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Original Article

Risk of extended viral shedding of Omicron BA.2 in Shanghai: Implications for vaccination strategy optimization

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ABSTRACT

Background: In late March 2022, an outbreak of coronavirus disease 2019 (COVID-19) caused by the Omicron BA.2 strain occurred in Shanghai, China. This retrospective study aimed to investigate the clinical characteristics, laboratory parameters, and vaccine protectiveness related to this disease in China.

Methods: We conducted a single-center retrospective study on 735 patients with COVID-19 hospitalized from March 17 to May 14, 2022. Clinical characteristics were analyzed based on vaccination status and viral shedding time (VST). The least absolute shrinkage and selection operator (LASSO) regression and 5-fold cross-validation were applied to screen factors linked to the rate of the VST. Generalized linear models were further applied to estimate the odds ratios for factors influencing the VST.

Results: The median VST of unvaccinated patients was 13 (11–16) days, which was longer than that of patients vaccinated with one or two doses (11 [9–13] days) and with completed booster doses (11 [8–12] days). A LASSO regression model and 5-fold cross-validation showed that age of ≥60 years ($\beta = 0.01$), pneumonia ($\beta = 0.53$), and higher number of comorbidities ($\beta = 0.69$) were positively associated with the VST, whereas the platelet count ($\beta = -8.0\times10^{-5}$) was inversely associated with the VST. Subgroup analysis revealed that the number of vaccinations was significantly associated with a decreased VST among patients with renal dysfunction (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.44–0.97; $P = 0.034$) and patients with two or more comorbidities (OR, 0.09; 95% CI, 0.03–0.28; $P < 0.001$). The lymphocyte count was significantly associated with a decreased VST among patients aged <60 years (OR, 0.51; 95% CI, 0.30–0.85; $P = 0.011$), patients with normal renal function (OR, 0.41; 95% CI, 0.21–0.80; $P = 0.009$), and patients with fewer than two comorbidities (OR, 0.49; 95% CI, 0.30–0.80; $P = 0.005$).

Conclusion: Our preliminary results suggest that the complete and booster vaccination contributes to the viral clearance of Omicron BA.2 variants, while the protectiveness of vaccination is most imperative in patients with impaired renal function and more comorbidities.

Introduction

A new variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), B.2, has become the dominant variant circulating in many countries because of increased transmissibility and capacity for immune escape (https://covariants.org/per–variant).[1] In late March 2022, an outbreak of coronavirus disease 2019 (COVID-19) caused by the Omicron BA.2 strain occurred in Shanghai, China. By early May, more than 500,000 cases had been diagnosed by reverse transcription–polymerase chain reaction (RT-PCR) for SARS-CoV-2 (https://www.shio.gov.cn/TrueCMS/shxwbgs/2022n_6y/2022n_6y.html). Certain clinical characteristics, such as older age, obesity, comorbidities, and presenting symptoms, as well as some laboratory parameters have been proven to be associated with a poor prognosis of COVID-19.[2,3]

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Vaccination is a key strategy to reduce the spread and severity of COVID-19. Three inactivated vaccines are the main types of vaccines in Shanghai: the CoronaVac inactivated vaccine, the BBIBP-CorV vaccine, and the WIBP-CorV vaccine. A demonstration in Hong Kong by the Chinese Center for Disease Control and Prevention revealed significant vaccine effectiveness for reducing COVID-19-associated mortality, regardless of the type of vaccine used.[4,5] Statistical data from Jilin province, China also showed fewer severe or critical cases of COVID-19 among patients who received full vaccination (two doses) and booster vaccination (three doses). In recent studies, Ai et al[6] reported that a third homologous dose showed a satisfactory safety profile and higher immune response.

To gain a deeper understanding of the theories underlying the disease pathogenesis and to assist with the development of risk stratification for the general population, we retrospectively analyzed the Omicron BA.2-related outcomes, clinical characteristics, laboratory parameters, and vaccine protectiveness at Ruijin Hospital in Shanghai, a designated hospital for COVID-19.

Methods

Study design and participants

This retrospective cohort study involved individual residents of Shanghai who had been confirmed to be infected with SARS-CoV-2 by the Shanghai Municipal Center for Disease Control and Prevention within 5 weeks between March 17 and May 14, 2022. We excluded patients with no vaccination information and inpatients who were confirmed to have a positive nucleic acid test within one week before May 14, 2022 but whose nucleic acid test result had not turned negative at the endpoint. All patients were hospitalized at the Northern District of Ruijin Hospital Affiliated to the Medical College of Shanghai Jiao Tong University. The study was approved by the ethics committees of Shanghai Public Health Clinical Center and Ruijin Hospital Affiliated to the Medical College of Shanghai Jiao Tong University. The ethical batch number was RJ2018NO197. All procedures performed in studies involving human participants followed the ethical standards of the institutional and/or national research committee and the *Declaration of Helsinki*.

Data collection

A confirmed case of Omicron was defined as a positive RT-PCR result from an upper respiratory tract pharyngeal swab sample. We collected epidemiological data, demographic data, vaccination status, clinical symptoms, and laboratory examination results from the patients' medical records. All data were checked by two physicians.

Outcomes

The study endpoint was a negative PCR test result. Specifically, according to the Diagnosis and Treatment Protocol for COVID-19 Patients (9th edition) issued by the National Health Commission of the People's Republic of China,[7] we considered the first day as the study endpoint when the threshold cycle values of both the *N* gene and *ORF* gene in the nucleic acid test were ≥35 for two consecutive negative tests. The viral shedding time (VST) was defined as the number of days between the first positive test and the first of two consecutive negative tests.

Variables

The severity of SARS-CoV-2 was judged according to the Diagnosis and Treatment Protocol for COVID-19 Patients (9th edition) issued by the National Health Commission of the People's Republic of China.[7] Pneumonia was diagnosed when computed tomography revealed pulmonary exudate or inflammatory lesions. In the biochemical examination, patients were considered to have abnormal liver function if their alanine aminotransferase and aspartate aminotransferase concentrations were higher than two times the upper limit of normal, abnormal renal function if their urea nitrogen concentration was >7 mmol/L and creatinine concentration was >106 mmol/L (men) or >80 mmol/L (women), and abnormal electrolytes if their serum electrolyte concentrations were beyond the reference ranges of sodium, potassium, calcium, magnesium, chlorine, and phosphorus.

Statistical analysis

We focused on the effectiveness of booster doses for individuals who were given inactivated SARS-CoV-2 vaccines. Therefore, we divided the overall population into three groups according to their vaccination status: no doses, one or two doses, and booster doses. The distribution of variables was mapped and checked by the Kolmogorov–Smirnov test. Normally distributed continuous variables are expressed as mean ± standard deviation, and continuous variables with a skewed distribution are expressed as median (Q_1, Q_3).

Continuous variables were compared between two groups using the *t*-test or Mann–Whitney *U* test, and continuous variables were compared among three or more groups using analysis of variance or the Kruskal–Wallis test. Categorical variables were compared using the χ^2 test or Fisher's exact test. A least absolute shrinkage and selection operator (LASSO) model was applied to screen factors linked to the rate of the VST. The "glmnet" package was utilized to fit the LASSO regression, and 5-fold cross-validation was conducted to select the penalty term, lambda (λ). We selected the largest λ that was within 1 standard error of the minimum binomial deviance (lambda.1se) and the minimum binomial deviance (lambda.min) to identify the most critical covariates affecting the VST. Generalized linear models were further applied to estimate the odds ratios (ORs) for factors influencing the VST. Principal component analysis (PCA) was applied to explore the correlations of variables with the platelet count. The "psych" package was applied to fit the PCA, and internal validation was performed by applying the 200 bootstrap-resampling technique.

Statistical analysis was performed using SPSS Version 26.0 statistical software (IBM Corp., Armonk, NY, USA), R 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism Software Version 8.0 (GraphPad Software, San Diego, CA, USA). Two-sided *P* values of <0.05 were considered statistically significant.

Results

Clinical characteristics of the population

In total, 735 of the hospitalized patients who met the study inclusion criteria were available for analysis (Supplementary Fig. 1). The baseline characteristics of all patients and comparisons between different vaccination status groups are shown in Table 1.

The proportion of patients aged ≥60 years (110/201, 54.7%) was significantly higher among unvaccinated patients than among patients who had been vaccinated with one or two doses (44/239, 18.4%) and patients who had completed booster doses (48/295, 16.3%). The proportions of patients with moderate (76/201, 37.8%), severe (2/201, 1.0%), and critical (7/201, 3.5%) disease in the unvaccinated group were higher than the proportions of patients who had been vaccinated with one or two doses (16/239, 6.7% moderate disease) and the proportions of patients who had completed booster doses (11/295, 3.7% moderate disease) (Table 1 and Supplementary Fig. 2). Patients in the unvaccinated group had more comorbidities compared with the other groups, including hypertension, diabetes, cardiovascular disease, renal failure, cerebrovascular disease, and cancer (Supplementary Fig. 3A). A total of 32.8% (66/201) of the patients in the unvaccinated group had two or more comorbidities, compared with only 6.7% (16/239) of the patients who had received one or two doses and 4.1% (12/295) of the patients who had completed booster doses. In addition, patients with

Table 1
Clinical features of patients on admission and comparison between different vaccination groups (*N*=735).

All participants	Unvaccinated	Vaccination status: one/two doses	Vaccination status: three doses	*P* values
Overall	201 (27.3)	239 (32.5)	295 (40.2)	
Male	106 (52.7)	140 (58.6)	165 (55.9)	0.474
Age group				**<0.001**
≥60 years	110 (54.7)	44 (18.4)*	48 (16.3)*	
Clinical classification				**<0.001**
Asymptomatic	50 (24.9)	116 (48.5)*	161 (54.6)*	
Mild	66 (32.8)	107 (44.8)*	123 (41.7)	
Moderate	76 (37.8)	16 (6.7)*	11 (3.7)*	
Severe	2 (1.0)	0 (0)	0 (0)	
Critical	7 (3.5)	0 (0)*	0 (0)*	
Hypertension	100 (49.8)	27 (11.3)*	34 (11.5)*	**<0.001**
Diabetes	33 (16.4)	10 (4.2)*	14 (4.7)*	**<0.001**
Respiratory diseases	9 (4.5)	5 (2.1)	8 (2.7)	0.299
Cardiovascular disease	18 (9.0)	4 (1.7)*	3 (1.0)*	**<0.001**
Renal failure	45 (22.4)	2 (0.8)*	1 (0.3)*	**<0.001**
Cerebrovascular disease	9 (4.5)	3 (1.3)	0 (0)*	**<0.001**
Cancer	12 (6.0)	3 (1.3)*	3 (1.0)*	**0.001**
Comorbidities				**<0.001**
None	78 (38.8)	201 (84.1)*	247 (83.7)*	
1	57 (28.4)	22 (9.2)*	36 (12.2)*	
2	37 (18.4)	16 (6.7)*	9 (3.1)*	
≥3	29 (14.4)	0 (0)*	3 (1.0)*	
Immunosuppression	2 (1.0)	0 (0)	0 (0)	0.075
Leucocyte ($\times10^9$/L)	5.05 (3.63, 6.38)	4.93 (3.90, 6.22)	5.12 (4.26, 6.42)	0.107
Neutrophil ($\times10^9$/L)	2.93 (2.10, 4.14)	2.74 (1.97, 3.88)	2.91 (2.19, 3.89)	0.283
Lymphocyte ($\times10^9$/L)	1.20 (0.6, 1.70)	1.59 (1.19, 2.04)*	1.66 (1.29, 2.09)*	**<0.001**
Eosinophils ($\times10^9$/L)	0.04 (0.01, 0.10)	0.07 (0.02, 0.11)*	0.07 (0.03, 0.14)*,†	**<0.001**
Hemoglobin (g/L)	124 (111, 142)	145 (131, 155)*	144 (132, 155)*	**<0.001**
Monocyte ($\times10^9$/L)	0.43 (0.21, 0.57)	0.40 (0.32, 0.55)	0.43 (0.33, 0.54)	0.891
Basophils ($\times10^9$/L)	0.01 (0.01, 0.02)	0.02 (0.01, 0.03)*	0.02 (0.01, 0.03)*	**<0.001**
Platelet ($\times10^9$/L)	169 (126, 217)	198 (158, 236)*	203 (174, 237)*	**<0.001**
Total bilirubin (μmol/L)	9.70 (7.88, 14.03)	10.30 (8.08, 13.63)	11.30 (8.28, 14.70)	0.153
ALT (IU/L)	18.0 (13.0, 28.0)	22.0 (15.0, 33.0)*	20.5 (15.0, 30.3)*	**0.007**
AST (IU/L)	21.0 (17.0, 29.0)	21.5 (18.0, 28.0)	21.0 (18.0, 26.0)	0.418
Abnormal liver function	13 (6.5)	7 (2.9)	5 (1.7)*	**0.012**
Albumin (g/L)	39.0 (37.0, 42.0)	42.0 (40.0, 44.0)*	41.0 (39.8, 43.0)*	**<0.001**
Urea (mmol/L)	5.90 (4.40, 23.78)	4.50 (3.68, 5.30)*	4.50 (3.90, 5.40)*	**<0.001**
Creatinine (mmol/L)	87.0 (71.0, 725.5)	76.0 (64.0, 87.3)*	75.5 (65.0, 85.3)*	**<0.001**
Abnormal renal function	113 (56.2)	91 (38.1)*	99 (33.6)*	**<0.001**
Electrolyte abnormality	129 (64.2)	104 (43.5)*	100 (33.9)*	**<0.001**
Days to nucleic negative	13 (11, 16)	11 (9, 13)*	11 (8, 12)*	**<0.001**
Days to nucleic negative >10	154 (76.6)	123 (51.5)*	166 (56.3)*	**<0.001**

Continuous parameters are presented as median (25th to 75th percentile), and categorical data are presented as *n* (%). Categorical variables are compared using the χ^2 test or Fisher's exact test, and continuous variables are compared using analysis of variance (ANOVA) or the Kruskal–Wallis test. *Compared with the unvaccinated group, P <0.05. †Compared with the group that had been vaccinated with one or two doses, P <0.05. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

more comorbidities were more likely to develop pneumonia. Pneumonia developed in 75.0% (24/32) of patients with more than three comorbidities (including patients with moderate, severe, and critical disease), whereas pneumonia developed in 48.4% (30/62), 38.3% (44/115), and 2.7% (14/526) of patients with two, one, and no comorbidities, respectively (Supplementary Fig. 3B).

The lymphocyte count, eosinophil count, hemoglobin concentration, basophil count, and platelet count were lower in unvaccinated patients than in patients who had received one or two doses and in those who had completed booster doses. Biochemical examination was another routine laboratory test conducted among the inpatients. The results showed that the serum albumin concentration was significantly lower in unvaccinated patients than in patients who had received one or two doses and in those who had completed booster doses. The proportions of patients with abnormal liver function, abnormal renal function, and electrolyte abnormalities were highest in the unvaccinated group.

Factors related to VST

The median VST was 13 (11–16) days in unvaccinated patients, 11 (9–13) days in patients who had been vaccinated with one or two doses, and 11 (8–12) days in patients with completed booster doses. The distribution maps of the patients' VST are shown in Supplementary Fig. 4. For simplicity, we divided the VST into two groups: a long time window (>10 days) and a short time window (≤10 days). Comparisons between patients with long and short time windows are shown in Supplementary Table 1.

There were significantly more patients aged ≥60 years and more patients with pneumonia in the long than short time window group. In addition, patients with a prolonged VST had more comorbidities. Higher proportions of patients with a history of hypertension, cardiovascular disease, and renal failure were observed in the long than short time window group. With respect to laboratory findings, the long time window group showed a lower leukocyte count, lymphocyte count, hemoglobin concentration, platelet count, and albumin concentration. Abnormal renal function indexes were present in 44.7% (198/443) and 36.0% (105/292) of patients in the long and short time window group, respectively.

The LASSO regression and 5-fold cross-validation were conducted to screen out the critical covariates that affect the VST. We included the laboratory examination findings, vaccination status, demographic data, and comorbidities that were significantly associated with the VST

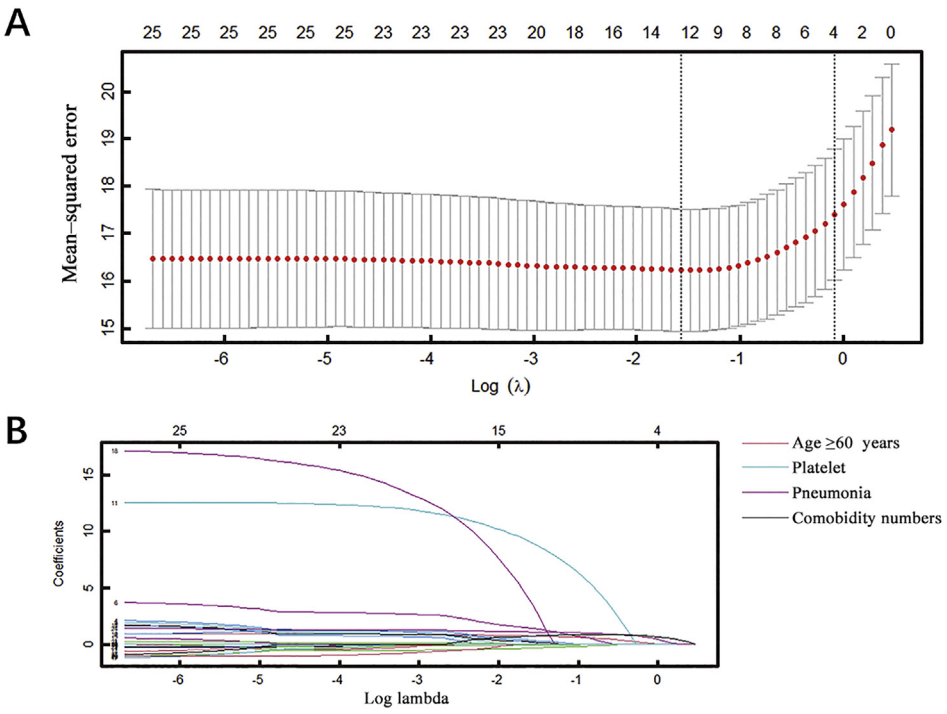

Fig. 1. LASSO regression of factors related to the viral shedding time. (A) Cross–validation plot for the penalty term. (B) Plots for LASSO regression coefficients over different values of the penalty parameter. LASSO: Least absolute shrinkage and selection operator.

Table 2
Estimated coefficients for logistic LASSO regression analysis of factors including laboratory examinations, vaccination status, demographics, and comorbidities associated with the time window of nucleic acid test negative conversion.

Variables	Coefficients (Lambda.1se)
Sex	0
Age ≥60 years	0.01
Vaccination numbers	0
Hypertension	0
Diabetes	0
Cardiovascular disease	0
Renal failure	0
Cerebrovascular disease	0
Cancer	0
Respiratory diseases	0
immunosuppression	0
Leucocyte	0
Hemoglobin	0
Neutrophil	0
Lymphocyte	0
Monocyte	0
Eosinophil	0
Basophil	0
Platelet	–8.0E–05
Abnormal liver function	0
Electrolyte abnormality	0
Abnormal renal function	0
Albumin	0
Pneumonia	0.53
Comorbidity numbers	0.69

LASSO: Least absolute shrinkage and selection operator; 1se: Within 1 standard error of the minimum binomial deviance.

in the model. When the lambda.min and lambda.1se values were 0.21 and 0.92 respectively, we filtered out four factors that were significantly associated with the VST (Fig. 1): an age of ≥60 years ($\beta = 0.01$), pneumonia ($\beta = 0.53$), and a higher number of comorbidities ($\beta = 0.69$) were positively associated with the VST, whereas the platelet count ($\beta = -8.0 \times 10^{-5}$) was inversely associated with the VST (Table 2). The λ values of the LASSO regression are shown in Supplementary Table 2.

Because the platelet count was the only factor that was inversely associated with the VST by LASSO regression, we utilized PCA to explore the variables closely correlated with the platelet count. Considering all indicators, including the vaccination status, demographics, and comorbidities, we found that the comorbid condition, especially renal function and number of comorbidities, was the most significant factor related to the platelet count (Supplementary Fig. 5). The details of the multivariate regression analysis by PCA of the platelet count as a dependent variable are shown in Supplementary Table 3.

Subgroup analysis of factors related to VST

Through the above analysis, we found that several host factors, including age, renal function, and number of comorbidities, were significantly associated with the VST. The proportion of patients receiving immunosuppressive therapy was too small to be included in subsequent analyses (2/735). Considering the heterogeneity of these characteristics in different vaccination groups (Table 1), we performed LASSO and generalized linear model regression in the subgroups and found that the completion of booster vaccinations was significantly associated with a decreased VST among patients with renal dysfunction (OR, 0.65; 95% confidence interval [CI], 0.44–0.97; $P = 0.034$) and patients with two or more comorbidities (OR, 0.09; 95% CI, 0.03–0.28; $P < 0.001$). The LASSO regression also showed that the number of vaccinations tended to be associated with a decreased VST among patients aged ≥60 years (Table 3). The λ values of the LASSO regression are shown in the Supplementary Tables 4–6. In the subgroup analysis, we found that higher lymphocyte count was significantly associated with a decreased VST among patients aged <60 years (OR, 0.51; 95% CI, 0.30–0.85; $P = 0.011$), patients with normal renal function (OR, 0.41; 95% CI, 0.21–0.80; $P = 0.009$), and patients with fewer than two comorbidities (OR, 0.49; 95% CI, 0.30–0.80; $P = 0.005$) (Table 3).

We further explored the platelet and lymphocyte counts according to the vaccination status through a subgroup analysis. The results showed that the platelet count in the unvaccinated group was lower than that in the group with completed booster doses among patients aged <60

Table 3
Generalized linear models of critical variables affecting viral shedding time in subgroup analysis.

Characteristics	Age <60 years			Age ≥60 years		
	OR (95% CI)	*t* values	*P* values	OR (95% CI)	*t* values	*P* values
Vaccination numbers	–	–	–	0.53 (0.27–1.04)	−1.85	0.067
Hypertension	2.45 (0.35–17.24)	0.90	0.369	–	–	–
CVD	–	–	–	9.13 (0.66–126.67)	1.65	0.101
Renal failure	8.86 (0.72–108.89)	1.70	0.089	–	–	–
Lymphocyte	0.51 (0.30–0.85)	−2.57	0.011	–	–	–
Platelet	0.99 (0.99–1.01)	−1.68	0.094	0.99 (0.98–1.00)	−2.06	0.041
Electrolyte abnormality	–	–	–	4.45 (0.77–25.69)	1.67	0.097
Pneumonia	3.09 (0.50–1.91)	1.21	0.226	2.37 (0.42–1.35)	0.97	0.332
Comorbidity numbers	1.18 (0.36–3.83)	0.27	0.786	1.56 (0.63–3.88)	0.97	0.343
Characteristics	Without renal dysfunction			With renal dysfunction		
	OR (95% CI)	*t* values	*P* values	OR (95% CI)	*t* values	*P* values
Age ≥60 years	4.61 (1.42–15.00)	2.54	0.012	1.34 (0.44–4.04)	0.52	0.604
Vaccination numbers	–	–	–	0.65 (0.44–0.97)	−2.14	0.034
Hypertension	–	–	–	2.21 (0.36–13.53)	0.86	0.390
CVD	81.57 (4.83–1377.72)	3.05	0.003	–	–	–
Lymphocyte	0.41 (0.21–0.80)	−2.63	0.009	–	–	–
Monocyte	–	–	–	7.06 (1.02–48.86)	1.98	0.048
Platelet	–	–	–	0.98 (0.98–0.99)	−3.94	<0.001
Electrolyte abnormality	–	–	–	1.75 (0.67–4.53)	1.15	0.251
Albumin	0.95 (0.81–1.12)	−0.58	0.560	–	–	–
Pneumonia	4.55 (0.82–25.15)	1.74	0.083	1.44 (0.34–6.10)	0.50	0.617
Comorbidity numbers	1.70 (0.78–3.68)	1.34	0.183	2.06 (0.81–5.23)	1.52	0.129
Characteristics	Comorbidity numbers <2			Comorbidity numbers ≥2		
	OR (95% CI)	*t* values	*P* values	OR (95% CI)	*t* values	*P* values
Age ≥60 years	2.89 (1.23–6.80)	2.43	0.015	–	–	–
Vaccination numbers	–	–	–	0.09 (0.03-0.28)	–4.20	<0.001
Hypertension	2.89 (1.01–8.26)	1.98	0.048	–	–	–
Diabetes	–	–	–	–	–	–
CVD	53.88 (0.74–3931.39)	1.82	0.069	–	–	–
Lymphocyte	0.49 (0.30–0.80)	−2.82	0.005	–	–	–
Basophil	–	–	–	–	–	–
Platelet	0.99 (0.99–1.00)	−1.99	0.047	–	–	–
Electrolyte abnormality	–	–	–	–	–	–
Pneumonia	5.20 (1.53–17.69)	2.64	0.009	–	–	–

CI: Confidence interval; CVD: Cardiovasuclar disease; OR: Odds ratio; –: Not applicable.

years, patients with normal renal function, and patients with fewer than two comorbidities; however, compared with unvaccinated group, the platelet count was higher in both the group that had been vaccinated with one or two doses and the group with completed booster doses among patients aged ≥60 years, patients with abnormal renal function, and patients with two or more comorbidities (Fig. 2). The lymphocyte count in the group with completed booster doses was significantly higher than that in the unvaccinated group among patients aged <60 and ≥60 years; while among patients aged <60 years, the lymphocyte count in both the group vaccinated with one or two doses and with completed booster doses was significantly higher than that in the unvaccinated group (Fig. 3). Among patients with normal renal function, the lymphocyte count in the unvaccinated group was only lower than that in the group with completed booster doses; however, the lymphocyte count in the unvaccinated group was lower than both the group that had been vaccinated with one or two doses and the group with completed booster doses among patients with renal dysfunction (Fig. 3). Among the subgroups with comorbidities <2 or ≥2, the lymphocyte count in the group with completed booster doses or with one or two doses was significantly higher than that in the unvaccinated group (Fig. 3).

Discussion

In this outbreak of Omicron BA.2 variants that emerged in Shanghai, most of the infected patients had asymptomatic or mild disease; they merely showed upper respiratory symptoms with no lower respiratory involvement.[8–10] We particularly focused on factors related to virus clearance and vaccine protection against Omicron. Overall, we demonstrated that the nucleic acid test result turns negative more slowly in patients who are aged ≥60 years, have a lower platelet count, have impaired renal function, and have more comorbidities. The relatively high lymphocyte count was significantly associated with a decreased VST among patients aged <60 years, patients with normal renal function, and patients with fewer than two comorbidities. With respect to the protection provided by vaccination, we found that the complete and booster vaccination was associated with a decreased VST among patients with renal dysfunction and patients with two or more comorbidities. Additionally, the lymphocyte and platelet counts were obviously lower in the unvaccinated group than in the group vaccinated with one or two doses and the group with completed booster doses, especially among patients aged ≥60 years, patients with abnormal renal function, and patients with two or more comorbidities. These findings highlight the importance of complete and booster vaccination in older patients, patients with impaired renal function, and patients with more comorbidities.

In several clinical studies of SARS-CoV-2, evidence suggested that the disease course was significantly longer in older patients.[3,11,12] Comorbid conditions and aging have been found to suppress adaptive T-cell responses, resulting in poor outcomes.[13,14] The immune responses of patients with comorbid conditions and aging might be impaired by the severe complications of multisystemic inflammatory syndrome after SARS-CoV-2 infection.[15] The size of the naïve T-cell repertoire decreases with advancing age. Age-dependent defects in lymphocyte function and a decreased lymphocyte count may lead to deficient control of viral replication and more prolonged proinflammatory responses.[16]

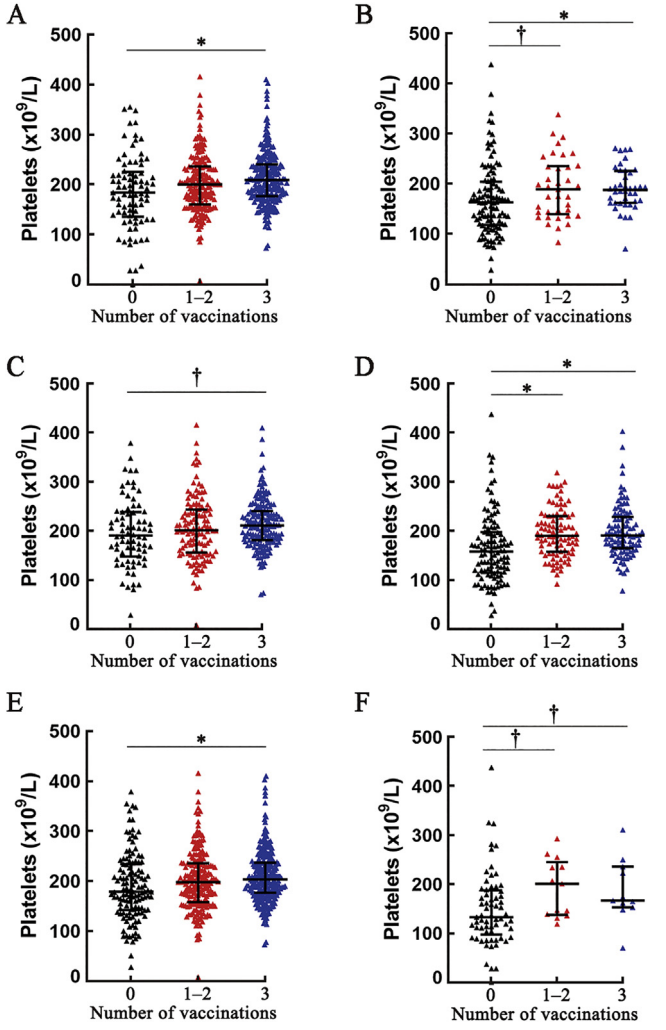

Fig. 2. Subgroup analysis of the effects of vaccination status on the platelet count of patients with different ages, renal functions, and number of comorbidities. Comparison of the lymphocyte count dependent on the vaccination status in patients aged <60 (A) and ≥60 years (B). Comparison of the platelet count dependent on the vaccination status in patients with normal (C) and abnormal (D) renal function. Comparison of the platelet count dependent on the vaccination status in patients with no and one comorbidity (E) and two or more comorbidities (F). $^{*}P < 0.01$, $^{\dagger}P < 0.05$.

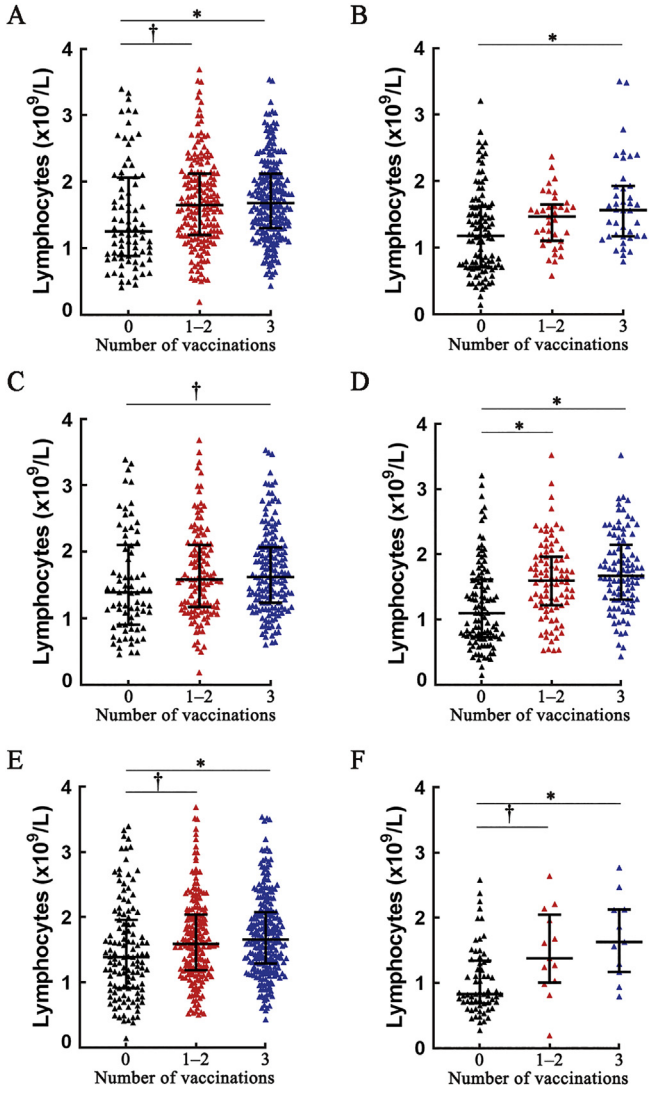

Fig. 3. Subgroup analysis of effects of vaccination status on lymphocyte count of patients with different ages, renal functions, and number of comorbidities. Comparison of lymphocyte count dependent on vaccination status in patients aged <60 (A) and ≥60 (B) years. Comparison of lymphocyte count dependent on vaccination status in patients with normal (C) and abnormal (D) renal function. Comparison of lymphocyte count dependent on vaccination status in patients with no and one comorbidity (E) and two or more comorbidities (F). $^{*}P < 0.01$, $^{\dagger}P < 0.05$.

In our cohort, patients aged ≥60 years had longer VST than those aged <60 years, and the vaccination rates of patients aged ≥60 years were relatively lower.

The prevalence of chronic kidney disease is high in various countries, and affected patients are likely to be infected with SARS-CoV-2 because of their immunocompromised status. A meta-analysis showed that approximately 20% of patients with chronic kidney disease develop severe COVID-19. The risk of severe COVID-19 among patients with chronic kidney disease was 3-fold higher than that in patients without chronic kidney disease.[17] Many studies have shown that the responses of T cells, especially CD4+ T cells, were significantly reduced in patients with chronic kidney disease compared with healthy controls; additionally, this was accompanied by broadly impaired effector cytokine production, memory differentiation, and activation-related signatures.[18] The above mechanisms may explain the results that patients with renal dysfunction have weaker antiviral ability and longer VST. Renal insufficiency is also common in patients with COVID-19. In a cohort study that examined both past and current data of 13,137 patients with COVID-19, the prevalence of acute kidney injury was 17%, and this was especially common in patients with specific complications such as diabetes or hypertension. The occurrence of acute renal injury is associated with a significantly worse prognosis in patients with COVID-19, along with decreased lymphocyte counts.[19]

Research has indicated that hypertension is the most frequent comorbidity in patients with COVID-19,[20] and non-survivors also exhibit a significantly high rate of hypertension. The underlying mechanism may be related to the angiotensin-converting enzyme/angiotensin II/angiotensin II receptor type 1 regulatory axis.[21] Patients with hypertension are more readily infected by SARS-CoV-2, but this does not necessarily correlate with higher mortality rates. The reason for this susceptibility is closely related to how SARS-CoV-2 enters type II alveolar epithelial cells in the human airway. It does so by binding to the angiotensin-converting enzyme 2 receptor with its spike protein on the surface.[22]

Effective clinical control of primary SARS-CoV-2 infection is associated with early T-cell and antibody responses.[23] During the hyperin-

flammatory response in patients with severe COVID-19, peripheral T lymphocytes are attracted to the infected lung and other injured organs in the late stage by chemokine signals emitted by these organs.[24] Additionally, functional exhaustion and antigen-driven overactivation of lymphocytes at the disease site cause cell death through a variety of mechanisms including apoptosis and pyroptosis, both of which contribute to peripheral lymphopenia during SARS-CoV-2 infection and severe disease.[13,25,26] Cellular immunity substantially contributes to vaccine protection against severe SARS-CoV-2 infection. T-cell responses also support the generation and maintenance of high-affinity antibodies, and previous studies have demonstrated that boosting vaccination with BBIBP-CorV can lead to reliable induction of B-cell responses.[27,28] Considering the essential role of cellular immune responses in clearing viral infections through T-cell activation after vaccination, ensuring both complete and booster vaccination is of clinical value. While older age and comorbidities impaired cellular and humoral immune responses, we found that the lymphocyte count was only significantly associated with VST among younger patients and patients with fewer comorbidities in this study.

Thrombocytopenia is documented in more than 50% of patients infected with severe acute respiratory syndrome (SARS), and this laboratory finding has been identified as a significant predictor of high mortality.[29,30] Consistent with previous evidence, our findings showed that patients with a long VST had lower platelet counts, as did unvaccinated patients. The platelet count should be monitored in patients with COVID-19 to help guide the prognosis. Evidence suggests that thrombocytopenia in patients with COVID-19 is due to increased consumption and reduced production. During the cytokine storm of COVID-19, overproduction of proinflammatory cytokines predisposes to the development of microthrombosis and disseminated intravascular coagulation, which can lead to platelet exhaustion. Activation of the immune system can cause an antibody-mediated phagocytic response and secondary hemophagocytic lymphohistiocytosis, both contributing to increased platelet clearance in patients with COVID-19.[31,32] Some comorbidities, such as renal failure and hypertension, further aggravated the degree of hypercoagulability.[33] Additionally, inhibition of megakaryocyte rupture in the pulmonary circulation and impaired hematopoiesis by bone marrow infection both contribute to decreased primary platelet formation.[34]

Booster vaccination of the COVID-19 vaccine has been globally implemented since the emergence of the Delta variant of concern and remarkably accelerated since the emergence of the Omicron variant of concern. Consistent with many areas in China, inactivated vaccines manufactured by domestic pharmaceutical companies, mainly the Sinovac and Sinopharm COVID-19 vaccines (Vero cell line), were predominantly used in Shanghai, and the booster vaccination strategy was almost homologous with the inactivated vaccine. However, the data collected by the Center for Disease Control and Prevention of Jilin City, China and that collected by the national health insurance program of Chile demonstrated that homologous inactivated vaccines can also produce reliable protectiveness against COVID-19 caused by variants of concern.[5,35] Our results demonstrated that the proportion of patients who received vaccines was relatively low among the patients with comorbid conditions and older age. This highlights the importance of promoting complete and booster vaccination in older patients and patients with more comorbidities.

Our research has two main limitations. First, because it was a single-center study, the sample size was relatively small. Second, because of incomplete information, our study did not include the interval after the priming vaccination, which is an important factor associated with the protection provided by vaccination.

Conclusions

We found a prolonged VST in patients aged ≥60 years, patients with lower lymphocyte or platelet counts, patients with impaired renal function, and patients with more comorbidities. We also found a significant positive association between booster vaccination and the platelet count. These findings may help to establish a policy of complete and booster vaccination in specific populations, especially the elderly patients with impaired renal function, and patients with more comorbidities.

Data Availability

After publication, the data will be made available on reasonable request to the corresponding author. Deidentified participant data will be provided after approval from the corresponding author and the Shanghai Public Health Clinical Center.

Conflict of interest

None.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pccm.2023.11.001.

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