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ORIGINAL RESEARCH

Differential Characteristics of Patients for Hospitalized Severe COVID-19 Infected by the Omicron Variants and Wild Type of SARS-CoV-2 in China

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Background: As multiple mutations of *SARS-Cov-2* exist, there are now many viral variants with regional differences in distribution. The clinical characteristics of patients hospitalized with the virus also vary significantly, with those of the Omicron variants being strikingly different from those of the earliest wild-type variant. However, comprehensive data on this subject is lacking. It is therefore crucial to explore these differences to develop better clinical strategies for the management of *COVID-19*.

Methods: A total of 554 confirmed *COVID-19* cases in China were clinically classified as mild, moderate, severe, and critical according to their diagnoses and treatment plans. We compared the demographics and clinical characteristics of patients infected with the Omicron vs wild-type strains, between severe and non-severe cases. Bacterial co-infections with *SARS-CoV-2* and correlation between inflammatory factors and T cells were analyzed.

Results: Compared to the wild-type cases, the severe Omicron cases were older (median age 48.36 vs 73.24), and had more upper-respiratory symptoms and comorbidities. Decreased leukocyte counts were less pronounced, although more instances of significantly decreased CD4+ and CD8+ T-cell counts, elevated infection-related biomarkers (eg procalcitonin and C-reactive protein), and abnormal coagulation factors (including increased D-dimer and fibrinogen levels) were detected in the severe Omicron cases. The mean length of hospital stay was significantly shorter in the severe Omicron cases. CD4+ and CD8+ T cell numbers were negatively correlated with neutrophil-to-lymphocyte ratios, as well as serum interleukin-6, procalcitonin, and C-reactive protein levels.

Conclusion: There were significant clinical differences between patients hospitalized with severe cases of Omicron- variant *COVID-19* vs wild-type. The Omicron cases tended to be older and had more upper respiratory tract symptoms, comorbidities and bacterial co-infections. Elevated levels of inflammatory cytokines with T-cell depletion correlated with poor disease progression and prognosis. We hope these data provide a theoretical basis for future integrated prevention and control plans for *COVID-19*.

Keywords: *COVID-19*, Omicron variants, wild-type*SARS-CoV-2*, clinical characteristics, T cell depletion

Introduction

Coronavirus disease 2019 (COVID-19) is an acute fulminant infectious respiratory disease that spread rapidly worldwide.[1–3] Human-to-human transmission is the main route of spread for most *COVID-19* infections, and its many mutations have raised concerns regarding its pathogenicity and ability to cause severe illness.[4] There are now several

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variants of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, including Alpha, Beta, Gamma, Delta, and Omicron variants, which vary in both temporal and regional distribution. Compared to the wild-type virus, the Omicron variants have several mutations in their spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins and were first identified in South Africa and Botswana on November 24, 2021. The clinical characteristics of current predominant Omicron *COVID-19* variants in China are different from those of the earliest epidemic strains, but comprehensive data on the subject is lacking. It is therefore crucial to compare their differences to develop better clinical strategies for their management.

The course of *COVID-19* illness can be rapid, causing acute respiratory distress syndrome, septic shock, metabolic acidosis, and dysfunctions in blood coagulation.[1,5,6] Although it was announced by the World Health Organization (WHO) that the proportion of severe and critical illnesses related to the Omicron strain decreased as the Omicron BA.2 became the dominant SARS-CoV-2 strain,[7–10] there were still large quantities of patients hospitalized with severe *COVID-19* as a result of the strain in China, due to its extensive population demographics. The basic reproduction number (R0) of the Omicron variant is between about 10 and 26, suggesting that its transmissibility is quite higher than those of the previous variants. It is therefore essential to identify differences in the clinical characteristics of patients infected with severe cases of Omicron and wild-type *COVID-19*, to reduce the number of severe cases and reduce the spread of the *SARS-CoV-2* virus.

The neutrophil-to-lymphocyte ratio (NLR) is the ratio of the counts of neutrophils and lymphocytes, which serves as an economical biomarker reflecting the inflammatory status of the body and is used in various conditions, including tumors, chronic obstructive pulmonary disease (COPD), and infectious diseases such as influenza and *SARS-CoV-2* viral infections.[11,12] It has been reported that the NLR has a high capacity to accurately predict the severity of *COVID-19*.[13–15] Lymphocytes are the principal cells involved in the immune response in viral infections. The activation and differentiation of naive T-cells into effector or memory T-cells also play critical roles in antiviral immunity.[16] Previous studies have proven that there are low expression levels of angiotensin converting enzyme 2 (ACE2) in T-cells and the *SARS-CoV-2* virus may enter this cell type in other way, but cannot replicate further.[17–19] However, it has also been reported that T-cell counts, including those of $CD4^+$ and $CD8^+$ cells, are significantly decreased, particularly in cases of severe and critical *COVID-19*. This can lead to rapid deterioration of the disease, respiratory failure, and even multiple organ failure.[1] However, it remains unknown just what causes these decreased T-cell counts following *SARS-CoV-2* infection. This study therefore evaluated the clinical characteristics of patients with *COVID-19* who were infected with the Omicron variants of the virus, assessed their differences compared to patients who were infected with the wild-type strain, identified the risk factors associated with severe Omicron-related *COVID-19*, and explored the relationships between T-cells and other inflammatory factors in *COVID-19*. Through this, we aimed to aid in the development of new strategies for the clinical prevention and treatment of severe *COVID-19*.

Materials and Methods

Participants

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Approval No: 2022371). A total of 554 patients who had been laboratory-confirmed as positive for *SARS-CoV-2* infection by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) of oropharyngeal and/or nasopharyngeal swab samples, according to the diagnostic criteria for new coronavirus pneumonia diagnosis and treatment plan (trial version 9)[5] from the wards of the First Affiliated Hospital of Anhui Medical University and the Second People's Hospital of FuYang City. The typing of the viral strains was done in the local laboratory of the Centers for Disease Control, using a Wild-type and Omicron Variant Detection RT-PCR Kit, or was searched through the Global Initiative of Sharing All Influenza Data (GISAID) platform for the genomic epidemiology of *SARS-CoV-2* based on the period of the confirmed infection date or the admission date and region (Available online: https://gisaid.org/phylodynamics/global/nextstrain/). There were 401 hospitalized patients infected with the Omicron strain between December 20, 2022, and February 1, 2023; while 153 hospitalized patients were infected with the wild-type strain between January 20, 2020 and February 25, 2020. All patients were clinically classified as mild,

moderate, severe, or critical cases, according to the diagnosis and treatment plan.[5] There were 116 and 28 severe or critical cases in Omicron and wild-type groups, respectively. All patients involved in this study gave written informed consent to participate.

Data Resources

Epidemiological and clinical data were extracted from electronic medical records. Laboratory parameters were extracted for each patient on their day of admission, including routine blood tests (leucocytes, lymphocyte and neutrophil counts and percentages, hemoglobin and platelets levels), blood biochemistry parameters (albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], total bilirubin [Tbil], blood glucose, creatine kinase [CK], creatine kinase isoenzymes [CK-MB], blood urea nitrogen [BUN], total cholesterol, brain natriuretic peptide [BNP] and creatinine clearance [Ccr]), infection-related biomarkers (C-reactive protein [CRP], procalcitonin [PCT] and interleukin-6 [IL-6]) and coagulation function (D-dimer, prothrombin time [PT], activated partial thromboplastin time [APTT] and fibrinogen). NLR was calculated as the ratio of neutrophil-to-lymphocyte counts and PLR was calculated as the ratio of platelet-to-lymphocyte counts. The demographics and clinical characteristics were compared between severe and critical Omicron and wild-type cases, as well as between severe and non-severe Omicron cases. Bacterial co-infections with *SARS-CoV-2* and correlations between inflammatory factors and T-cells were also analyzed.

Statistical Analyses

Data analyses were done using SPSS 22.0 software. The Shapiro–Wilk test (S–W test), a type of non-parametric test, was used to determine whether variables conformed to a normal distribution. P values > 0.05 were considered to indicate that the data conformed to a normal distribution. The normally-distributed data were expressed as mean±SD, and compared using the Student's *t*-test. The non-normally distributed data were expressed as medians (interquartile ranges) and the rank-sum test was used. Differences between measured data were detected by Chi-squared or the Fisher's exact tests. When theoretical frequency (T) was ≥ 5 and sample size (N) was ≥ 40, the Chi-squared test was used. When $1 \leq T < 5$ and $N \geq 40$, the Chi-squared test with Yates's correction for continuity was used. When $T < 1$ or $N < 40$, Fisher's exact test was used. Statistical significance in more than two groups was tested using one-way analysis of variance for variables with normal distributions, and the Kruskal–Wallis test otherwise. The correlations between inflammatory factors and T-cell counts were analyzed using Spearson test. $P < 0.05$ was considered statistically significant.

Results

Comparison of Demographics and Clinical Characteristics Between Hospitalized Patients Infected with Omicron Vs Wild-Type Strain

The mean age of the patients infected with the Omicron strain was 69.00 years, which was significantly higher than the mean age of 40.48 for those infected with the wild-type strain ($P < 0.001$). There was no statistically significant difference in sex distribution between the Omicron and wild-type groups, at 218 (54.4%) and 86 (56.2%) males, respectively. The incidences of cough, sputum, shortness of breath, chest pain, and muscle ache symptoms were much higher in patients infected with the Omicron strain (all $P < 0.001$). Of the hospitalized patients in the Omicron group, 84.8% had comorbidities. This was significantly higher than the 26.1% of the wild-type group ($P < 0.001$; Table 1). The proportion of patients with decreased leucocyte, lymphocyte, and neutrophil counts and percentages was lower in the Omicron group. The levels of infection-related biomarkers, including PCT and CRP, were significantly higher in the Omicron group ($P < 0.001$). $CD4^+$ and $CD8^+$ T-cell counts were both significantly lower in patients of the Omicron group. The ratio of $CD4^+$ to $CD8^+$ T-cells, however, was not significantly different between the two groups. D-dimer levels were higher, while serum albumin levels were lower, in the Omicron patients. Liver function tests (ALT, AST, Tbil) were normal in most patients. In terms of renal function, BUN levels were higher, but Ccr levels were mostly normal in the Omicron patient group (Table 2).

Table 1 Comparison of Demographics and Clinical Characteristics Between Hospitalized Patients Infected with Wild and Omicron Strains

Variables	Virus Strains (All Patients)		P-value	Virus Strains (Severe and Critical Patients)		P-value
	Wild-Type (n=153)	Omicron-Type (n=401)		Wild-Type (n=28)	Omicron-Type (n=116)	
Age, years	40.48 (15.03)	69.00 (59.00, 79.00)	0.000	48.36 (12.46)	73.24 (14.14)	0.000
Male sex	86 (56.2%)	218 (54.4%)	0.696	19 (67.9%)	74 (63.8%)	0.687
BMI, kg/m^2	24.06 (3.34)	24.30 (23.74, 25.46)	0.817	24.53 (1.78)	24.30 (24.30, 24.30)	0.621
≤25	91 (59.5%)*	276 (68.8%)*		16 (57.1%)**	94 (81.0%)**	
>25	62 (40.5%)*	125 (31.2%)*		12 (42.9%)**	22 (19.0%)**	
Clinical classification						0.001
Mild and moderate	125 (81.7%)*	285 (71.1%)*		NA	NA	
Severe	25 (16.3%)#	74 (18.5%)#		NA	NA	
Critical	3(2.0%)*	42 (10.5%)*		NA	NA	
Signs and symptoms at admission						
Cough	126 (82.4%)	401 (100%)	0.000	25 (89.3%)	116 (100.0%)	0.000
Fever	132 (86.3%)	342 (85.3%)	0.789	26 (92.9%)	105 (90.5%)	0.698
Sputum	62 (40.5%)	400 (99.8%)	0.000	13 (46.4%)	116 (100.0%)	0.000
Shortness of breath	59 (38.6%)	319 (79.8%)	0.000	20 (71.4%)	111 (95.7%)	0.000
Chest pain	0(0.0%)	25 (6.2%)	0.000	0(0.0%)	8(6.9%)	0.355
Sore throat	25 (16.3%)	67 (16.7%)	1.000	4(14.3%)	16 (13.8%)	0.946
Diarrhea	55 (35.9%)	39 (9.7%)	0.000	6(21.4%)	15 (12.9%)	0.253
Nausea and vomiting	17 (11.1%)	162 (40.4%)	0.000	1(3.6%)	42 (36.2%)	0.000
Muscle ache	53 (34.6%)	213 (53.1%)	0.000	12 (42.9%)	58 (50.0%)	0.497
Respiratory rate			0.607			0.000
≤20	99 (64.7%)#	250 (62.3%)#		19 (63.3%)**	23 (19.8%)**	
>20	54 (35.3%)#	151 (37.7%)#		11 (36.7%)**	93 (80.2%)**	
Fingertip oxygen saturation (%)	98.00 (96.00, 98.75)	96.00 (91.00, 98.00)	0.000	94.00 (91.00, 97.50)	92.00 (88.00, 94.50)	0.000
Comorbidity						
Any	40 (26.1%)	340 (84.8%)	0.000	13 (46.4%)	104 (89.7%)	0.000
Cardiovascular diseases	21 (13.7%)	189 (47.1%)	0.000	6(21.4%)	66 (56.9%)	0.565
Diabetes	9(5.9%)	87 (21.7%)	0.000	6 (21.4%)	31 (26.7%)	0.706
Digestive diseases	9(5.9%)	32 (8.0%)	0.395	3 (10.7%)	8 (6.9%)	0.447
Respiratory diseases	4(2.6%)	110 (27.4%)	0.000	2 (7.1%)	27 (23.3%)	0.042
Central nervous system diseases	11 (7.2%)	55 (13.7%)	0.034	1 (3.6%)	26 (22.4%)	0.028
Hematological diseases	1(0.7%)	3(0.7%)	1.000	1 (3.6%)	1 (0.9%)	0.352
Immune diseases	2(1.3%)	21 (5.2%)	0.053	0 (0.0%)	8 (6.9%)	0.355
Urinary diseases	0(0.0%)	19 (4.7%)	0.003	0 (0.0%)	5(4.3%)	0.583
Cancer	2(1.3%)	29 (7.2%)	0.006	1 (3.6%)	7 (6.0%)	1.000
Treatment						
Oxygen therapy	119 (77.8%)#	285 (71.1%)#		27 (96.4%)##	114 (98.3%)##	
Nasal catheter to snuff oxygen	98 (64.1%)*	186 (46.4%)*		8 (28.6%)##	18 (15.5%)##	
Mechanical ventilation	21 (13.8%)	99 (24.7%)		19 (67.8%)	96 (82.8%)	
Non-invasive	18 (11.8%)#	70 (17.5%)#		16 (57.1%)##	67 (57.8%)##	
Invasive	3(2.0%)*	29 (7.2%)*		3 (10.7%)##	29 (25.0%)##	
Glucocorticoids	40 (26.1%)	204 (50.9%)	0.000	20 (71.4%)	87 (75.0%)	0.698
Days from first admission to discharge	15.00 (12.00, 20.00)	8.00 (6.00, 13.00)	0.000	15.54 (3.45)	11.70 (5.60)	0.017

Notes: Data are presented as number (%) or means (standard deviation) or median (interquartile range). P values indicate differences between wild and omicron strain. *In the same row indicate significant differences between wild-type strain and omicron-type strain in all patients. #In the same row indicate no differences between wild-type strain and omicron-type strain in all patients. **In the same row indicate significant differences between wild-type strain and omicron-type strain in severe and critical patients. ##In the same row indicate no differences between wild-type strain and omicron-type strain in severe and critical patients.

Comparison of Demographics and Clinical Characteristics Between Severe and Critical Omicron and Wild-Type Cases

To further explore differences in the treatment strategies for severe *COVID-19* cases, we compared the characteristics between hospitalized severe and critical with Omicron (116 cases) and wild-type (28 cases). The mean age was 73.24 in the severe/critical Omicron group, which was significantly higher than 48.36 in the severe/critical wild-type group ($P < 0.001$). The percentages of patients with upper-respiratory symptoms, including cough, sputum, and shortness of breath; and the proportions of comorbidities such as cardiovascular, respiratory, and central nervous system diseases, were significantly higher in the Omicron group (all P values < 0.05; Table 1). Decreased leucocyte, total lymphocyte, and neutrophil counts were less pronounced in severe/critical patients of the Omicron, compared to the wild-type, although $CD4^+$ and $CD8^+$ T-cell counts were significantly lower in patients infected with the Omicron variant ($P = 0.002$ and $P = 0.004$, respectively). The percentage of severe cases with increased levels of IL-6 was similarly high between the different strain groups ($P = 0.246$), but that of infection-related biomarkers, including PCT and CRP (as indicators of bacterial co-infections), were significantly higher in the severe Omicron group ($P < 0.001$). Abnormal coagulation, including increased D-dimer and fibrinogen levels, was significantly higher in the severe and critical Omicron groups (both P values < 0.001). Serum albumin levels were significantly lower in severe and critical Omicron groups ($P < 0.001$). The results of liver function tests, including AST and Tbil were similar between the groups, but biomarkers of myocardial damage, including CK-MB and LDH, as well as levels of the renal function indicator BUN, were significantly higher in the severe and critical Omicron groups. Ccr levels were 18.1% lower in the 116 severe Omicron cases, and 21.4% lower in the wild-type cases, with no significant difference ($P = 0.686$; Table 2). Most cases in both strain groups required oxygen therapy, and the rate of use of invasive mechanical ventilation was higher for the severe and critical Omicron groups. The length of hospital stay were significantly lower in severe and critical Omicron groups ($P = 0.017$; Table 1).

Comparisons of Clinical Characteristics Between Severe and Non-Severe Patients with Omicron-Variant *COVID-19*

According to our clinical classification criteria, the 285 patients with mild or moderate Omicron-variant *COVID-19* were classified into the non-severe group, and the other 116 with severe or critical cases of the disease were placed into the severe group, for the purposes of this study. The mean age of the patients in the severe group was 73.24, while that of the non-severe patients was 65.00 years, which was statistically different ($P < 0.001$). Compared to the non-severe patients, there were significantly more comorbidities, including cardiovascular and central nervous system diseases, in the severe group ($P = 0.012$ and $P = 0.001$, respectively; Table 3). Compared to the non-severe group, $CD4^+$ and $CD8^+$ T-cell and serum albumin levels were significantly decreased, while neutrophil counts and levels of BNP, CK, CK-MB, LDH, PCT, CRP, IL-6, and NLR were significantly higher in the severe group (all P values < 0.05). Increased D-dimer, PT, APTT, and fibrinogen levels, which suggested abnormal coagulation, were found in the severe and critical Omicron groups ($P < 0.001$). The percentage of patients with increased fasting blood glucose levels was 70.7% in the severe Omicron group, which was significantly higher than the 40.4% of the non-severe Omicron group ($P < 0.001$; Table 4). Compared to the non-severe group, the proportion of patients with bacterial co-infections was significantly higher in the severe and critical Omicron groups. Older patients, as well as those who had obesity, decreased lymphocyte counts, increased inflammatory marker and blood glucose levels, abnormal coagulation functions, and bacterial co-infections, were found to be at higher risk of developing severe Omicron-variant *COVID-19*.

Bacterial Co-Infections

Compared to the non-severe patients, the proportion of patients who had bacterial co-infections was significantly higher in the severe and critical Omicron groups. In the non-severe patients, the detection rates for *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus, Escherichia coli*, and other bacteria were 30.77%, 15.38%, 23.08%, 7.69%, 7.69%, and 15.38%, respectively. In severe patients, the detection rates of

Table 2 Comparison of Laboratory and Radiographic Results Between Hospitalized Patients Infected with Wild and Omicron Strains

Variables	Virus Strains (All Patients)			Virus Strains (Severe and Critical Patients)		
	Wild-Type (n=153)	Omicron-type (n=401)	P-value	Wild-Type (n=28)	Omicron-Type (n=116)	P-value
Blood routine						
Leucocytes (× 10^9 /L)	4.97 (3.87, 6.25)	6.46 (4.99, 9.32)	0.000	4.58 (3.48, 6.27)	8.61 (6.34, 10.92)	0.000
Increased	6(3.9%)	89 (22.2%)	0.000	2 (7.1%)	42 (36.2%)	0.002
Decreased	24 (15.5%)	26 (6.5%)	0.001	7 (25.0%)	4(3.4%)	0.001
Neutrophils (× 10^9/L)	3.43 (2.44, 4.77)	4.49 (2.89, 7.07)	0.000	3.10 (2.20, 5.34)	5.58 (3.18, 8.20)	0.001
Increased	14 (9.2%)	129 (32.2%)	0.000	3 (10.7%)	48 (41.4%)	0.002
Neutrophil percentage (%)	69.08 (10.92)	71.15 (13.03)	0.359	73.65 (60.35, 79.38)	72.35 (59.95, 83.98)	0.645
Lymphocytes (× 10^9/L)	1.07 (0.33)	1.28 (0.65)	0.004	0.80 (0.67, 1.36)	1.20 (0.81, 1.90)	0.005
Increased	1(0.7%)	10 (2.5%)	0.305	0 (0.0%)	3 (2.6%)	1.000
Decreased	72 (47.1%)	160 (39.9%)	0.127	19 (67.9%)	51 (44.0%)	0.023
Lymphocyte percentage (%)	22.23 (9.15)	19.93 (10.78)	0.033	17.25 (13.30, 29.13)	19.31 (11.67)	0.369
Erythrocyte (× 10^{12}/L)	4.53 (0.48)	3.91 (0.64)	0.000	4.48 (0.46)	3.84 (0.73)	0.000
Decreased	47 (30.7%)	279 (69.6%)	0.000	7(25.0%)	83 (71.6%)	0.000
Platelets (× 10^9/L)	166.00 (135.00, 212.00)	230.90 (90.18)	0.000	168.44 (75.57)	203.00 (148.00, 279.00)	0.005
Decreased	22 (14.4%)	43 (10.7%)	0.232	8(28.6%)	14 (12.1%)	0.029
Hemoglobin (g/L)	140.21 (15.92)	119.14 (18.60)	0.000	138.39 (15.61)	117.50 (107.00, 130.00)	0.000
Decreased	6(3.9%)	141 (35.2%)	0.000	2(7.1%)	49 (42.2%)	0.000
Infection-related biomarkers						
Procalcitonin (ng/mL)	0.02 (0.02, 0.07)	0.06 (0.04, 0.25)	0.000	0.05 (0.02, 0.11)	0.34 (0.10, 1.08)	0.000
Increased	4(2.6%)	149 (37.2%)	0.000	2 (7.1%)	51 (44.0%)	0.000
C-reactive protein (mg/L)	16.10 (3.40, 36.50)	28.60 (4.70, 103.30)	0.000	27.50 (7.85, 65.80)	80.95 (47.93, 212.08)	0.000
Increased	79 (51.6%)	278 (69.3%)	0.000	19 (67.9%)	108 (93.1%)	0.000
IL-6 (pg/mL)	18.30 (5.70, 37.10)	10.60 (5.00, 67.20)[a]	0.834	34.10 (13.75, 58.25)	15.00 (5.10, 70.00)[b]	0.246
Increased	102 (66.7%)	189 (62.2%)[a]	0.346	23 (82.1%)	77 (78.6%)[b]	0.680
NLR	3.36 (2.11, 4.87)	4.04 (2.31, 7.12)	0.051	4.22 (2.39)	3.71 (2.20, 8.91)	0.314
Increased	112 (73.2%)	299 (74.6%)	0.743	21 (75.0%)	93 (80.2%)	0.545
PLR	161.76 (126.95, 218.18)	176.92 (138.76, 298.04)	0.146	166.34 (129.48, 226.32)	167.78 (121.93, 263.59)	0.705
Increased	45 (29.4%)	159 (39.7%)	0.025	9(32.1%)	43 (37.1%)	0.626
CD4 cell count (/μL)	435.74 (208.15)	297.00 (157.00, 596.00)[c]	0.000	234.50 (179.00, 454.50)	156.50 (86.50, 267.25)[d]	0.002
Decreased	95 (62.1%)	237 (70.5%)[c]	0.064	22 (78.6%)	89 (89.0%)[d]	0.151
CD8 cell count (/μL)	321.22 (167.09)	221.00 (129.00, 340.00)[e]	0.000	186.00 (133.25, 324.00)	119.00 (61.25, 224.50)[d]	0.004
Decreased	85 (55.6%)	231 (69.0%)[e]	0.004	21 (75.0%)	86 (86.0%)[d]	0.165
CD4/CD8	1.33 (1.04, 1.96)	1.44 (1.15, 2.02)[e]	0.544	1.48 (0.72)	1.44 (0.96, 1.86)[d]	0.952
Increased	32 (20.9%)	94 (28.1%)[e]	0.094	7 (25.0%)	22 (22.0%)[d]	0.737
Decreased	77 (50.3%)	159 (47.5%)[e]	0.557	15 (53.6%)	53 (53.0%)[d]	0.957

Blood biochemistry						
Albumin (g/L)	41.47 (4.23)	35.52 (5.57)	0.000	39.11 (3.69)	32.44 (4.66)	0.000
Decreased	8(5.2%)	167 (41.6%)	0.000	4 (14.3%)	81 (69.8%)	0.000
Alanine aminotransferase (U/L)	26.00 (14.00, 38.00)	24.00 (15.00, 41.00)	0.928	24.00 (16.25, 37.00)	26.00 (15.00, 49.00)	0.805
Increased	22 (14.4%)	72 (18.0%)	0.316	4 (14.3%)	27 (23.3%)	0.442
Aspartate aminotransferase (U/L)	26.00 (21.00, 33.00)	25.00 (17.00, 38.00)	0.320	28.00 (23.00, 30.75)	30.00 (21.00, 46.75)	0.492
Increased	21 (13.7%)	75 (18.7%)	0.166	6 (21.4%)	40 (34.5%)	0.184
Lactic dehydrogenase (U/L)	234.00 (201.00, 279.00)	227.00 (177.00, 354.00)	0.301	282.29 (78.16)	296.00 (240.25, 407.75)	0.004
Increased	60 (39.2%)	161 (40.1%)	0.841	16 (57.1%)	84 (72.4%)	0.115
Total bilirubin (μmol/L)	9.60 (6.50, 15.10)	13.50 (10.00, 18.30)	0.000	11.00 (7.78, 19.20)	13.05 (10.13, 16.38)	0.370
Increased	9(5.9%)	19 (4.7%)	0.583	3 (10.7%)	6 (5.2%)	0.377
Glucose (mmol/l)	6.07 (5.50, 6.99)	6.82 (5.57, 9.36)	0.405	6.23 (5.51, 7.24)	7.64 (5.83, 11.49)	0.101
Increased	72 (47.1%)	197 (49.1%)	0.663	17 (60.7%)	82 (70.7%)	0.307
Creatine kinase (U/L)	66.00 (45.00, 88.00)	47.00 (32.00, 86.00)	0.001	68.50 (45.75, 97.00)	61.00 (33.25, 119.00)	0.603
Increased	3(2.0%)	14 (3.5%)	0.423	2 (7.1%)	9 (7.8%)	1.000
Isoenzyme of creatine kinase (U/L)	7.00 (4.00, 12.00)	10.00 (8.00, 14.00)	0.000	8.50 (5.25, 13.00)	13.00 (10.00, 15.00)	0.004
Increased	9(5.9%)	26 (6.5%)	0.795	3(10.7%)	11 (9.5%)	0.736
Blood urea nitrogen (mmol/L)	3.97 (1.28)	5.80 (4.30, 8.30)	0.000	4.31 (1.64)	7.00 (4.78, 9.30)	0.000
Increased	3(2.0%)	95 (23.7%)	0.000	2 (7.1%)	51 (44.0%)	0.000
Creatinine clearance (mL/min)	64.57 (16.59)	73.00 (54.00, 83.00)	0.738	69.86 (15.83)	68.00 (56.25, 93.50)	0.745
Decreased	43 (28.1%)	113 (28.2%)	0.986	6 (21.4%)	21 (18.1%)	0.686
Total cholesterol (mmol/L)	0.28 (0.20, 0.51)	4.25 (3.39, 5.02)[f]	0.000	0.34 (0.22, 0.55)	4.00 (1.24)[g]	0.000
Increased	0(0.0%)	22 (22.2%)[f]	0.000	0 (0.0%)	7 (22.6%)[g]	0.011
D-dimer (mg/L)	0.28 (0.20, 0.51)	0.76 (0.30, 1.75)	0.000	0.34 (0.22, 0.55)	1.32 (0.58, 2.13)	0.000
Increased	39 (25.5%)	238 (59.4%)	0.000	9(32.1%)	89 (76.7%)	0.000
Fibrinogen (g/L)	3.30 (2.62, 4.13)	4.75 (3.73, 5.77)	0.000	3.54 (1.19)	5.10 (1.35)	0.000
Increased	46 (30.1%)	260 (64.8%)	0.000	8(28.6%)	91 (78.4%)	0.000

Notes: Data are presented as number (%) or means (standard deviation) or median (interquartile range). P values indicate differences between wild and omicron strain. [a, b, c, d, e, f, g]Indicate that the numbers of all cases were 304, 98, 336, 100, 335, 99 and 31, respectively.

Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio.

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Table 3 Demographics and Clinical Characteristics of Hospitalized Patients with Omicron Variant

Variables	Omicron-Type Strains		
	Mild and moderate (n=285)	Severe and critical (n=116)	P-value
Age, years	65.00 (54.00, 77.00)	73.24 (14.14)	0.000
<20	1 (0.4%)[#]	0 (0.0%)[#]	
≥20, <60	107 (37.5%)*	19 (16.4%)*	
≥60	177 (62.1%)*	97 (83.6%)*	
Male sex	144 (50.5%)	74 (63.8%)	0.016
BMI, kg/m^2	24.30 (21.70, 26.86)	24.30 (24.30, 24.30)	0.513
≤25	182 (63.9%)*	94 (81.0%)*	
>25	103 (36.1%)*	22 (19.0%)*	
Signs and symptoms at admission			
Cough	284 (99.6%)	116 (100%)	0.523
Fever	237 (83.2%)	105 (90.5%)	0.059
Duration of fever, d	3.00 (2.00, 5.00)	5.00 (3.00, 8.00)	0.000
Temperature, °C	38.50 (38.00, 39.00)	38.60 (38.00, 39.00)	0.103
Sputum	284 (99.6%)	116 (100%)	0.523
Shortness of breath	208 (73.2%)	111 (95.7%)	0.000
Chest pain	17 (6.0%)	8 (6.9%)	0.726
Sore throat	51 (17.9%)	16 (13.8%)	0.318
Diarrhea	24 (8.4%)	15 (12.9%)	0.167
Nausea and vomiting	120 (42.1%)	42 (36.2%)	0.275
Muscle ache	155 (54.4%)	58 (50.0%)	0.425
Respiratory rate	20.00 (18.00, 20.00)	23.00 (21.00, 25.00)	0.000
≤20	227 (79.6%)*	23 (19.8%)*	
>20	58 (20.4%)*	93 (80.2%)*	
Fingertip oxygen saturation, %	98.00 (96.00, 98.00)	92.00 (88.00, 94.50)	0.000
Bacterial co-infection	8 (2.8%)	15 (12.9%)	0.000
Comorbidity			
Any	236 (82.8%)	104 (89.7%)	0.083
Cardiovascular diseases	123 (43.2%)	66 (56.9%)	0.012
Diabetes	56 (19.6%)	31 (27.6%)	0.119
Digestive diseases	24 (8.5%)	8 (6.9%)	0.603
Respiratory diseases	83 (29.1%)	27 (23.3%)	0.234
Central nervous system diseases	29 (10.2%)	26 (22.4%)	0.001
Hematological diseases	2 (0.7%)	1 (0.9%)	0.866
Immune diseases	13 (4.6%)	8(6.9%)	0.341
Urinary diseases	14 (4.9%)	5 (4.3%)	0.797
Cancer	22 (7.7%)	7 (6.0%)	0.555
Treatment			
Oxygen therapy	171 (60.0%)*	114 (98.3%)*	0.000
Nasal catheter to snuff oxygen	168 (58.9%)*	18 (15.5%)*	
Mechanical ventilation	3 (1.1%)*	96 (82.8%)*	
Non-invasive	3 (1.1%)*	67 (57.8%)*	
Invasive	0 (0.0%)*	29 (25.0%)*	
Glucocorticoids	117 (41.1%)	87 (75.0%)	0.000
Days from first admission to discharge	7.00 (6.00, 9.00)	11.70 (5.60)	0.000

Notes: Data are presented as number (%) or means (standard deviation) or median (interquartile range). P values indicate differences between mild/moderate type and severe/critical type. *In the same row indicate significant differences between mild/moderate type and severe/critical type. [#]In the same row indicate no differences between mild/moderate type and severe/critical type.

Table 4 Laboratory and Radiographic Results of Patients with Omicron Variant

Variables	Omicron-Type Strains			
	Standard values	Mild and Moderate (n=285)	Severe and Critical (n=116)	P-value
Blood routine				
Leucocytes (× 10^9 /L)	4.00–10.00	6.02 (4.66, 8.53)	8.61 (6.34, 10.92)	0.000
Increased		47 (16.5%)	42 (36.2%)	0.000
Decreased		22 (7.7%)	4 (3.4%)	0.177
Neutrophils (× 10^9/L)	2.00–7.00	4.15 (2.79, 6.63)	5.58 (3.18, 8.20)	0.009
Increased		81 (28.4%)	48 (41.4%)	0.012
Neutrophil percentage (%)	50.00–70.00	68.09 (14.70)	72.35 (59.95, 83.98)	0.049
Lymphocytes (× 10^9/L)	0.80–4.00	1.28 (0.84, 1.73)	1.20 (0.81, 1.90)	0.585
Increased		7 (2.5%)	3 (2.6%)	1.000
Decreased		109 (38.2%)	51 (44.0%)	0.289
Lymphocyte percentage (%)	20.00–40.00	20.70 (13.00, 30.65)	19.31 (11.67)	0.034
Erythrocyte (× 10^{12}/L)	4.00–5.50	4.00 (3.60, 4.40)	3.84 (0.73)	0.158
Decreased		196 (68.8%)	83 (71.6%)	0.583
Platelets (× 10^9/L)	100.00–300.00	219.00 (170.00, 282.50)	203.00 (148.00, 279.00)	0.268
Decreased		29 (10.2%)	14 (12.1%)	0.578
Hemoglobin (g/L)	120.00–170.00	123.00 (110.00, 133.50)	117.50 (107.00, 130.00)	0.154
Decreased		92 (32.3%)	49 (42.2%)	0.058
Infection-related biomarkers				
Procalcitonin (ng/mL)	<0.05	0.08 (0.04, 1.08)	0.34 (0.10, 1.08)	0.000
Increased		98 (34.4%)	51 (44.0%)	0.072
C-reactive protein (mg/L)	<5	20.20 (4.65, 65.08)	80.95 (47.93, 212.08)	0.000
Increased		170 (59.6%)	108 (93.1%)	0.000
IL-6 (pg/mL)	<7	7.85 (4.18, 21.38)[a]	15.00 (5.10, 70.00)[b]	0.000
Increased		112 (54.4%)[a]	77 (78.6%)[b]	0.000
NLR	NA	3.28 (1.84, 6.22)	3.71 (2.20, 8.91)	0.043
Increased		206 (72.3%)	93 (80.2%)	0.100
PLR	NA	171.08 (118.36, 281.10)	167.78 (121.93, 263.59)	0.941
Increased		116 (40.7%)	43 (37.1%)	0.500
CD4 cell count (/μL)	450.00–1440.00	379.50 (234.00, 633.50)[c]	156.50 (86.50, 267.25)[d]	0.000
Decreased		148 (62.7%)[c]	89 (89.0%)[d]	0.000
CD8 cell count (/μL)	320.00–1250.00	271.00 (166.00, 393.00)[e]	119.00 (61.25, 224.50)[d]	0.000
Decreased		145 (61.7%)[e]	86 (86.0%)[d]	0.000
CD4/CD8	1.00–2.87	1.44 (1.16, 2.04)[e]	1.44 (0.96, 1.86)[d]	0.179
Increased		72 (30.6%)[e]	22 (22.0%)[d]	0.107
Decreased		106 (45.1%)[e]	53 (53.0%)[d]	0.186
Blood biochemistry				
Albumin (g/L)	35.00–55.00	37.90 (34.20, 41.00)	32.44 (4.66)	0.000
Decreased		86 (30.2%)	81 (69.8%)	0.000
Alanine aminotransferase (U/L)	0.00–40.00	21.00 (14.00, 36.50)	26.00 (15.00, 49.00)	0.089
Increased		45 (15.8%)	27 (23.3%)	0.077
Aspartate aminotransferase (U/L)	0.00–40.00	22.00 (16.00, 35.00)	30.00 (21.00, 46.75)	0.000
Increased		35 (12.3%)	40 (34.5%)	0.000
Lactic dehydrogenase (U/L)	109.00–245.00	206.00 (175.00, 254.50)	296.00 (240.25, 407.75)	0.000
Increased		77 (27.0%)	84 (72.4%)	0.000
Total bilirubin (μmol/L)	1.71–21.00	12.30 (9.60, 16.15)	13.05 (10.13, 16.38)	0.276
Increased		13 (4.6%)	6 (5.2%)	0.794
Glucose (mmol/l)	3.60–6.10	5.86 (5.18, 6.98)	7.64 (5.83, 11.49)	0.000
Increased		115 (40.4%)	82 (70.7%)	0.000
Creatine kinase (U/L)	18.00–198.00	46.00 (32.00, 71.00)	61.00 (33.25, 119.00)	0.007

(*Continued*)

Table 4 (Continued).

Variables	Omicron-Type Strains			
	Standard values	Mild and Moderate (n=285)	Severe and Critical (n=116)	P-value
Increased		5 (1.8%)	9 (7.8%)	0.003
Isoenzyme of creatine kinase (U/L)	0.00–25.00	10.00 (7.00, 13.00)	13.00 (10.00, 15.00)	0.000
Increased		15 (5.3%)	11 (9.5%)	0.120
Blood urea nitrogen (mmol/L)	3.20–6.10	4.80 (3.80, 6.55)	7.00 (4.78, 9.30)	0.000
Increased		44 (15.4%)	51 (44.0%)	0.000
Creatinine clearance (mL/min)	80.00–120.00	61.00 (50.00, 74.50)	68.00 (56.25, 93.50)	0.000
Decreased		92 (32.3%)	21 (18.1%)	0.004
Total cholesterol (mmol/L)	2.86–5.72	4.45 (3.56, 5.10)[f]	4.00 (1.24)[g]	0.112
Increased		15 (22.1%)[f]	7(22.6%)[g]	0.954
Blood uric acid (μmol/L)	208.00–428.00	234.00 (190.00, 293.50)	231.00 (173.75, 350.00)	0.964
Increased		10 (3.5%)	16 (13.8%)	0.000
NT-proBNP (pg/mL)	0.00–300.00	614.00 (108.00, 1409.22)	1409.22 (454.75, 1711.25)	0.000
Increased		219 (76.8%)	110 (94.8%)	0.000
Triglyceride (mmol/L)	0.48–1.88	1.12 (0.92, 1.97)[h]	1.13 (0.91, 1.89)[g]	0.911
Increased		20 (29.9%)[h]	8 (25.8%)[g]	0.680
Coagulation function				
D-dimer (mg/L)	0.00–0.30	0.57 (0.28, 1.46)	1.32 (0.58, 2.13)	0.000
Increased		149 (52.3%)	89 (76.7%)	0.000
Fibrinogen (g/L)	2.00–4.00	4.48 (3.49, 5.22)	5.10 (1.35)	0.000
Increased		169 (59.3%)	91 (78.4%)	0.000
PT (s)	11.00–14.00	11.00 (10.40, 11.64)	12.00 (11.30, 12.90)	0.000
Increased		1 (0.4%)	6 (5.2%)	0.003
Decreased		137 (48.1%)	22 (19.0%)	0.000
APTT (s)	25.00–37.00	30.10 (27.35, 31.80)	33.45 (28.73, 37.33)	0.000
Increased		4 (1.4%)	9 (7.8%)	0.003
Decreased		171 (60.0%)	41 (35.3%)	0.000

Notes: Data are presented as number (%) or means (standard deviation) or median (interquartile range). P values indicate differences between mild/moderate type and severe/critical type. [a, b, c, d, e, f, g, h]Indicate that the numbers of all cases were 206, 98, 236, 100, 235, 68, 31 and 67, respectively.
Abbreviations: NLR, Neutrophil-to-Lymphocyte Ratio; NA, Not applicable; PLR, Platelet-to-Lymphocyte Ratio; BNP, Brain natriuretic peptide.

Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, and other bacteria were 47.83%, 26.09%, 8.70%, 4.35%, 4.35%, and 8.70%, respectively (Figure 1).

Correlation Analysis Between Inflammatory Factors and T-Cells

Serum levels of IL-6, CRP, PCT, and NLR, as well as $CD4^+$ and $CD8^+$ T-cell counts, were evaluated for the patients with severe *COVID-19*, and the results revealed that elevated levels of IL-6, CRP, PCT, and NLR were negatively correlated with both $CD4^+$ and $CD8^+$ counts in cases of severe or critical *COVID-19*. This suggested that increased levels of inflammatory cytokines may lead to T-cell depletion. The correlation coefficients between $CD4^+$ counts and levels of IL-6, CRP, PCT, and NLR were 0.2223, 0.2732, 0.3512, and 0.5213, respectively ($P = 0.0262$, $P = 0.0018$, $P < 0.0001$ and $P < 0.0001$, respectively). The correlation coefficients between $CD8^+$ counts and levels of IL-6, CRP, PCT, and NLR were 0.2189, 0.2559, 0.3440, and 0.5177 ($P = 0.0287$, $P = 0.0035$, $P < 0.0001$ and $P < 0.0001$; Figure 2).

Discussion

At the time of writing this report, the Omicron variant of the *SARS-CoV-2* virus has a particularly high rate of transmission and has spread rapidly. The sharp increase in patients hospitalized with severe Omicron *COVID-19* has placed great pressure on medical institutions across the country. Although the overall pathogenicity of the Omicron variant has decreased in some countries,[7–9,20,21] the rate of patients who develop severe diseases in China, which has

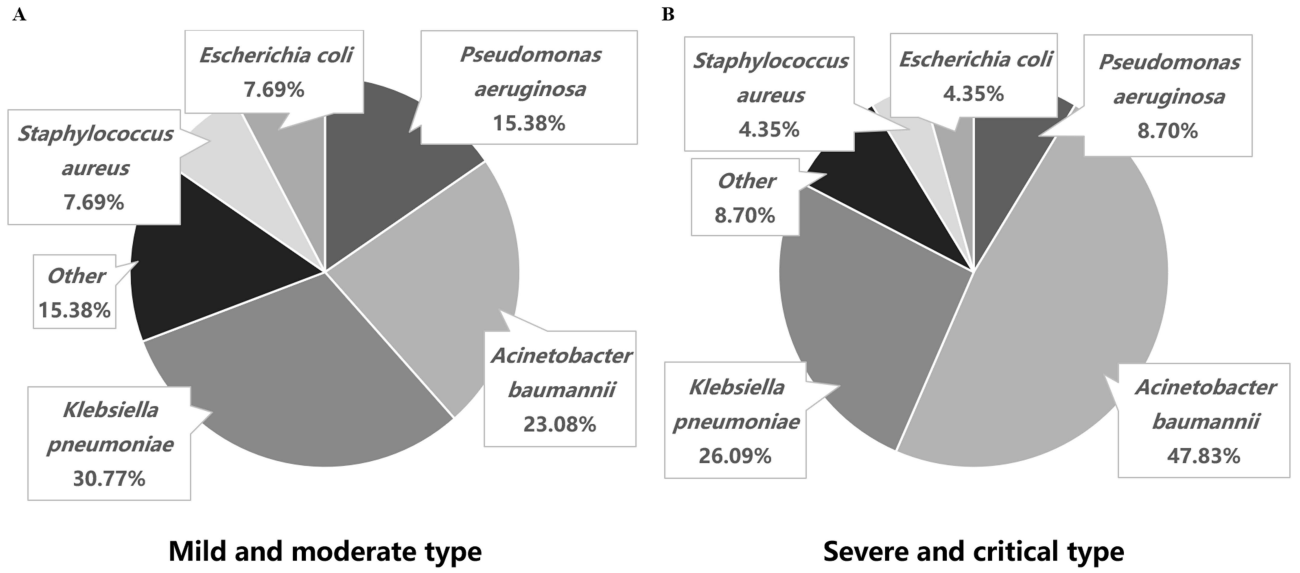

Figure 1 Bacterial co-infections concurrent with *SARS-CoV-2*. (**A**) The proportion of bacterial co-infections in cases of mild and moderate *COVID-19*. (**B**) The proportion of bacterial co-infections in cases of severe and critical *COVID-19*.

a particularly large population, cannot be ignored. Omicron variants are constantly emerging, and our understanding regarding the differences in clinical characteristics of patients that are caused by the different variants is still very limited. This study summarized the differences in the clinical characteristics between the Omicron and wild-type variants, the risk factors related to developing severe Omicron-related disease, and explored the relationships between T-cell counts and inflammatory factors in *COVID-19*, to provide more evidence for the development of future prevention and treatment strategies for the disease.

In this study, the percentage of male patients was comparable to females, which indicated there were no sex-based differences between Omicron and wild-type *COVID-19*. The mean age of hospitalized patients infected with the Omicron strain was significantly higher than that of patients infected with the wild strain, and even higher in those who had severe Omicron infections. This indicated that the elderly are more susceptible to the Omicron variant, and are more likely to develop severe *COVID-19* from it, consistent with the results of previous studies in Japan and South Africa.[22–24]

Compared to previous variants, upper-respiratory symptoms, including cough, sputum, shortness of breath, and others, were more frequently observed in Omicron *COVID-19*. Previous studies have suggested that the viral load levels in the noses of hamsters infected with the Omicron strain were similar to those of animals infected with the earlier strains, but that the levels in their lungs were 10% lower.[25] The TMPRSS2 proteins that help most strains of *SARS-CoV-2* enter cells are highly expressed on the surfaces of many lung cells but have low levels of expression in the upper-respiratory tract.[26,27] The Omicron variant does not bind to TMPRSS2 as well as some previous strains of the virus and preferentially enters cells in the upper-respiratory tract through other routes such as endocytosis, after which it also replicates faster than the earlier viral strains.[27,28] This indicates a higher transmissibility of the strain, and that positivity and accuracy rates of nucleic acid sampling are highest for samples taken from the nasopharynx, for the Omicron strain.

In this study, liver function tests, including AST and Tbil, and biomarkers related to myocardial damage, including CK, CK-MB, and LDH, as well as levels of the renal function indicator BUN, were significantly elevated in severe cases of both Omicron and wild-type *COVID-19*, suggesting that *COVID-19* affects multiple organs. It should be noted that the percentage of increased biomarkers related to myocardial damage was as high as 8% in cases of severe Omicron *COVID-19*, and some patients with mild diseases experienced sudden death even though their clinical symptoms were minor or had improved significantly. It has been reported that extensive impairments of left ventricular systolic function in the early stages of *COVID-19* were associated with the severity of the infection.[29,30] It has been speculated that *SARS-CoV-2* may attack the heart by activating ACE2 in endothelial cells of the cardiovascular system and that an inflammatory storm may play a key role in the progression of the disease, but this notion merits further exploration.[31] Many patients with

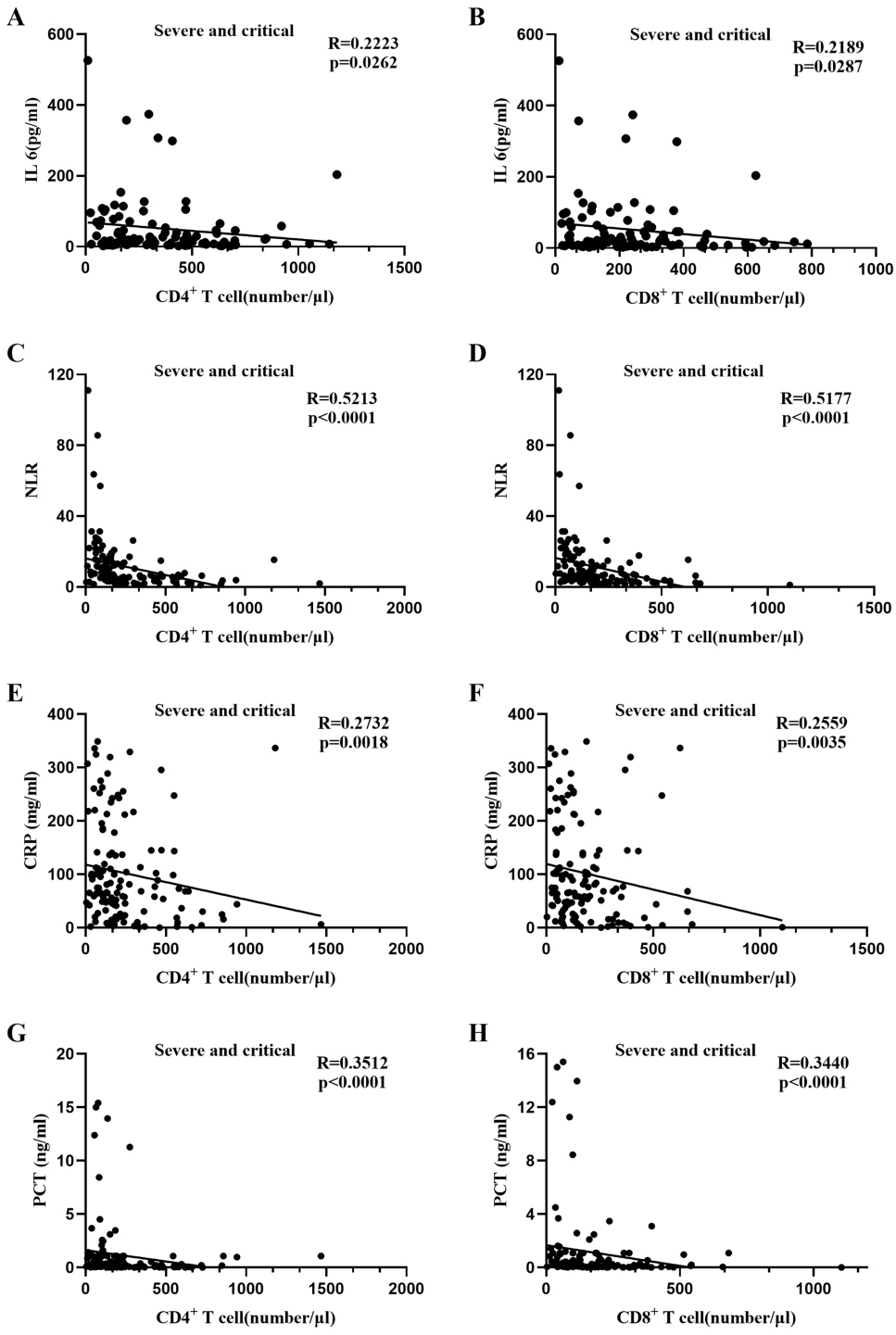

Figure 2 Analysis of the correlation between levels of inflammatory factors and counts of T-cells in cases of severe and critical *COVID-19*. (**A**) Correlation between levels of IL-6 and counts of $CD4^+$ T-cell. (**B**) Correlation between levels of IL-6 and counts of $CD8^+$ T- cell. (**C**) Correlation between neutrophil-to- lymphocyte ratio and counts of $CD4^+$ T-cell. (**D**) Correlation between neutrophil-to- lymphocyte ratio and counts of $CD8^+$ T-cell. (**E**) Correlation between C-reactive protein and counts of $CD4^+$ T-cell. (**F**) Correlation between C-reactive protein and counts of $CD8^+$ T-cell. (**G**) Correlation between procalcitonin and counts of $CD4^+$ T-cell. (**H**) Correlation between procalcitonin and counts of $CD8^+$ T-cell.

severe *COVID-19* in this study had comorbidities, including cardiovascular, digestive, and respiratory diseases, as well as diabetes. This proportion was much higher in the group that had severe Omicron-related *COVID-19*. Chronic respiratory diseases such as COPD may lead to chronic hypoxia and decreased oxygen saturation, which predisposes patients to severe Omicron *COVID-19*. Decreased fingertip oxygen saturation is a risk factor for severe disease; therefore, providing

suitable oxygen therapy and adequate oxygen supply for patients is important. In our study, 70.7% of the patients had hyperglycemia and 27.6% of patients with severe Omicron *COVID-19* had diabetes, which can inhibit the phagocytosis of white blood cells and worsen immune function.[32] During the SARS outbreak, diabetic patients had a 3× higher rate of mortality, admission to intensive care units (ICUs), and treatments that required mechanical ventilation.[33] One study published in the Lancet suggested that medications used to treat diabetes, such as metformin, glitazone, and betel, may prevent or suppress acute respiratory distress syndrome (ARDS) and reduce mortality.[34] Therefore, glucose levels should be monitored and adjusted continually for patients with *COVID-19*, especially for diabetic ones, to reduce the risk of disease progression.

It has been reported that the levels of inflammatory reactions in cases of Omicron infection were not as severe as those of Delta infection, However, in this study, the levels of inflammatory mediators and cytokines including CRP, IL-6, fibrinogen, and NLR, were higher in patients with severe Omicron *COVID-19*, which may reflect excessive activation of the immune system.[35] It is therefore still necessary to adopt appropriate anti-inflammatory therapies at the most optimal times. Glucocorticoids have been recommended for severe or critical cases with worsening oxygenation, rapid imaging progression, or the activation of excessive inflammatory responses. However, it is critically important to carefully control the occasion, dose, and course of this type of therapy. When the immune system is exhausted, particularly in cases of severe *COVID-19* where patients require endotracheal intubation, glucocorticoid treatments can prolong the time taken for virus clearance and lead to secondary infections.[36] Immune cell and inflammatory factor levels typically return to normal, however, in discharged patients. Therefore, inflammatory factors, including CRP, IL-6, fibrinogen, and NLR can serve as effective biomarkers to predict disease prognosis and direct the use of anti-inflammatory therapy in cases of severe *COVID-19*.

This study demonstrated that decreased counts of leucocytes, lymphocytes, and neutrophils were less pronounced in severe and critical patients with Omicron *COVID-19* compared to those with the wild-type disease, but that $CD4^+$ and $CD8^+$ T-cell counts were significantly decreased. Decreased $CD4^+$ and $CD8^+$ levels were found to be risk factors for severe *COVID-19*. The activation and differentiation of T-cells play critical roles in antiviral immunity by secreting various cytokines,[37] and there have been reports of inflammatory storms accompanied by the production of excessive inflammatory factors in cases of severe Omicron *COVID-19*.[38] Our results showed that elevated levels of inflammatory factors were negatively correlated with both $CD4^+$ and $CD8^+$ counts in cases of severe and critical *COVID-19*, suggesting that excessive inflammatory responses contributed to the depletions of T cell, and in turn led to rapid deterioration of the disease, respiratory failure, and even multiple organ failure. T-cell exhaustion also aggravated immune system imbalances, and ultimately caused poor prognosis.[39,40] Therefore, the rapid decline of T-cell counts can be a clinical warning indicating severe Omicron infection. Treatments based on inhibiting T-cell exhaustion and promoting the differentiation of T-cells into long-term memory T-cells to quickly respond to and fight the virus, as well as avoid re-infection,[40] may represent a future direction for the treatment of severe *COVID-19* infection.

In this study, there were high percentages of bacterial co-infections in patients who were hospitalized for severe Omicron *COVID-19*. Furthermore, the bacterial spectrum of co-infection varies greatly among patients with different disease severities. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* accounted for the highest proportion in patients with non-severe diseases, while *Acinetobacter baumannii* was detected the most in patients with severe *COVID-19*. These results differ from others, which reported that the detection rates of *Klebsiella pneumoniae* and *Aspergillus fumigatus* in patients with severe *COVID-19* were higher than those in patients with non-severe disease in Guangzhou, China.[41] This discrepancy may be due to regional differences. Meanwhile, temperature, neutrophil counts, and levels of PCT and CRP were found to be significantly increased in cases of severe Omicron *COVID-19*, which may indicate bacterial co-infection. Therefore, it is necessary to strengthen the monitoring of co-infections in patients with severe *COVID-19* and avoid inappropriate treatments involving antibiotics, particularly broad-spectrum ones. Rapid and accurate etiological diagnoses should be performed, to provide solid laboratory bases for the precise usage of antibiotics in cases of severe Omicron *COVID-19*.

The major limitation of this study is its retrospective design and lack of follow-up data. The duration of the study was also insufficient to classify results according to the subtypes of Omicron variants, which may have impacted the study's ability to provide comprehensive details regarding the differential characteristics between the Omicron variant and wild-

type *COVID-19*, in terms of guiding clinical treatments. Therefore, prospective multicenter studies with larger sample studies are warranted to further explore this topic in the future.

Conclusions

The Omicron variant of the *SARS-CoV-2* virus has a particularly high rate of transmission and has spread rapidly. The sharp increase in patients hospitalized with severe Omicron *COVID-19* has placed great pressure on medical institutions across the country. Omicron variants are constantly emerging, and it is crucial to investigate the differences in clinical characteristics of patients that are caused by the different variants. This study proved that there were significant clinical differences between patients hospitalized with severe cases of Omicron-variant *COVID-19* vs wild-type. The Omicron cases tended to be older and had more upper respiratory tract symptoms, comorbidities and bacterial co-infections. Elevated levels of inflammatory cytokines with T-cell depletion correlated with poor disease progression and prognosis. These data provide a theoretical basis for future integrated prevention and control plans for *COVID-19*.

Abbreviations

SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; ACE2, angiotensin converting enzyme 2; RT-PCR, Reverse Transcription-Polymerase Chain Reaction; PCT, procalcitonin; CRP, C-reactive protein; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Tbil, total bilirubin; BUN, blood urea nitrogen; Ccr, Creatinine Clearance Rate; IL-6, interleukin 6; CK, creatine kinase; CK-MB, isoenzyme of creatine kinase; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PT, Prothrombin time; APTT, activated partial thromboplastin time; SARS, Severe Acute Respiratory Syndrome; ICU, Intensive Care Unit; ARDS, acute respiratory distress syndrome.

Data Sharing Statement

All data reported in this study are available from the corresponding authors (Guang-He Fei and Ming-Feng Han) upon reasonable request, following institutional approval.

Ethics Approval

The study complied with the Declaration of Helsinki and was approved by the First Affiliated Hospital of Anhui Medical University Ethics Committee (No: 2022371).

Consent for Publication

All patients involved in this study gave written informed consent to participate, and the authors have reviewed and approved the final version of the manuscript.

Author Contributions

All authors made a significant contributions to the work reported, including the conception, study design, execution, acquisition of data, analysis and interpretation, in addition to participating in drafting, revising, or critically reviewing the article. All authors provided final approvals of the version to be submitted for publication, as well as agreed on the journal to which the article has been submitted, with full accountability for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to disclose for this work.

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