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A Comparative Study of Clinical Characteristics and COVID-19 Vaccine Effectiveness Against SARS-CoV-2 Variants: Wild-Type, Alpha, Delta, and Omicron in Beijing, China

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Background: To compare the clinical characteristics of symptoms and laboratory findings across SARS-CoV-2 variants (Wild-type, Alpha, Delta, Omicron) and assess the effectiveness of COVID-19 vaccines in preventing symptoms and laboratory abnormalities.

Methods: We conducted a retrospective cohort study of individuals with SARS-CoV-2 infection at Beijing Ditan Hospital, Capital Medical University. Patients were grouped by the SARS-CoV-2 variant (Wild-type, Alpha, Delta, Omicron) based on whole-genome sequencing. Thirteen symptoms and 22 laboratory indices were compared across variants, and Omicron patients were further analyzed by vaccination status with generalized estimating equations (GEE) model.

Results: One thousand four hundred and thirteen participants were included for the analysis as following: Wild-type group (N=322), Alpha group (N=67), Delta group (N=98), and Omicron group (N=926). Omicron patients showed the highest proportion (30.1%) of respiratory symptoms across groups. Patients displayed normal laboratory manifestation, except for inflammatory markers, coagulation function index and glucose. Meanwhile, the Omicron variant was featured by higher inflammatory biomarkers (serum amyloid A protein [SAA] and C-reactive protein [CRP]). In addition, Omicron patients with three or more vaccine doses had fewer symptoms and higher values of SAA and CRP compared to those with fewer than three doses. Results of GEE showed, when compared with ≤ 1 vaccine dose, red blood cell count, white blood cell count, neutrophil count, platelet count, haemoglobin, and C-reactive protein in patients with ≥ 3 doses of vaccine significantly increased; while aspartic transaminase, creatine kinase, blood urea nitrogen, activated partial thromboplastin time, prothrombin time and thrombin time dramatically decreased, respectively.

Conclusion: Omicron variant resulted in abnormal inflammatory response. Individuals with three or more vaccine doses are more likely to experience fewer symptoms and have stronger protection against the virus. This study highlights key differences in symptom onset and laboratory profiles across SARS-CoV-2 variants, reinforcing the importance of three vaccine doses in providing strong protection against the Omicron variant.

Keywords: COVID-19, clinical characteristics, vaccines, variants

Introduction

The COVID-19 is caused by the SARS-CoV-2 virus, which has had a devastating impact on the global population.[1] As of February 4, 2024, more than 985 million people infected and more than 7 million deaths reported worldwide.[2] Rapid evolution of SARS-CoV-2 has led to the emergence of several variants, as detected by clinical and wastewater surveillance efforts,

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including Alpha variant of concern, beta variant, gamma variant, Delta variant and Omicron variant.[3] These new variants have shown evasion against vaccines and molecular diagnostic tests.[4,5] The virus variants have different characteristics which might incite variable host immune and inflammatory responses.[6] Increasing evidence suggests that the enhanced receptor binding affinity of the Receptor Binding Domain (RBD) of the Omicron variant to the human angiotensin-converting enzyme 2 (ACE2) receptor leads to increased viral transmissibility.[7]

As a result, differences may exist in the clinical characteristics and outcomes of patients who test positive for variants of the SARS-CoV-2 virus. Being aware of the clinical characteristics of the different variants of SARS-CoV-2 infection would help in the appropriate response to the next epidemic. The multi-wave nature of the COVID-19 pandemic underscores the importance of continuously updating clinical features regarding various variants, thereby enhancing disease recognition of the disease.[8] Early studies suggested that the clinical presentation of omicron is different from previous variants.[9–11] The virulence of Omicron and its ability to evade neutralizing antibodies surpass those of the Alpha and Delta variants, but the severe outcomes including hospital admissions, hospital admissions for symptoms, ICU admission, ventilation, and death are reported to be low.[12,13] Several studies have compared the symptoms between early or late phases or between variant waves. However, few studies have been able to draw on examining outcomes longitudinally across SARS-Cov-2 variants' waves. A latest study found symptoms induced by the wild-type and Delta were generally similar among unvaccinated symptomatic individuals, while symptoms were different between the wild-type and Omicron, with seven symptoms (fatigue, fever, chest pain, running nose, sputum production, nausea/vomiting, and sore throat) more frequent in the Omicron cohort.[14] However, since the onset and extent of symptoms were not reported, they failed to explain the difference between the same symptoms well. Additionally, the symptom profiles of COVID-19 vary from region to region, but we have not found any study comparing infection symptom patterns in variants and vaccination status in Beijing. To master the clinical characteristics of different COVID-19 variants in Beijing is of great importance for formulating epidemic prevention and control policies and allocating medical resources reasonably. Furthermore, there are reported data regarding the clinical and biomarker characterization of Omicron and other variants.[15,16] Little is known about the difference of clinical laboratory indicators across five waves of SARS-Cov-2 variants.

Effective and safe vaccines are essential to control the COVID-19 pandemic. The current types of vaccines are inactivated vaccines, viral vector vaccines, DNA vaccines, and mRNA vaccines. Among these, more than 90% of Beijing has received 2 doses of inactivated vaccines produced by Sinovac Biotech Ltd. and Sinopharm Group Co. Ltd.[17] It was developed based on Wild-type SARS-CoV-2 in 2020 and experienced a remarkably decline in effectiveness during the Delta variant wave. In Omicron BA.2 variant wave. Wan et al have reported effectiveness of 19.8% for coronavirus vaccines after a third dose and not observed after 2 doses.[18] However, the protective effects of different vaccine doses on laboratory indicators remain unclear.

Given these research gaps, we compare the clinical characteristics of COVID-19 in association with the SARS-CoV-2 wild type, Alpha, Delta, and omicron variants which clustered outbreaks occurred in Beijing from January 2020 to June 2022. The aim of the current study is to: (i) characterize the effect of variants on symptom onset, and (ii) assess the effectiveness of COVID-19 vaccines in preventing symptoms and laboratory abnormalities. Unlike other studies, our research has several novelties. Firstly, we are the first to compare the initial symptoms of different variants. Secondly, we observe the impact of different variants on laboratory indicators through longitudinal data. Thirdly, we use longitudinal data analysis method to analyze the effectiveness of vaccines, the research results are more reliable. We strive for our research findings to serve as a reference for the formulation and adjustment of epidemic prevention and control policies.

Methods

Study Design and Patients

We performed a retrospective study to analyze the clinical features of patients admitted to hospital with laboratory confirmed COVID-19 in Beijing Ditan Hospital, Capital Medical University, Beijing, China, from January 2020 to June 2022. Eligible patients were those in whom SARS-CoV-2 was detectable by transcription-quantitative polymerase chain reaction (RT-qPCR) test on sputum or nasopharyngeal swabs and those in whom COVID-19-specific pneumonitis was detectable by chest computed tomography (CT) scan. Patients identified with variant strains through genome sequencing

conducted by Beijing Center for Disease Control and Prevention are included in the study. If the count of patients identified with a specific variant strain is fewer than 50, those patients are subsequently excluded from the analysis. Patients with incomplete clinical data or conflicting test results were excluded from the study. Informed consent was obtained from each subject. The study protocol was approved by the Ethics Committees of Beijing Ditan Hospital, Capital Medical University (No. DTEC-KY2023-011-01). Patient data were anonymized, and confidentiality was maintained throughout the study in compliance with institutional guideline.

Data Collection

The demographic information (gender, and age), clinical characteristics (onset date, admission date, discharge date, hospital stay, vaccination status, comorbidity, and outcome), related symptoms (cough, sore throat, expectoration, running nose, chest congestion and dyspnea, inappetence, diarrhea, nausea and vomiting, fever, fatigue, muscle soreness, headache, and dizziness) and laboratory findings (blood routine index, myocardial enzymes, infection indicators, coagulation function index, liver function index, renal function index, and biochemical indicators) of each patient were obtained and collected from the Beijing Ditan Hospital, Capital Medical University. Symptom onset was defined as the first day of reported symptoms, and laboratory data were recorded daily for the first seven days of hospitalization. All data entered into an electronic data collection system (EDC) by a group of trained study members. The doses information of vaccine received on or before the reverse transcription-quantitative polymerase chain reaction (RT-qPCR) positive date were collected, and cases were classified into three groups (0–1 dose, 2 doses and 3 – doses). Furthermore, asymptomatic patients who had positive RT-qPCR results but no clinical symptoms were admitted to the hospital. The discharge criterion is two consecutive negative RT-qPCR tests.

Statistical Analysis

Categorical data are aggregated in frequencies and proportion, and quantitative data are described as the median and interquartile 25–75th percentile range (IQR). The chi-squared test or Fisher's exact probability method was used for group comparisons of categorical variables. Comparisons between groups for quantitative data were performed by Kruskal–Wallis test. We conducted multivariate analyses to evaluate the effects of vaccination with generalized estimating equations (GEE), a development of generalized linear models for measuring data containing autocorrelation. GEE was selected as it provides robust standard errors and is particularly useful for longitudinal data with potential correlations among repeated measures. The dependent variables were laboratory indicators during hospitalization and the covariates included days from admission, number of comorbidities, gender, and age. The test level for hypothesis testing was $\alpha \leq 0.05$, and differences were considered statistically significant with a P value of < 0.05. Statistical analyses were performed in R project (version 4.2.2).

Results

Study Population

As of June, 2022, a total of 3501 Chinese patients were diagnosed as COVID-19 and admitted to Beijing Ditan Hospital. And, 2091 patients were successful conducted viral genomic sequencing covering 25 variant strains (Table S1). Among them, 129 patients were excluded from analysis owing to the number of patients with a variant strain is fewer than 50. Furthermore, 549 patients were excluded for the severity of missing data. Finally, 1413 participants were included for further analysis, as shown in Figure 1. They were classified into four groups according to variants strains of SARS-CoV-2. And patients were infected with SARS-CoV-2 as follows: June to July 2020, the Wild-type group (N=322); January to February 2021, the Alpha group (N=67); January 2022 to February 2022, the Delta group (N=98); and March 2022 to June 2022, the Omicron group (N=926).

Table 1 summarized the demographic and clinical characteristics of patients infected with SARS-CoV-2 variants at admission. A total of 782 patients (55.3%) were male. The median age of all cases was 43 years, and 145 patients (10.3%) were children, 262 patients (18.5%) were elderly. The median interval between the initial positive and negative RT-qPCR results was 14 days in all patients, and that was 24 days in Wild-type group, 22 days in Alpha group, 14 days in Delta group, and 12 days in Omicron group, respectively. Infected patients with Delta and Omicron variant received the

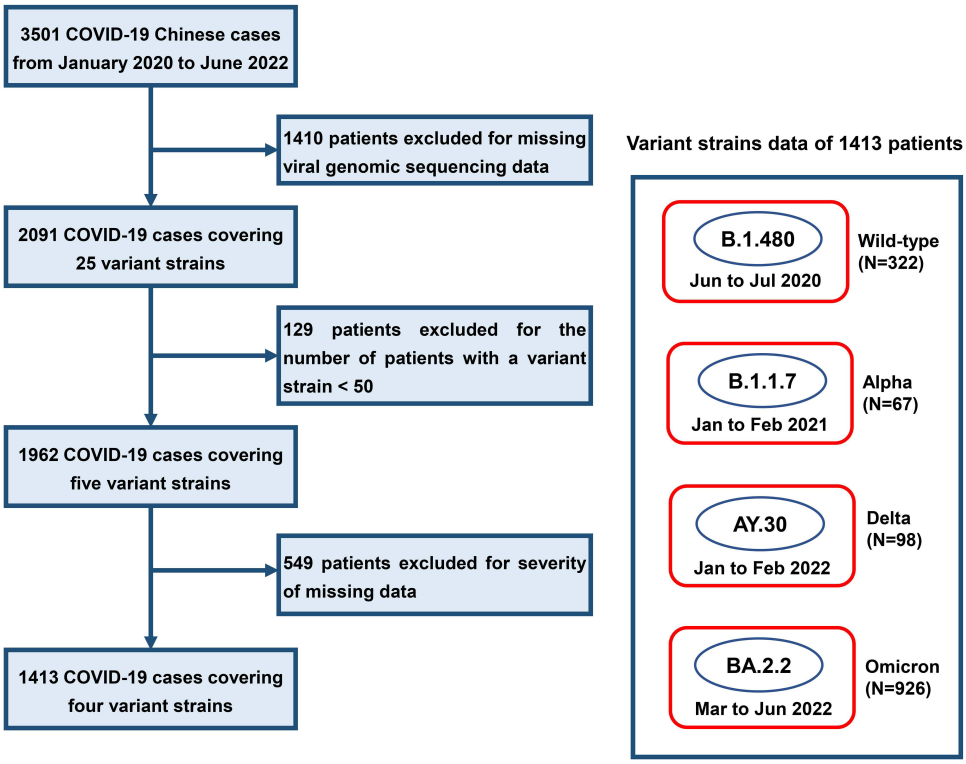


Figure 1 Flow diagram of patients screening and variant strains data of patients.

vaccine, 62 patients (63.3%) received three or more doses in the Delta group, and 528 patients (57.0%) received three or more doses in the Omicron group.

Prevalence of Symptoms in Patients Infected with Different Variants

In the current study, 13 symptoms were described, including respiratory symptoms (cough, sore throat, expectoration, running nose, chest congestion and dyspnea), gastrointestinal symptoms (inappetence, diarrhea, nausea and vomiting) and non-specific symptoms (fever, fatigue, muscle soreness, headache, and dizziness). As shown in Figure 2, cough, fever and inappetence were the most frequent respiratory symptom, gastrointestinal symptom and non-specific symptom, respectively. The average proportion (30.1%) of five respiratory symptoms in Omicron was the highest.

In terms of cough, 153 patients (47.5%) had cough in Wild-type group (Figure 2A), with the median developing time of 1 (1–2) days from admission. Forty-two (62.7%) had cough in Alpha group (Figure 2B), with the median time of 1 (0–3) days. Twenty-six (26.5%) in Delta group (Figure 2C), with the median time of 2 (0.25–5) days. Five hundred and nineteen (56.0%) in Omicron group (Figure 2D), with the median time of 1 (0–2).

As fever, 135 patients (41.9%) had fever in the Wild-type group (Figure 2A), 28 (41.8%) in Alpha group (Figure 2B), 36 (36.7%) in Delta group (Figure 2C), and 325 (35.1%) in Omicron group (Figure 2D). The median developing time of Wild-type, Alpha, Delta, and Omicron groups were 0 (0–1), 0 (0–1.25), 1 (0–2), 0 days, respectively.

As far as inappetence was concerned, 99 patients (30.7) had inappetence in Wild-type group (Figure 2A), 20 (29.9%) in Alpha group (Figure 2B), 6 (6.1%) in Delta group (Figure 2C), and 54 (5.8%) in Omicron group (Figure 2D). The median developing time of Wild-type, Alpha, Delta, and Omicron groups were 1 (0–3), 1.5 (0–5.5), 3 (1–6.5), 0 (0–1) days, respectively. These findings underscore the main symptoms of different variants infection patients were similar, and fever was the mainly initial symptom.

Comparison of Laboratory Assay in Patients Infected with Different Variants

There were 22 laboratory indexes for which a statistically significant difference was observed in four variants (Table S2). Omicron group was featured by higher values of inflammatory biomarkers, including C-reactive protein (CRP) and

Table 1 Demographic and Clinical Characteristics of Patients Infected with SARS-CoV-2 Variants at Admission

Characteristics	Total, N = 1413	Wild-Type, N = 322	Alpha, N = 67	Delta, N = 98	Omicron, N = 926	*P*-value
Gender, male, n (%)[&]	782 (55.3)	179 (55.6)	39 (58.2)	75 (76.5)	489 (52.8)	<0.001
Age, years (m, IQR)[†]	43 (29–56)	44 (31–52)	37 (29–47)	45 (35–53)	42 (26–59)	0.074
Age groups, n (%)[&]						<0.001
< 18	145 (10.3)	8 (2.5)	9 (13.4)	4 (4.1)	124 (13.4)	
19–40	505 (35.7)	132 (41)	34 (50.7)	36 (36.7)	303 (32.7)	
41–60	501 (35.5)	153 (47.5)	14 (20.9)	52 (53.1)	282 (30.5)	
≥ 61	262 (18.5)	29 (9)	10 (14.9)	6 (6.1)	217 (23.4)	
Interval between the initial positive and negative RT-qPCR result, days (m, IQR)[†]	14 (10–20)	24 (19–30)	22 (10–30)	14 (12–19)	12 (10–15)	<0.001
Hospital stay, days (m, IQR)[†]	17 (13–23)	28 (24–33)	26 (16–36)	19 (15–22)	14 (12–18)	<0.001
Symptoms, yes, n (%)[&]	1312 (92.9)	296 (91.9)	59 (88.1)	89 (90.8)	868 (93.7)	0.218
Vaccination status before admission[&]						0.489[a]
0–1 dose	590 (41.8)	–	–	17 (17.3)	184 (19.9)	
2 doses	233 (14.4)	–	–	19 (19.4)	214 (23.1)	
3 – doses	590 (41.8)	–	–	62 (63.3)	528 (57.0)	
Comorbidity, n (%)[&]						
Diabetes	140 (9.9)	23 (7.1)	6 (9)	8 (8.2)	103 (11.1)	0.196
Hyperlipidemia	51 (3.6)	6 (1.9)	1 (1.5)	3 (3.1)	41 (4.4)	0.136
Hypertension	294 (20.8)	42 (13.0)	11 (16.4)	16 (16.3)	225 (24.3)	<0.001
Chronic lung disease	27 (1.9)	4 (1.2)	2 (3)	0 (0)	21 (2.3)	0.293
Chronic kidney disease	23 (1.6)	7 (2.2)	3 (4.5)	0 (0)	13 (1.4)	0.116
Chronic liver disease	103 (7.3)	47 (14.6)	7 (10.4)	7 (7.1)	42 (4.5)	<0.001
Cardio-cerebro-vascular diseases	97 (6.9)	10 (3.1)	3 (4.5)	3 (3.1)	81 (8.7)	0.002

Notes: [&]Statistical testing by χ^2 test. [†]Statistical testing by Kruskal–Wallis test. [a]Statistical testing between Delta and Omicron groups.
Abbreviations: m, median; IQR, interquartile range; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

serum amyloid A (SAA) on admission. Alpha group exhibited higher values of coagulation function indexes, including activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT). Delta group was featured by highest values of blood routine index of red blood cell count (RBC), white blood cell count (WBC), neutrophil count (NEU), platelet count (PLT) and haemoglobin (HGB) in four groups. The results suggested that different variants have different effects on laboratory indicators of body function.

We furtherly presented laboratory assay values at admission in four variant groups to identify that whether virus resulted in dysregulated laboratory assay values (Figure 3 and Figure S1). The patients of four groups displayed normal results of most laboratory indexes, excluding inflammatory biomarkers, coagulation function indexes and glucose. Omicron variant showed notably higher levels of SAA and CRP than those in other three groups (Figure 3A). Alpha variant was more likely to cause coagulopathy (D-Dimer [DD], PT), Figure 3B. These observations suggested that the damage to the organs caused by the four SARS-CoV-2 variants was not serious at admission, while inflammatory response and coagulation function could be influenced.

Symptoms Prevalence and Laboratory Assay Values During Hospitalization in Patients with Omicron Infection Grouped by Vaccinations

As shown in Figure 4, in ≥ 3 doses of vaccine group, patients with one symptom during hospital stay accounted for the highest proportion (116, 22.0%). The proportion of over five symptoms in patients with ≥ 3 vaccine doses was the lowest (9.1%<11.7%<12.0%), and that of no symptom was the highest (16.7%>14.5%>13.0%). In other words, patients with ≥ 3 vaccine doses had fewer symptoms, while patients with 0–1 vaccine dose had more symptoms.

There were 19 laboratory indexes identified a statistically significant difference in three kinds of vaccine doses (Table 2). In the ≥ 3 doses of vaccine group, values of NEU, HGB, SAA, CRP, and creatinine are the highest across groups, while aspartic transaminase (AST), creatine kinase (CK), potassium, DD, APTT and TT are the lowest. Meanwhile, in the ≤ 1 vaccine dose group, values of AST, alanine aminotransferase (ALT), CK, blood urea nitrogen

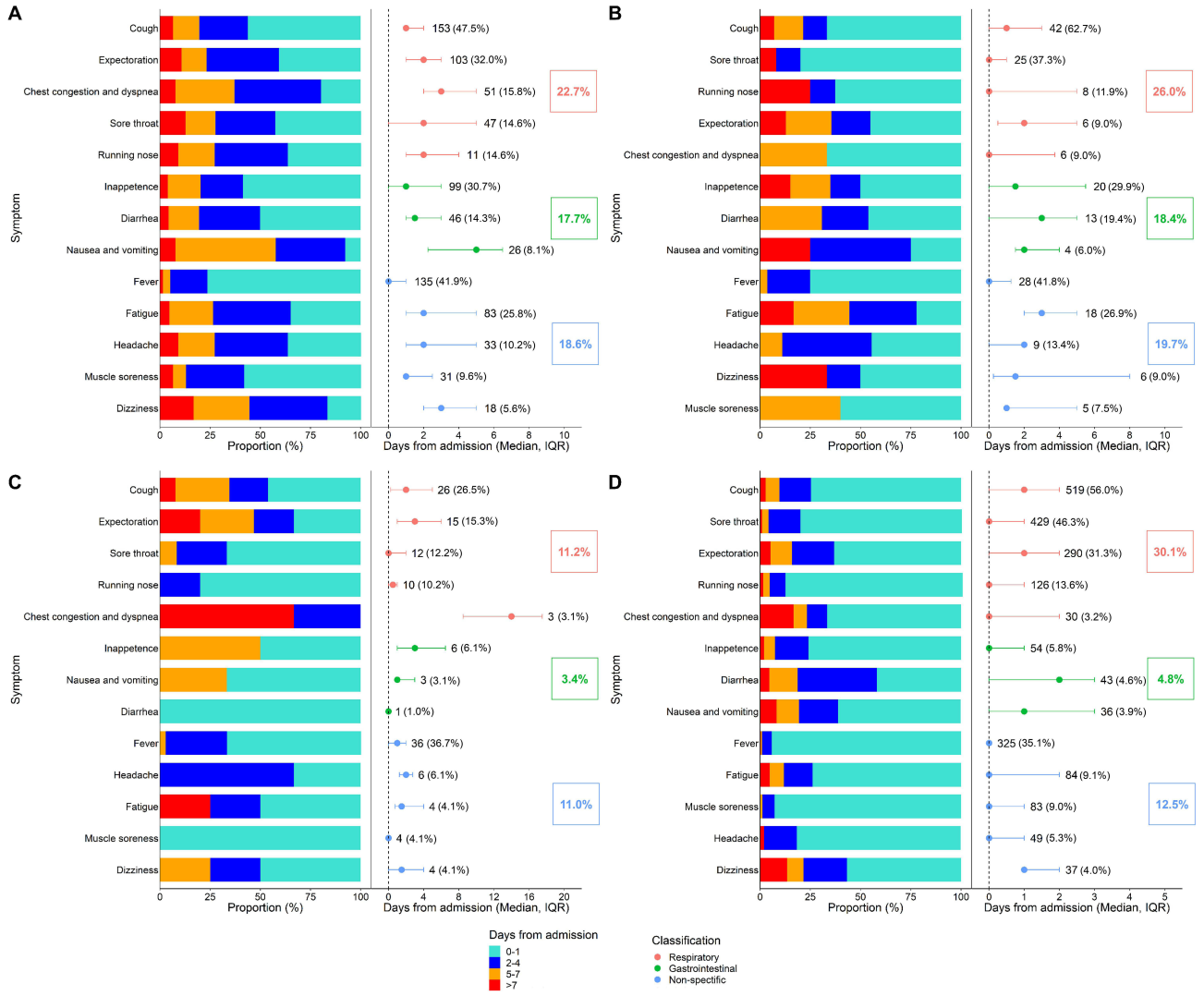


Figure 2 The onset time for clinical symptoms of patients infected with different variants during hospitalization. (**A**) Wild-type group (N=322); (**B**) Alpha group (N=67); (**C**) Delta group (N=98); (**D**) Omicron group (N=926). The left panel represented distribution of onset time for each clinical symptom, the proportion was calculated by using the total number of patients with symptoms as denominators. The onset time of each clinical symptom was calculated as the days from admission. The dots and the error bars denoted median and interquartile range. The number in the rectangular box represent the average percentage of patients with respiratory symptoms, gastrointestinal symptoms and non-specific symptoms, respectively.

(BUN), potassium, glucose, DD and TT are the highest across groups, while NEU, albumin (ALB), creatinine kinase-myocardial band (CKMB), SAA and CRP are the lowest.

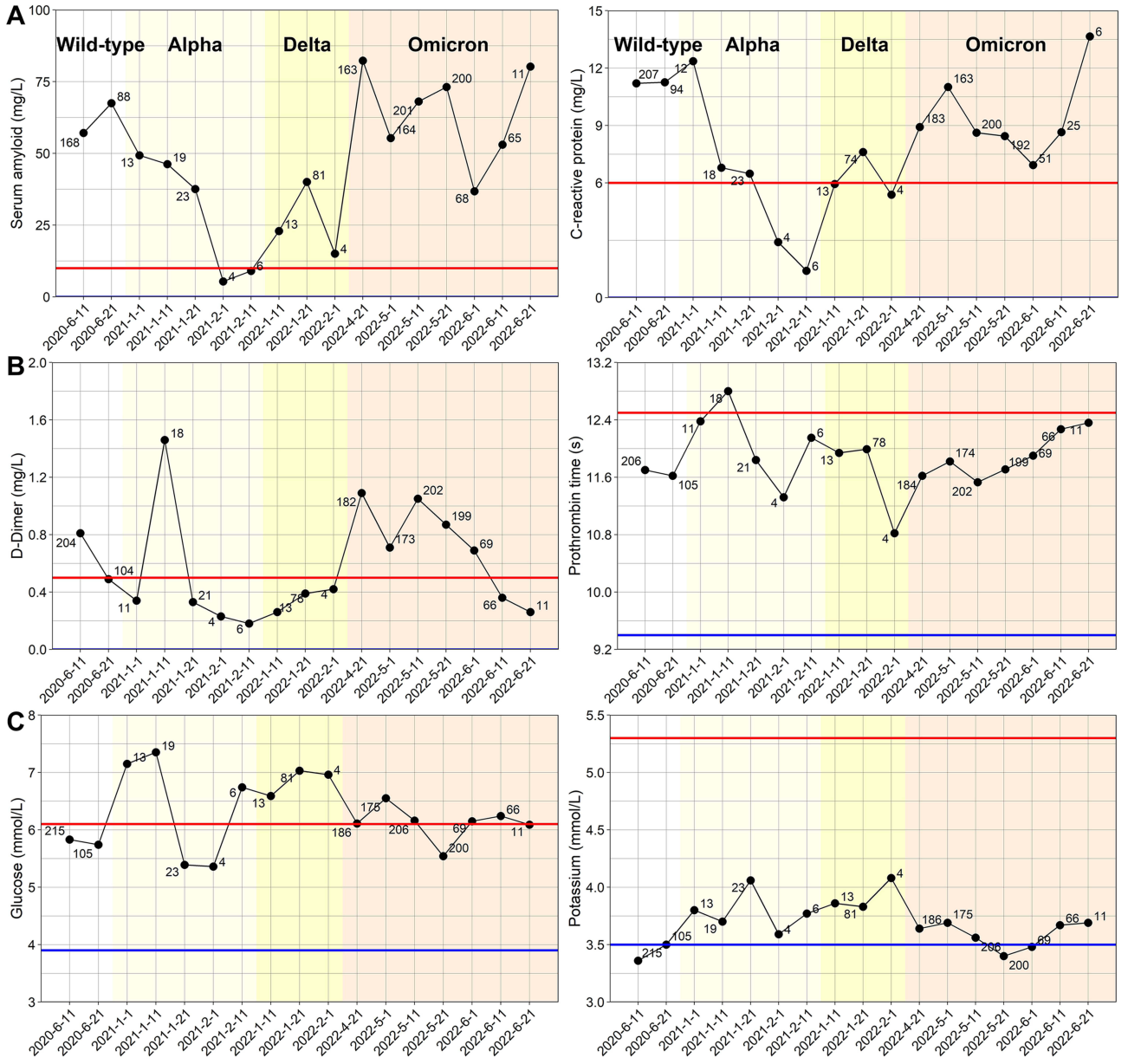
Additionally, trends in laboratory indicators during hospitalization are summarized in Figure 5 and Figure S2. The patients of three groups displayed normal results of most laboratory indexes, excluding inflammatory biomarkers and coagulation function indexes. Patients with ≤ 1 dose of vaccine displayed higher SAA, CRP, DD and PT values than those in patients with 2 doses and ≥ 3 doses of vaccine (Figure 5A and B). These findings collectively highlight the inflammatory function and coagulation function during hospitalization of Omicron patients might be associated with the vaccination condition.

Associations Between Vaccination Before Admission and Laboratory Indicators During Hospitalization in Omicron Infection Patients

Table 3 presented results of GEE analysis of vaccine dose and laboratory indicators. When compared with patients with ≤ 1 vaccine dose, the adjusted *β*s (95% CIs) of RBC, WBC, NEU, PLT, HGB, and CRP in patients with ≥ 3 vaccine doses

significantly increased by 0.144 (0.063, 0.225), 0.375 (0.078, 0.672), 0.394 (0.126, 0.662), 15.422 (5.389, 25.455), 3.994 (1.370, 6.615), and 2.474 (0.320, 4.628), respectively; while values of AST, CK, BUN, APTT, PT and TT dramatically decreased by −5.330 (−7.485, −3.176), −27.399 (−45.343, −9.455), −0.285 (−0.533, −0.037), −0.819 (−1.465, −0.172), −0.310 (−0.531, −0.089), and −0.935 (−1.648, −0.222), respectively. These results that the more doses the vaccine received, the higher blood routine indexes and inflammatory markers were, and the lower renal function index, liver function index and coagulation function index were.

In addition, age usually dramatically decreased the *β*s of blood routine index, liver function index, myocardial enzymes and coagulation function index, and comorbidities could significantly increase the *β*s of lymphocyte count, ALT, CKMB, BUN, and glucose.



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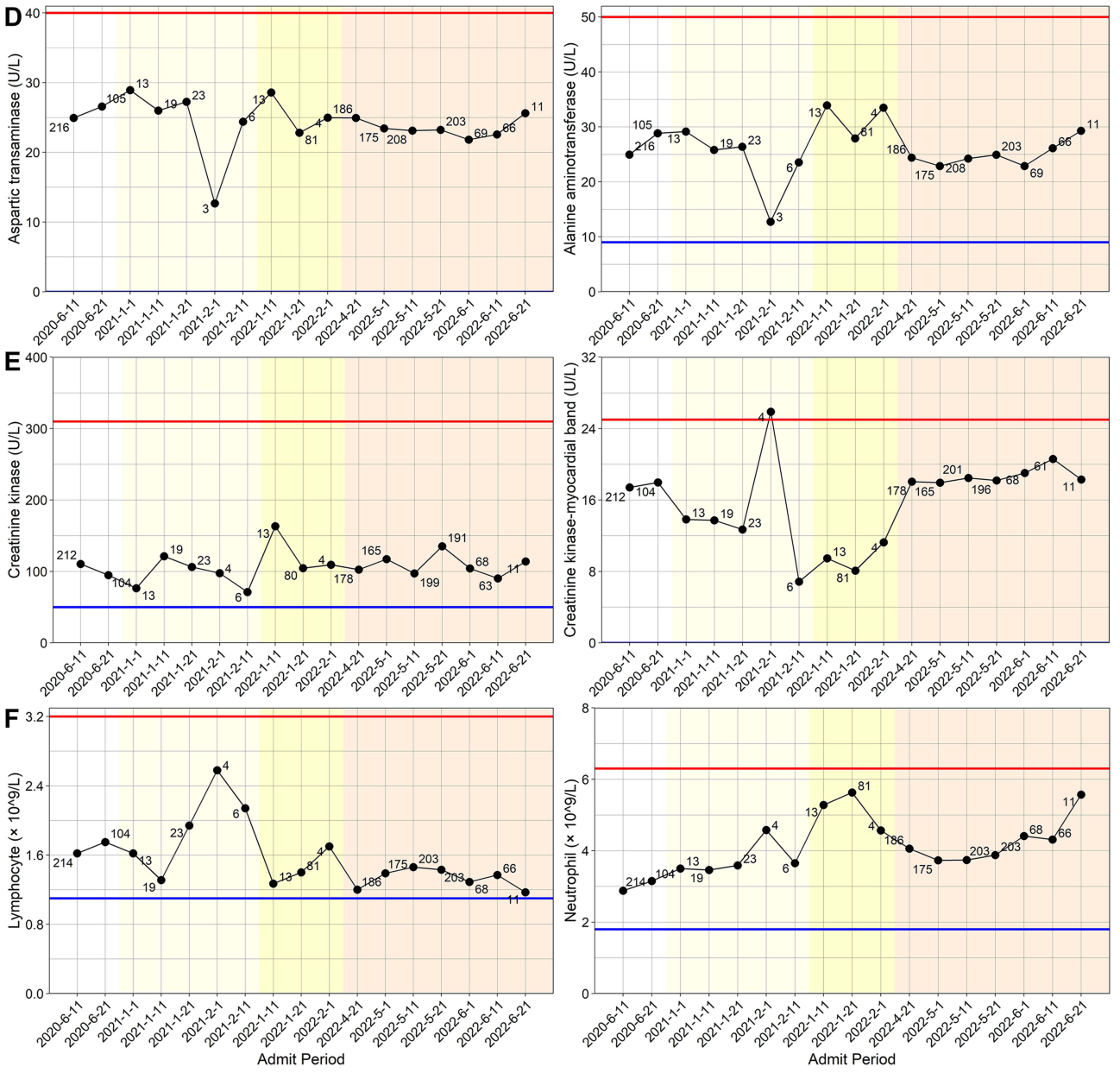

Figure 3 Patient laboratory assay values at admission in four variant groups from June 2020 to June 2022. (**A**) Serum amyloid and C-reactive protein; (**B**) D-Dimer and Prothrombin time; (**C**) Glucose and Potassium; (**D**) Aspartic transaminase and Alanine aminotransferase; (**E**) Creatinine kinase and Creatinine kinase-myocardial band; (**F**) Lymphocyte and Neutrophil. The red solid line and blue solid line represent the upper and lower limits of the normal range, respectively.

Sensitivity Analysis

After excluding asymptomatic patients before admission, the associations between vaccination and laboratory indicators were slightly changed, with adjusted βs for RBC, NEU, PLT, HGB, CRP, AST, CK, BUN, APTT, PT and TT in patients with ≥ 3 vaccine doses of 0.149, 0.339, 15.230, 4.473, 2.591, −4.872, −26.222, −0.354, −0.857, −0.310, and −0.955, respectively (Table S3). After excluding unvaccinated patients before admission and further adjusting the interval of last vaccination-to-admission. The adjusted βs of direct bilirubin and CKMB in patients with ≥ 3 doses of vaccine significantly increased by 0.631, and 2.177, respectively; while values of ALB, APTT and TT significantly decreased by −1.270, −1.458 and −0.477, respectively (Table S4). The results suggested asymptomatic patients did not affect the stability of vaccine protection, but the time interval between vaccinations before admission did.

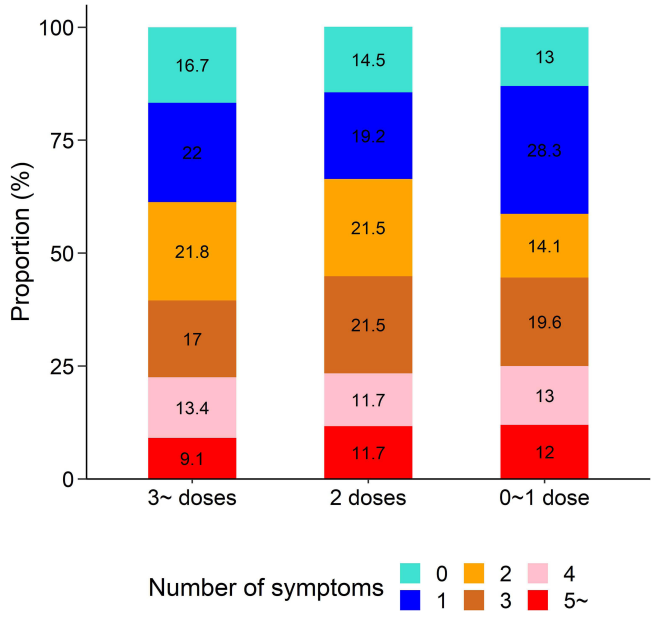

Figure 4 Symptoms prevalence during hospitalization in patients with Omicron infection grouped by vaccinations.

Discussion

In this study, we compared the onset and duration of symptoms and dynamic changes of laboratory data of patients with COVID-19 pneumonia during four viral epidemic waves in China, Beijing (Wild-type, Alpha variant, Delta variant, and omicron variant). We substantiate that fever and cough were common symptoms in all SARS-CoV-2 variants.[19,20] Meanwhile, respiratory symptoms have the highest incidence in the Omicron group. This supports previous findings which compared to the Wild type or the Delta variant, the Omicron variant demonstrated significantly diminished viral

Table 2 Laboratory Indexes in Patients Infected with Omicron Variant at Admission

Laboratory Indexes	Unit	Total, N = 926	0–1 Dose, N = 184	2 Doses, N = 214	3 – Doses, N = 528	*P*-Value
Blood routine index						
Red blood cell count	$\times 10^{12}$/L	4.76 (4.43–5.13)	4.69 (4.34–5.01)	4.79 (4.48–5.15)	4.78 (4.44–5.16)	0.006
White blood cell count	$\times 10^{9}$/L	5.55 (4.42–7.03)	5.42 (4.19–6.87)	5.66 (4.36–7.10)	5.60 (4.51–7.05)	0.237
Lymphocyte count	$\times 10^{9}$/L	1.24 (0.91–1.67)	1.23 (0.79–1.65)	1.32 (0.90–1.77)	1.23 (0.93–1.64)	0.531
Neutrophil count	$\times 10^{9}$/L	3.63 (2.56–4.99)	3.31 (2.36–4.66)	3.45 (2.44–5.11)	3.73 (2.73–4.93)	0.037
Platelet count	$\times 10^{9}$/L	209 (175–248)	197 (158–235)	214 (183–253)	208 (177–248)	0.002
Haemoglobin	g/L	140 (130–153)	137 (128–149)	137 (130–152)	141 (130–154)	0.013
Infection indicators						
Serum amyloid A	mg/L	24.6 (9.5–82.8)	17.7 (8.9–49.7)	23.6 (9.6–83.4)	28.1 (9.5–89.8)	0.025
C-reactive protein	mg/L	4.9 (1.7–11.4)	2.9 (1.5–7.9)	4.2 (1.3–10.4)	6.1 (2.0–12.8)	<0.001
Liver function index						
Aspartic transaminase	U/L	19.9 (16.1–25.0)	22.1 (17.9–31.1)	20.4 (17.0–25.8)	18.6 (15.8–23.1)	<0.001
Alanine aminotransferase	U/L	17.0 (12.9–26.7)	18.8 (12.9–27.5)	16.1 (11.7–24.0)	17.2 (13.4–27.5)	0.019
Direct bilirubin	μmol/L	3.20 (2.30–4.30)	3.10 (2.20–4.38)	3.00 (2.20–4.10)	3.30 (2.30–4.35)	0.136
Albumin	g/L	45.3 (42.6–47.5)	44.8 (41.6–47.4)	46.2 (43.6–48.3)	45.3 (42.8–47.3)	0.002
Myocardial enzymes						
CKMB	U/L	17.8 (14.9–21.2)	17.3 (13.9–21.9)	18.6 (15.1–22.7)	17.7 (15.1–20.6)	0.020
Creatine kinase	U/L	83 (62–120)	88 (64–131)	84 (64–121)	82 (57–115)	0.046

(*Continued*)

Table 2 (Continued).

Laboratory Indexes	Unit	Total, N = 926	0–1 Dose, N = 184	2 Doses, N = 214	3 – Doses, N = 528	*P*-Value
Renal function index						
Blood urea nitrogen	mmol/L	4.33 (3.57–5.42)	4.61 (3.80–5.64)	4.10 (3.52–4.96)	4.30 (3.54–5.33)	0.003
Creatinine	μmol/L	61.6 (52.1–74.9)	62.5 (52.3–77.0)	58.1 (47.3–72.8)	63.2 (54.0–74.4)	<0.001
Biochemical indicators						
Potassium	mmol/L	3.54 (3.28–3.83)	3.64 (3.32–3.91)	3.56 (3.30–3.89)	3.52 (3.27–3.79)	0.038
Glucose	mmol/L	5.32 (4.71–6.34)	5.45 (4.75–6.63)	5.11 (4.49–6.13)	5.40 (4.78–6.34)	0.002
Coagulation function index						
D-Dimer	mg/L	0.37 (0.25–0.58)	0.46 (0.30–0.75)	0.39 (0.24–0.62)	0.36 (0.25–0.51)	<0.001
APTT	s	32.1 (30.0–34.3)	32.1 (30.2–34.6)	33.3 (30.8–35.4)	31.9 (29.8–33.9)	<0.001
Prothrombin time	s	11.5 (11.0–12.3)	11.5 (11–12.3)	11.9 (11.4–12.8)	11.5 (10.9–12.1)	<0.001
Thrombin Time	s	14.0 (13.3–14.7)	14.3 (13.7–15.1)	14.3 (13.7–15.1)	13.7 (13.1–14.4)	<0.001

Notes: Data was displayed as median with interquartile range, and Statistical testing by Kruskal–Wallis test.
Abbreviations: CKMB, creatinine kinase-myocardial band; APTT, activated partial thromboplastin time.

replication capabilities within intestinal organoids, leading to a substantial reduction in the incidence of gastrointestinal manifestations, including diarrhea, vomiting, and abdominal pain, among those infected with the variant.[21] The most striking difference was that the symptoms of the Omicron variant appear more quickly than those of other strains, with eight of the 13 symptoms emerging simultaneously within 1–2 days from admission.

Additionally, our results reveal a notable variation in the severity of hematological profiles in COVID-19 patients when infected by the Wild type, the Alpha, the Delta or omicron variant. Our data has revealed that Omicron patients exhibit elevated levels of inflammatory biomarkers, including CRP and SAA. Paradoxically, our results diverge from previous studies, which consistently reported Omicron patients to exhibit notably reduced inflammatory profiles when compared to those infected with the Alpha and Delta variants of SARS-CoV-2.[22] The possible reason is that the Omicron group has a particularly high proportion of patients who have received three doses of the vaccine, and these patients exhibited higher levels of inflammation. Additionally, we conducted a sensitivity analysis on the impact of age and number of comorbidities on the inflammatory response and found that these two factors had no statistical effect on the inflammatory response. The increasing inflammatory biomarkers suggests the presence of inflammation in the patients, which requires clinicians to enhance monitoring of the patient, promptly identifying and addressing potential complications or worsening of the condition.

Previous studies have suggested that infections caused by the Omicron variant are associated with a comparatively milder inherent severity when compared to those by the earlier variants.[23–25] This could potentially be attributed to the fact that human ACE2 enters the cell through the endocytic pathway, allowing the Omicron variant to display a broader cellular tropism and infect ACE2+ cells more effectively. Simultaneously, this route of entry may also attenuate the virus's replication capabilities.[26] Our results, as reported herein, are congruent with those findings, as infection with the variant did not elicit severe pathological alterations in the hematological profiles of the majority of patients. Similarly, our findings here reveal a mitigated coagulation dysfunction in patients infected with the Alpha variant of SARS-CoV-2, as compared to those infected with the Wild-type virus or the Delta variant.[27] Nevertheless, in the present study, on admission, the indicators for blood routine and liver function are all within the normal range. This indicates that all patients were in the early stages of infection upon admission, owing to China's strict pandemic control measures. In this situation, patients can be identified at the initial stages of symptom onset or even in the asymptomatic phase, enabling our results to more accurately reflect the true situation, potentially differentiating these results from studies conducted in countries with less stringent measures.

In this study, we only included the Omicron strain for the study of the protective efficacy of vaccines. The main reason was that during the Wild-type and Alpha variant outbreaks, there were no vaccines available. Additionally, due to the limited sample size, we also did not conduct an analysis of the vaccine's protective efficacy. Nevertheless, our

analysis revealed an obvious correlation between vaccination status and symptom presentation in individuals infected with Omicron strains. Patients who received a full course of three doses of the vaccine had fewer symptoms presentation compared to those who received fewer doses. Previous studies have demonstrated that individuals infected during periods of Omicron prevalence exhibited a greater reduction in symptom duration when they had received a third dose of vaccine compared with those infected during Delta prevalence,[28] similar to our findings.

We further analyzed the protective effect of the vaccine on laboratory indicators. By observing the dynamic changes of laboratory indicators during the first 7 days of hospitalization, we found that patients with ≤ 1 dose of vaccine displayed higher SAA, CRP and DD values than those in patients with 2 doses and ≥ 3 doses of vaccine group. A China Guangzhou study showed that the difference in vaccination status is related to inflammation responses, which leads to liver damage that were usually more severe in patients who did not receive the vaccination.[29] Furthermore, GEE analysis indicated that receiving three doses of the vaccine has a protective effect on most laboratory indicators, which suggests vaccination was protective against the development of inflammatory responses during Omicron predominance. Previous

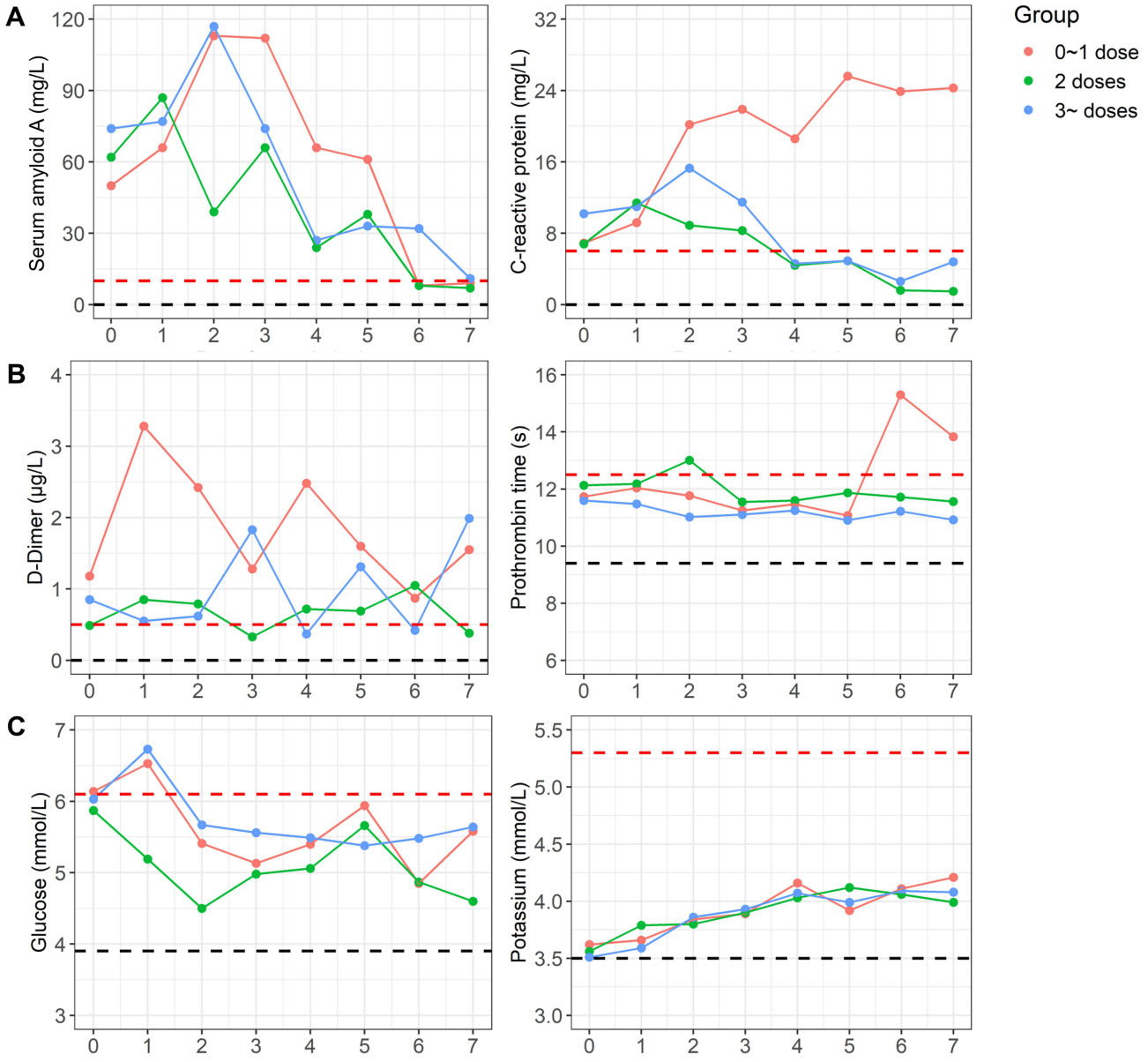

Figure 5 Continued.

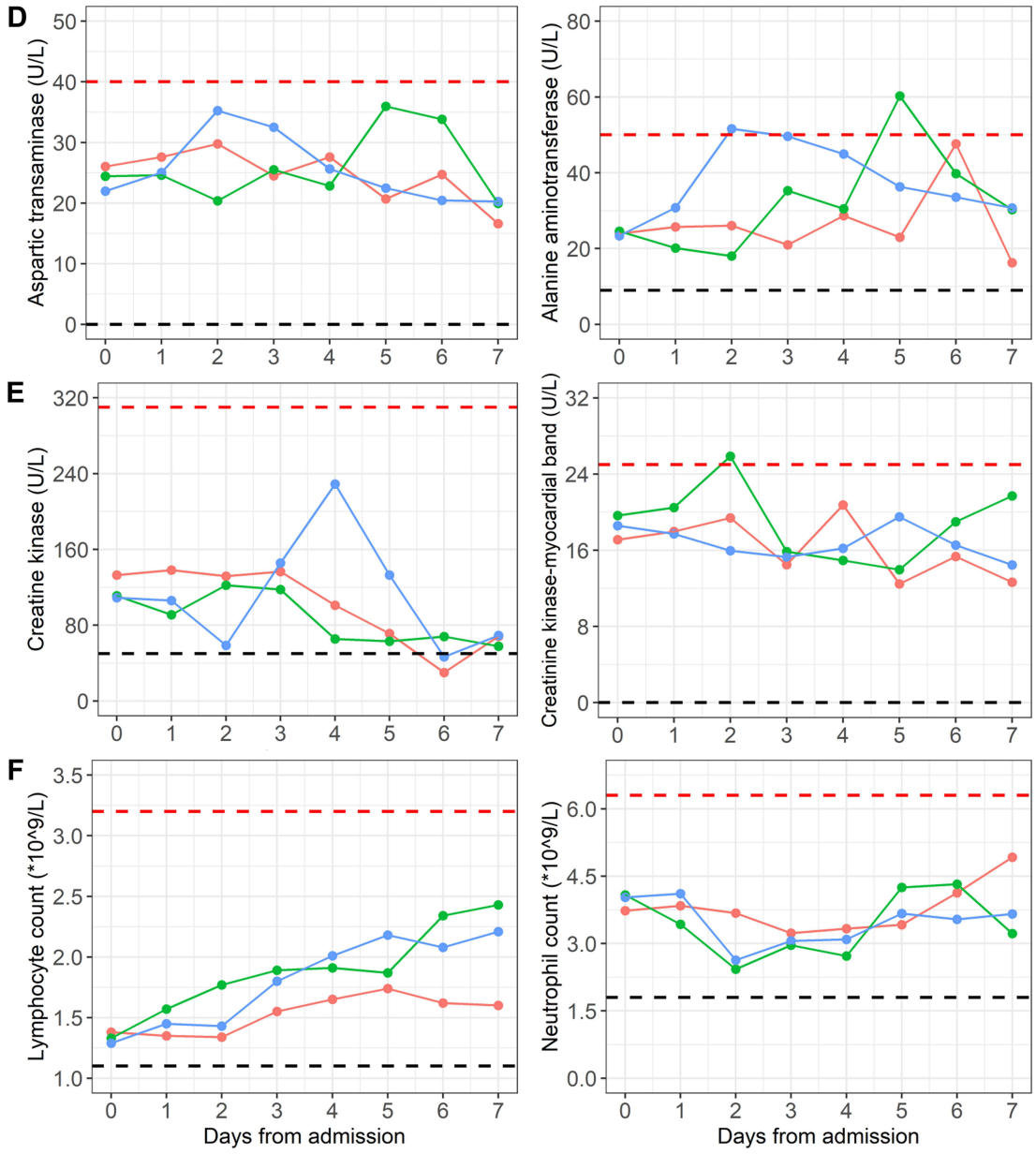

Figure 5 Laboratory assay values during hospitalization in patients with Omicron infection grouped by vaccinations. (**A**) Serum amyloid and C-reactive protein; (**B**) D-Dimer and Prothrombin time; (**C**) Glucose and Potassium; (**D**) Aspartic transaminase and Alanine aminotransferase; (**E**) Creatinine kinase and Creatinine kinase-myocardial band; (**F**) Lymphocyte and Neutrophil. The red dashed line and black line represent the upper and lower limits of the normal range, respectively.

studies have already found strong protection against the omicron variant after receipt of a third dose.[30] In summary, our result enhances the importance of stronger vaccination campaigns focusing on booster doses. Our findings are not only crucial for enhancing public acceptance of the vaccine but also have the potential to exert a profound impact on the entire vaccination system. By enhancing public trust in vaccines, we can better address future public health challenges.

Some limitations of this study should be underlined. Firstly, this study was a single-center retrospective study, we relied on the records that were directly documented into the electronic health record, which may be subject to potential biases due to underreporting of patient characteristics. Secondly, the small sample size of Alpha and Delta strains limits our ability to accurately interpret the prevalence of different symptoms across SARS-CoV-2 variants. It is recommended to conduct studies with larger sample sizes for Alpha and Delta variants. Thirdly, vaccination data is only presented for the Omicron variant, and it's not clear if the same trends would apply to earlier variants. Future studies should explore

Table 3 Results of Multivariate Generalized Estimating Equation Analysis of Vaccine Dose and Laboratory Indicators in Omicron Patients

Dependent Variables	*β* (95% CI)					
	2 Doses (0–1 Dose as Reference)	3 – Doses (0–1 Dose as Reference)	Days from Admission	Female (Male as Reference)	Age	Number of Comorbidities
Blood routine index						
RBC	0.037 (−0.058, 0.133)	0.144 (0.063, 0.225)***	0.013 (0.003, 0.023)**	−0.503 (−0.558, −0.448)***	−0.007 (−0.008, −0.005)***	0.013 (−0.029, 0.054)
WBC	0.204 (−0.163, 0.571)	0.375 (0.078, 0.672)*	0.045 (−0.001, 0.091)	−0.494 (−0.727, −0.262)***	−0.008 (−0.015, −0.001)*	0.096 (−0.070, 0.263)
LYM	−0.071 (−0.252, 0.110)	−0.001 (−0.134, 0.132)	0.148 (0.135, 0.162)***	−0.066 (−0.148, 0.015)	−0.010 (−0.013, −0.007)***	0.059 (0.002, 0.116)*
NEU	0.309 (−0.028, 0.645)	0.394 (0.126, 0.662)**	−0.108 (−0.154, −0.061)***	−0.301 (−0.510, −0.092)**	0.003 (−0.004, 0.010)	0.028 (−0.114, 0.170)
PLT	6.847 (−4.858, 18.552)	15.422 (5.389, 25.455)**	4.122 (2.941, 5.302)***	16.8 (9.354, 24.246)***	−0.707 (−0.946, −0.468)***	−2.877 (−7.877, 2.122)
HGB	1.065 (−2.000, 4.129)	3.994 (1.370, 6.615)**	−0.024 (−0.300, 0.253)	−19.055 (−20.800, −17.306)***	−0.058 (−0.120, 0.005)	−0.351 (−1.780, 1.076)
Infection indicators						
SAA	1.698 (−13.823, 17.218)	10.025 (−3.127, 23.176)	−23.609 (−29.553, −17.665)***	−3.061 (−13.729, 7.606)	0.130 (−0.199, 0.459)	−3.655 (−10.894, 3.585)
CRP	1.221 (−0.947, 3.388)	2.474 (0.320, 4.628)*	−2.341 (−3.491, −1.191)***	−2.130 (−3.611, −0.649)**	0.043 (−0.009, 0.095)	0.495 (−0.725, 1.715)
Liver function index						
AST	−3.929 (−6.617, −1.241)**	−5.330 (−7.485, −3.176)***	−2.359 (−3.417, −1.302)***	−2.036 (−3.655, −0.417)*	−0.040 (−0.093, 0.012)	1.006 (−0.248, 2.260)
ALT	−3.481 (−7.334, 0.373)	−0.824 (−3.960, 2.311)	−3.146 (−4.809, −1.483)***	−6.666 (−9.065, −4.267)***	−0.069 (−0.134, −0.004)*	2.838 (0.704, 4.972)**
DBIL	−0.185 (−0.584, 0.213)	0.041 (−0.316, 0.399)	−0.092 (−0.174, −0.010)*	−1.069 (−1.309, −0.829)***	0.001 (−0.007, 0.009)	0.086 (−0.097, 0.270)
ALB	−0.145 (−0.977, 0.688)	0.479 (−0.197, 1.155)	−0.503 (−0.610, −0.396)***	−0.926 (−1.363, −0.489)***	−0.075 (−0.089, −0.061)***	−0.029 (−0.363, 0.305)
Myocardial enzymes						
CKMB	0.668 (−1.520, 2.856)	0.494 (−1.065, 2.053)	−0.560 (−0.946, −0.174)**	−0.818 (−1.969, 0.333)	−0.077 (−0.120, −0.033)***	0.996 (0.109, 1.883)*
CK	−22.253 (−41.620, −2.886)*	−27.399 (−45.343, −9.455)**	−24.036 (−41.743, −6.329)**	−37.760 (−48.737, −26.784)***	0.188 (−0.199, 0.575)	−6.984 (−14.219, 0.251)
Renal function index						
BUN	−0.017 (−0.294, 0.260)	−0.285 (−0.533, −0.037)*	0.001 (−0.038, 0.040)	−0.713 (−0.877, −0.549)***	0.022 (0.016, 0.028)***	0.296 (0.156, 0.437)***
Cr	0.455 (−3.238, 4.147)	2.830 (−0.418, 6.078)	−0.228 (−0.688, 0.232)	−18.023 (−19.846, −16.201)***	0.210 (0.143, 0.277)***	0.794 (−0.591, 2.179)
Biochemical indicators						
K^+	0.010 (−0.068, 0.087)	−0.050 (−0.110, 0.010)	0.101 (0.091, 0.111)***	−0.095 (−0.139, −0.051)***	0.001 (−0.001, 0.002)	0.011 (−0.020, 0.043)
Glu	0.193 (−0.233, 0.619)	0.293 (−0.099, 0.684)	−0.225 (−0.273, −0.177)***	−0.102 (−0.378, 0.174)	0.016 (0.009, 0.022)***	0.892 (0.638, 1.146)***
Coagulation function index						
DD	−0.963 (−2.335, 0.408)	−0.544 (−1.859, 0.772)	0.246 (−0.194, 0.687)	−0.276 (−0.808, 0.257)	−0.005 (−0.030, 0.020)	0.366 (−0.448, 1.180)
APTT	−0.125 (−0.987, 0.737)	−0.819 (−1.465, −0.172)*	−0.093 (−0.203, 0.018)	−1.023 (−1.462, −0.585)***	−0.033 (−0.048, −0.017)***	0.108 (−0.204, 0.419)
PT	0.053 (−0.209, 0.315)	−0.310 (−0.531, −0.089)**	−0.163 (−0.239, −0.088)***	−0.177 (−0.310, −0.044)**	−0.013 (−0.018, −0.008)***	−0.041 (−0.134, 0.053)
TT	−0.248 (−0.819, 0.323)	−0.935 (−1.648, −0.222) *	−0.004 (−0.125, 0.116)	0.144 (−0.156, 0.444)	0.001 (−0.009, 0.010)	0.166 (−0.284, 0.616)

Notes: All variables in models: vaccine dose (0–1 dose, 2 doses and 3 – doses), days from admission, number of comorbidities, gender and age. *, *P*<0.05; **, *P*<0.01; ***, *P*<0.001.

Abbreviations: RBC, red blood cell count; WBC, white blood cell count; LYM, lymphocyte count; NEU, neutrophil count; PLT, platelet count; HGB, haemoglobin; SAA, serum amyloid A protein; CRP, C-reactive protein; AST, aspartic transaminase; ALT, alanine aminotransferase; DBIL, direct bilirubin; ALB, albumin; CKMB, creatinine kinase-myocardial band; CK, creatine kinase; BUN, blood urea nitrogen; Cr, creatinine; K^+, potassium; Glu, glucose; DD, D-Dimer; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

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how vaccination impacts the clinical profiles of earlier variants (eg, Alpha and Delta) if such data becomes available by other researchers. Fourthly, some factors were not considered in the analysis, such as COVID severity, breakthrough infections and re-infections with other variants occurred post-vaccination. Finally, our analysis was confounded by differences in age, gender and comorbidities which may bias the severity of symptoms and laboratory indicators, affecting the results of clinical symptoms for different variants and the protective efficacy of vaccines. It is important to explore immune responses across different age groups and comorbidity profiles in the future. Overall, these limitations resulted in deviations between our findings and the actual situation and thereby constraining the generalizability of our findings. Despite these limitations, definitive classification of the variants determined by genome sequencing over the study period ensured the reliability of variant classification and data analysis.

In conclusion, our findings revealed that patients infected with the Omicron variant experienced more respiratory symptoms, as well as caused inflammatory response, compared to those infected with previous SARS-CoV-2 variants. Additionally, this study also suggest that three doses of vaccination is critical for protecting populations against severe illness. Our findings underscore the importance of actively monitoring the evolution of SARS-CoV-2 variants which is critical for gaining insights into their clinical characteristics and the implications for effective management of COVID-19.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Ethics Committees of Beijing Ditan Hospital, Capital Medical University (No. DTEC-KY2023-011-01).

Informed Consent Statement

ll subjects in the study signed an informed consent.

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Disclosure

The authors declare no conflict of interest.

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