to optimize prognosis.

In this study, the median negative nucleic acid transition time of the vaccinated group was slightly shorter than that of the unvaccinated group, but this was no significantly different. A study on a Texas prison outbreak of the Delta variant reported similar results, with a median interval of 9 and 11 days between symptom onset and the last positive real-time polymerase chain reaction result in the fully vaccinated and unvaccinated individuals, respectively (P=0.37) (19). However, some researchers have asserted that vaccination can shorten the time for the virus nucleic acid to turn negative. For example, in Luo *et al.*'s study on the November 2022 outbreak in Guangzhou, China, inoculation with inactivated vaccine and booster could shorten the nucleic acid transition time of patients with no symptoms or mild COVID-19 caused by the Omicron infection (20). In Li *et al.*'s. study on the outbreak caused by the Omicron variant in Shanghai, China, in the summer of 2022, the number of positive days of nucleic acid in vaccinated patients with mild COVID-19 was shorter than that in unvaccinated patients (5.3±2.9 *vs.* 5.9±3.3; P<0.01) (21). The patients in these studies had mild COVID-19 in the Omicron period. However, the patients included in our study were all adults with COVID-19 in the region during the Delta variant period, which is more representative of the entire infected population. Therefore, whether the vaccine can shorten the negative time of nucleic acid warrants further investigation.

This study found differences in symptoms between vaccinated and unvaccinated patients. Vaccinated patients had a higher frequency of upper respiratory symptoms (such as sore throat, stuffy nose, or runny nose) and a lower frequency of lower respiratory symptoms (such as shortness of breath) and other systemic symptoms (such as fever, fatigue, diarrhea, or nausea or vomiting). Jang *et al.*'s study reported that fully vaccinated patients had lower rates

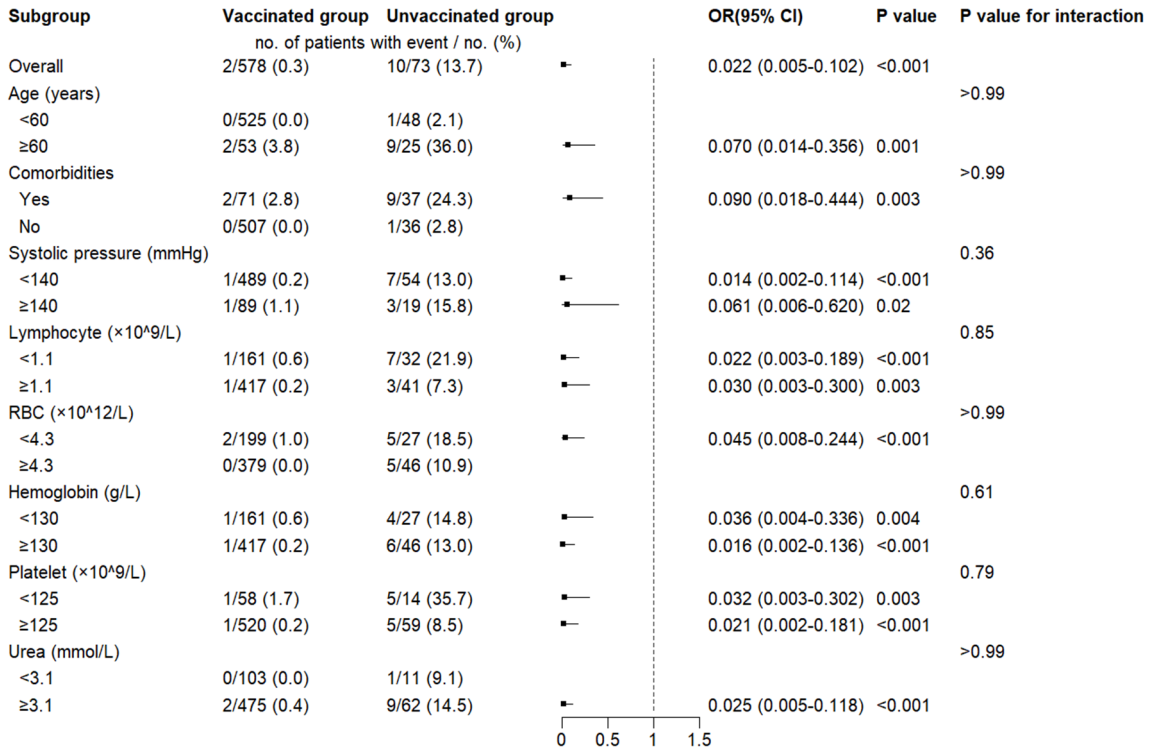

Figure 5 The subgroup analyses on the associations of vaccination and mechanical ventilation or death. OR, odds ratio; CI, confidence interval; RBC, red blood cell.

of cough, phlegm, shortness of breath, fever, and myalgia but higher rates of runny nose compared to unvaccinated patients (22). In another study on an outbreak of the COVID-19 Delta variant in Yangzhou, China, from August to September 2021, Wang *et al.* found that the frequency of dyspnea and fever in the two-dose vaccine group was lower than that in the unvaccinated group (dyspnea: 0% *vs.* 9.4%, P=0.045; fever: 11.4% *vs.* 32.1%, P=0.03) (23). In addition, the incidence of fatigue, myalgia, and diarrhea in the two-dose vaccine group was lower than that in the unvaccinated group, while the incidence of sore throat was higher than that in the unvaccinated group. These results are basically consistent with the results of this study. It is well known that the COVID-19 vaccine can induce specific humoral and cellular immune responses in humans (24-26). We speculate that after people who have been vaccinated against COVID-19 are infected with SARS-CoV-2, due to the presence of neutralizing antibodies and immune cells in the blood, it is difficult for the virus to enter the blood, and it is mainly confined to the respiratory tract. Therefore, vaccinated patients mainly present with upper respiratory tract symptoms, and the incidence of other systemic symptoms is low.

This study involved several limitations that should be discussed. First, the sample size was small, especially the number of patients in the unvaccinated group. This is due to China's aggressive vaccination policy, with the vast majority of people being vaccinated against COVID-19. Second, we did not analyze the relationship between different vaccine types, vaccine doses, complete vaccination, and postvaccination time and outcomes. Of the 578 vaccinated patients, 93.3% received the inactivated vaccine, while the recombinant subunit vaccine and adenovirus vector vaccine accounted for only 6.2% and 0.5% of patients, respectively (Table S2). Among the patients, 84.4% received two doses, 12.5% received three doses, and only 3.1% of patients received one dose, with most (88.9%) being completely inoculated. Partial and intensive vaccination accounted for 3.8% and 7.3% of patients, respectively. In terms of time from vaccination to onset, 42 patients were missing the time of last vaccination. Of the 536 patients who reported the date of last vaccination, 95.3% were infected with SARS-

CoV-2 within 6 months of vaccination, and the highest concentration was between 4 and 6 months, accounting for 81.7% of patients. This is mainly due to the fact that the COVID-19 vaccine is administered in batches, so the vaccination time is more concentrated. This study included all patients with COVID-19 admitted to designated hospital in the Xi'an region within a specified period of time, and the main results were basically consistent with the results of relevant studies. Therefore, the results of this study have a certain extrapolatory value. Larger studies in the general population could be carried out in the future, and further analysis as to whether COVID-19 vaccine can shorten the negative nucleic acid transition time should be conducted.

Conclusions

For those infected with the Delta variant of SARS-CoV-2, vaccination reduces the risk of receiving oxygen therapy, severe illness, and mechanical ventilation or death. Moreover, our results suggest that vaccination against COVID-19 can reduce the incidence of pneumonia. Vaccinated patients had a high incidence of sore throat and a low incidence of shortness of breath, diarrhea, and nausea or vomiting. However, vaccination was not associated with a shortened time for nucleic acid to become negative.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1351/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1351/coif). X.L. reports funding from Scientific Research Project of Air Force Equipment Comprehensive Research (No. KJ2023C0KYD23). L.S. reports funding from Key Projects of Basic Research of Natural Science in Shaanxi Province (No. 2022JZ-58). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Air Force Medical University (also known as Xijing Hospital) (approval No. KY20222118-F-1). The requirement for individual consent was waived due to the retrospective nature of the analysis.

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