A comprehensive analysis of immune characteristics and clinical prognosis in Asian COVID-19 patients infected with SARS-CoV-2 Omicron strain XBB sub-variants: a retrospective study of 450 cases

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Submitted: 5 October 2023; **Accepted:** 8 January 2024
Online publication:

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/178422

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Abstract

Introduction: The pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has posed a severe threat to human health since December 2019. Immune characteristics and clinical symptoms manifested by COVID-19 patients of the most recent new strains have not been reported.

Material and methods: We retrospectively investigated 450 patients with laboratory-confirmed COVID-19 infection from December 2022 to January 2023. Clinical information and peripheral blood of the patients were obtained and analyzed for serum IL-6 levels and T cell sub-types. Post hoc analysis was performed to uncover immunological and involved COVID-19-associated pneumonia differences between patients with different underlying diseases and ages.

Results: The median age of the patients was 75.5 years old. 60% of the patients were male and 40% were female. The most common symptoms were cough (344/450,76.4%), fever (317/450, 70.4%), expectoration (199/450, 44.2%) and wheeze (143/450, 31.8%). The mean hospital stay was 11.85 days (range: 1–57). 92% of the patients recovered in a month. The level of serum IL-6 was significantly higher in patients without underlying diseases compared with patients with hypertension, chronic obstructive pulmonary disease (COPD), cancer and diabetes ($p < 0.001$). Serum IL-6 level was significantly higher in patients who were 66–79 years old than that in patients aged 65 years and younger ($p < 0.001$). Peripheral CD8+T cell percentage was significantly higher in patients aged 65 years and younger than that in patients aged 80 years and older ($p = 0.05$). The mean involved ground-glass opacity area of the lung of all studied patients found by chest computed tomography (CT) at the time of initial onset of symptoms was 35.7%. Fifty-seven out of 132 (43.2%) patients who had assessable CT scans at 4–12 weeks after infection completely recovered with no chest CT abnormality. Involved ground-glass area of the lung of patients with diabetes or without underlying disease was significantly more severe than that in patients with COPD ($p = 0.041$ and $p = 0.017$, respectively). Involved ground-glass area of the lung of patients aged 80 years and older was significantly more severe than that in patients aged 65 years and younger ($p = 0.031$).

Conclusions: 92% of COVID-19 patients infected with Omicron XBB sub-variants of SARS-CoV-2 can recover well in a month. Patients aged 80 years and older who have a lower lymphocyte percentage experienced more severe pneumonia than patients aged 65 years and younger having a higher lymphocyte percentage. Serum IL-6 level can be a recovery indicator for patients with COVID-19 infection.

Key words: COVID-19, immune status, lung parenchyma, prognosis, interleukin-6.

Introduction

The initial outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which happened in December 2019, was first reported in Wuhan, China [1]. As there was originally a lack of COVID-19 virus-specific treatment, the adoption of effective community quarantine was applied to contain this pandemic virus internationally. Despite taking approaches to prohibit the virus spreading, SARS-CoV-2 had infected over 200 countries worldwide by June 2020 [2]. An average case fatality rate (CFR) of 1–7% was reported in Mexico, Italy, the UK, Spain, France, and Russia [3]. Since then, significant efforts have been made to develop effective vaccines and new anti-virus drugs against this virus [2, 4–7]. The administration of several world leading COVID-19 vaccines, including Pfizer/BioNTech, Novavax, Moderna and Johnson & Johnson, has greatly reduced severe COVID-19 infection, especially for the elder population [8–10]. However, the vaccine efficacy is reduced due to the emerging of new virus variants which can partially escape the immune response induced by these vaccines [8–10]. With the development of rapid molecular diagnostics methods, emerged major COVID-19 variants were detected including B.1.1.7 (Alpha, reported on 14 December 2020, United Kingdom), P.1 (Gamma, detected on 6 January 2021, Japan), B.1.351 (Beta, identified on 18 December 2020, South Africa), and other variants of B.1.427/B.1.429 (Epsilon), B.1.617.2 (Delta) and BA.1 (Omicron), which contains various significant mutations in the S-glycoprotein of the COVID-19 virus [11, 12].

As of March 2022, there were about 480 million confirmed COVID-19 infection patients worldwide, and 6 million patients died of respiratory failure caused by viral infection or related severe complications (https://coronavirus.jhu.edu/) [13]. Vaccination is the most important strategy to halt and reverse the pandemic. The implementation of COVID-19 vaccinations was high in America, Europe and Asia, where over 100 doses have been administered per 100 population [13–15]. As the administration of the vaccination increased, the numbers of critically ill patients and mortality rates significantly decreased [13].

The clinical prognosis and outcome of COVID-19 infection were a mystery during the initial onset of the outbreak. There was particular concern about whether the virus infection would affect children's development or threaten the life of elderly people. Among clinical features of the original strain of COVID-19 infection initially reported in February 2020, the most common symptoms were fever, cough and diarrhea in the studied 1099 Chinese patients [1]. Ground-glass opacity was found in about 56.4% of the 1099 patients, which was the most common radiologic finding on the chest computed tomography (CT) scan [1]. Importantly, 83.2% of the patients experienced post-infection lymphocytopenia [1]. Moreover, most studies focused on COVID-19 vaccination development and vaccine-induced immune activities; there are very few studies on CD4+T, CD8+T and interleukin-6 (IL-6) based immunological studies of COVID-19 infected patients. IL-6 as a multi-tasking cytokine often presents high activity in COVID-19 patients following virus infection; it may be an explanation for the occurrence of cytokine release syndrome (CRS) in patients with severe disease [16]. However, there is very limited information of immunological characteristics, clinical features, prognosis and outcome of infection with the emerged COVID-19 variants including B.1.1.7, P.1, B.1.351, B.1.427/B.1.429, B.1.617.2 and most recent reported Omicron sub-variants (BA.1, BA.2, BA.3 and XBB) [17, 18].

In order to prevent the pneumonia epidemic caused by COVID-19, China has taken a series of effective prevention and isolation approaches including quarantine and vaccination to control the spread of the epidemic from January 2020 until December 2022. Therefore, there was a very low prevalence of COVID-19 infection in China during this period. With the emergence of more and more variants, the virulence and pathogenicity of COVID-19 were weakening. Thus, China lifted various quarantine and control measures in December 2022, and there was a peak of COVID-19 infection from December 2022 to January 2023. Herein, we retrospectively studied 450 COVID-19 patients infected with Omicron XBB sub-variants to first reveal its immune characteristics, clinical symptoms, prognosis and associated pneumonia in different populations of patients. These results provide key clinical information of COVID-19 infection of Omicron XBB sub-variants for understanding the immunological and clinical features in patients with different underlying diseases and different ages, and pave the way for further vaccination development and molecular study of the SARS-CoV-2 virus induced immune response.

Material and methods

Patients and blood sample collection

A total of 450 patients who were infected with SARS-CoV-2 from December 2022 to January 2023 at the Tianjin Beichen Hospital (Tianjin, China) were retrospectively investigated (Figure 1 A). This study was approved by the ethics committee of the Tianjin Beichen Hospital and conformed to the ethical guidelines of the Declaration of Helsinki. Inclusion criteria of the studied patients are as follows: 1) confirmed with Omicron XBB sub-variants of SARS-CoV-2 infection by laboratory RT-PCR

test; 2) diagnosed with SARS-CoV-2 infection from December 2022 to January 2023; 3) patients were admitted to the hospital; 4) treated with glucocorticoid and antibiotics, but no anti-virus drugs; 5) patients all received 3 doses of COVID-19 vaccination (Kexing, China). Patients who did not meet the criteria above were excluded. Blood samples of patients were collected on the first day and/or last day of the hospital stay. Basic clinical characteristics of the 450 studied patients are shown in Table I. All patients' data were collected from the hospital medical records, and patients with incomplete

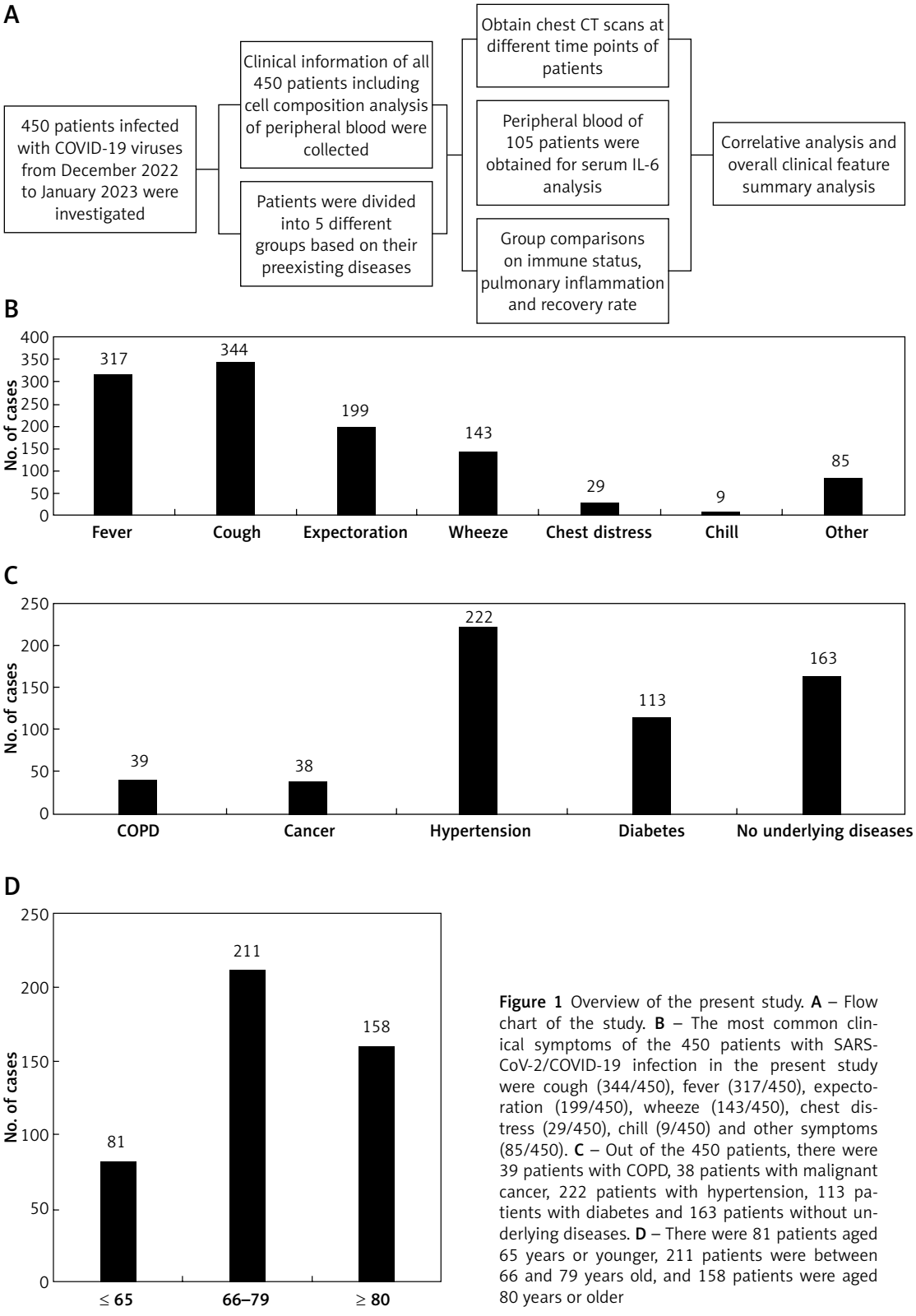

Figure 1 Overview of the present study. **A** – Flow chart of the study. **B** – The most common clinical symptoms of the 450 patients with SARS-CoV-2/COVID-19 infection in the present study were cough (344/450), fever (317/450), expectoration (199/450), wheeze (143/450), chest distress (29/450), chill (9/450) and other symptoms (85/450). **C** – Out of the 450 patients, there were 39 patients with COPD, 38 patients with malignant cancer, 222 patients with hypertension, 113 patients with diabetes and 163 patients without underlying diseases. **D** – There were 81 patients aged 65 years or younger, 211 patients were between 66 and 79 years old, and 158 patients were aged 80 years or older

Table I. Clinical and demographic characteristics at baseline of all 450 studied patients

Characteristic	Mean ± SD (*n* = 450)	Range
Age [years]	76.34 ±10.56	19–97
Gender (male/female)	270/180	–
CRP [mg/l]	45.07 ±58.28	0.25–296.28
D-dimer [mg/ml]	2.09 ±3.57	0.05–32
Basic diseases (*n*)		
COPD	39	–
Cancer	38	–
Hypertension	222	–
Diabetes	113	–
None	163	–
Pleural effusion (yes/no)	158/292	–
Combined with other pulmonary viruses or mycoplasma infection (yes/no)	102/348	–
Antibiotic treatment (yes/no)	384/66	–
Hospital stay [days]	11.84 ±8.5	1–57

CRP – C-reactive protein, COPD – chronic obstructive pulmonary disease.

medical records were excluded. Informed consent of all patients was obtained from either the patient or their dependents for the study.

RT-PCR assay of the virus ribonucleic acid for XBB subvariant of SARS-CoV-2

Nasopharyngeal samples of all the studied 450 patients were collected and multiple PCR library were established using the ATOPlex RNA kit (940-000133-00, BGI, China) according to the instruction sheet. Libraries were measured via an RT-PCR analyzer (QuantStudio3, Thermo Fisher, USA).

Peripheral blood cell composition analysis via flow cytometry

Peripheral blood samples (2–3 ml) of 105 patients were successfully collected at the beginning and end of the hospital stay. Serum samples were isolated and stored at –80°C for further analysis. Blood cell samples were analyzed via an automatic blood analyzer (BC-7500CS, Mindray, Shenzhen, China) according to the manufacturer's instruction sheet. The concentrations and percentages of total white cells, lymphocytes and neutrophils were calculated.

Enzyme-linked immunosorbent assay (ELISA)

Serum samples of 105 patients at the beginning and ending of the hospital stay were thawed at room temperature for cytokine secretion analysis (Figure 1 A). IL-6 expression levels were measured by enzyme-linked immunosorbent assay (ELISA) using a Human IL-6 Pre-coated ELISA kit (1110603, Dayou, China) according to the operation instruction sheet. A standard curve was made according to the manufacturer's instructions and the values of samples were calculated.

Involved lung pneumonia area determination by CT severity scores

CT scans were normally performed every 7–10 days for the studied patients during the hospitalization to closely monitor the changes of lung parenchyma in real time. The CT severity scores of the involved lung pneumonia area of each patient were determined based on visual assessment of involved lung parenchyma, using either small increments (< 10%, 10–25%, 25–50%, 50–75%, > 75%) [19] or assessing the involvement (0, < 50% or > 50%) per lung segment to indicate the degree of lung parenchyma of the infection [20].

Statistical analysis

Statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software, La Jolla, California, USA). The unpaired *t* test was used to analyze the statistical significance of differences between two groups. Correlation analysis between two groups was done using the χ^2 test. A *p*-value less than or equal to 0.05 was considered to be statistically significant.

Results

Clinical characteristics and symptoms of the studied patients

The median age of the 450 patients was 75.5 years. 60% of the patients were male and 40% were female. The most common symptoms were cough (344/450, 76.4%), fever (317/450, 70.4%), expectoration (199/450, 44.2%), wheeze (143/450, 31.8%), chest distress (29/450, 6.4%), chill (9/450, 2%) and other symptoms (85/450, 18.9%) (Figure 1 B). The mean hospital stay of the patients was 11.85 days (range: 1–57) (data not shown). These symptoms were greatly recovered in most patients after treatment. 92% of the patients recovered and were discharged. Out of the 450 patients, 39 had chronic obstructive pulmonary disease (COPD), 38 had malignant cancer including 20 lung cancer cases, 222 patients had hypertension, 113 patients had diabetes and 163 patients had no underlying diseases (Figure 1 C). It is worth noting that a few patients had two to four underlying conditions that we did not subject to post hoc analysis. We also divided these

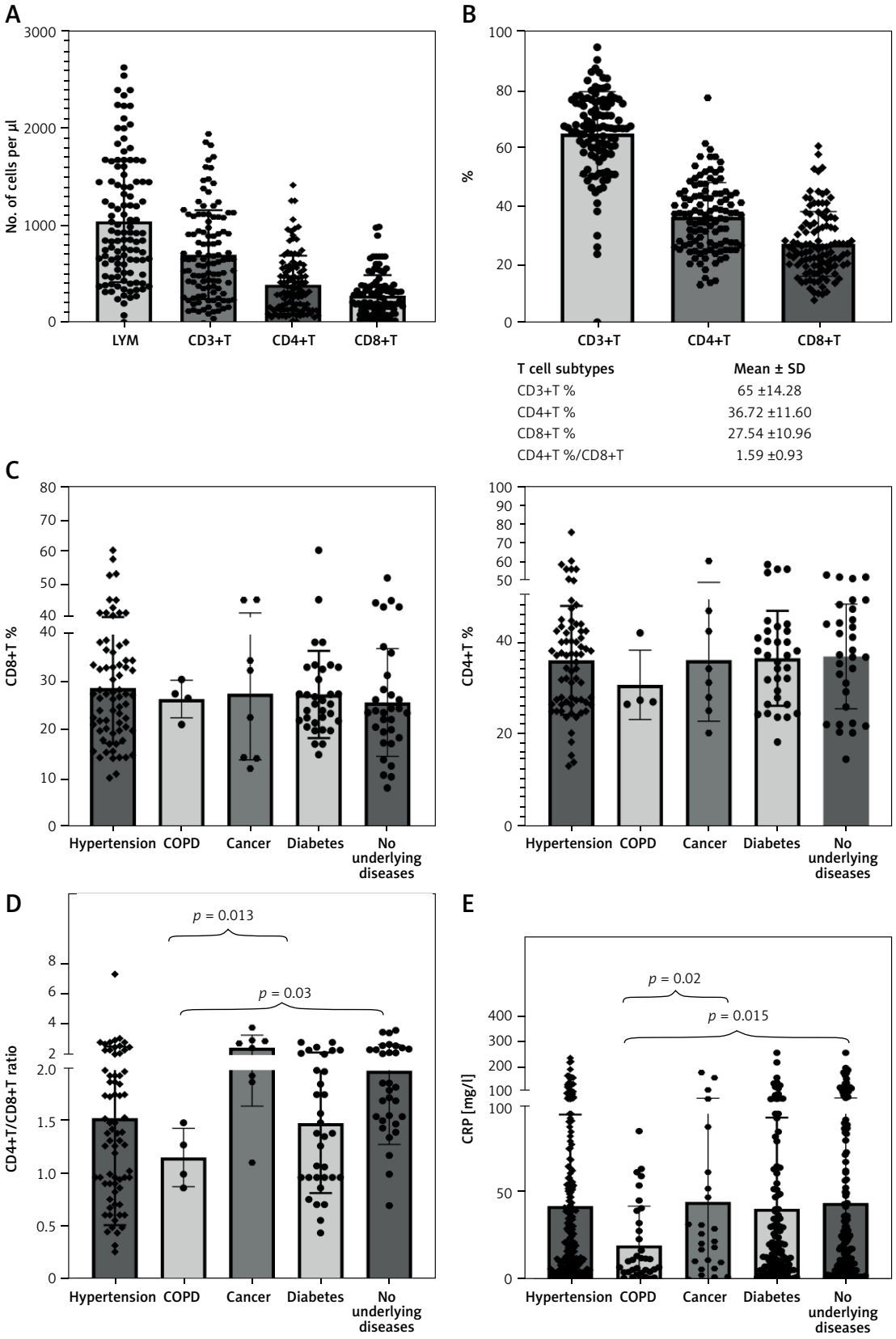

Figure 2. Systematic immune features of the 450 SARS-CoV-2/COVID-19 infected patients with different underlying diseases. **A** – Lymphocyte count decreased with aging. **B** – There were an average of 65% CD3+T cells, 36.72% CD4+T cells and 27.54% CD8+T cells in the peripheral blood of the 450 patients. **C** – There were no significant differences in CD4+T and CD8+T cell percentages in peripheral blood in patients with different underlying diseases. **D** – There was a significantly lower CD4+T/CD8+T ratio when comparing patients with COPD and patients with diabetes and no underlying diseases. **E** – There was a lower serum C-reaction protein (CRP) level in patients with COPD compared with patients with diabetes and no underlying diseases

patients by age: there were 81 patients aged 65 years or younger, 211 patients were between 66 and 79 years old and 158 patients were aged 80 years or older (Figure 1 D).

Systematic immune features of the patients with SARS-CoV-2/COVID-19 infection

After summarizing the clinical characteristics and symptoms of the 450 patients, we next analyzed the systematic immune status of these patients. There were an average of 65% CD3+T cells, 36.72% CD4+T cells and 27.54% CD8+T cells in the peripheral blood of the 450 patients (Figures 2 A, B). There was no significant difference in percentages of CD4+T and CD8+T cells in peripheral blood in patients with different underlying diseases (Figure 2 C, Supplementary Table SI). Interestingly, we found that there was a significantly lower CD4+T/CD8+T ratio when comparing patients with COPD and patients with diabetes and no underlying diseases (p = 0.013, and p = 0.03, respectively) (Figure 2 D). Correspondingly, we found there was a lower serum C-reaction protein (CRP) level in patients with COPD compared with patients with diabetes and no underlying diseases (p = 0.02, and p = 0.015, respectively) (Figure 2 E). There was no significant difference in other cell components in patients with different underlying diseases (Supplementary Figures S1 A–E, Supplementary Tables I, II). These results suggest that there may a suppressed immune status of patients with COPD.

We then performed similar analysis of systematic immune status for patients of different ages. We observed that there was a steady increase of serum CRP expression and D-dimer level in patients aged 65 years and younger, 66 to 79 years old and aged 80 years and older (Figures 3 A, B). Interestingly, there was a significant decreasing trend of peripheral lymphocyte percentages, but a significant increasing trend of neutrophil percentages in patients aged 65 years and younger, 66 to 79 years old and aged 80 years and older (Figure 3 C). Furthermore, patients aged 65 years and younger had a significantly higher peripheral CD8+T cell percentage and lower CD4+T/CD8+T ratio compared with patients who were 66 to 79 years old (p = 0.05, and p = 0.05, respectively) (Figure 3 D). There were no significant differences in white blood cell count and neutrophil count in patients of different ages (Supplementary Figure S1 F).

An essential component of the immune response of IL-6 level in patients with SARS-CoV-2/COVID-19 infection

Patients infected with SARS-CoV-2/COVID-19 usually experience a "cytokine storm" in which patients often have elevated pro-inflammatory cytokines, such as TNF-α, CCL2 , IL-6, IL-1β, IL-2, IL-7,

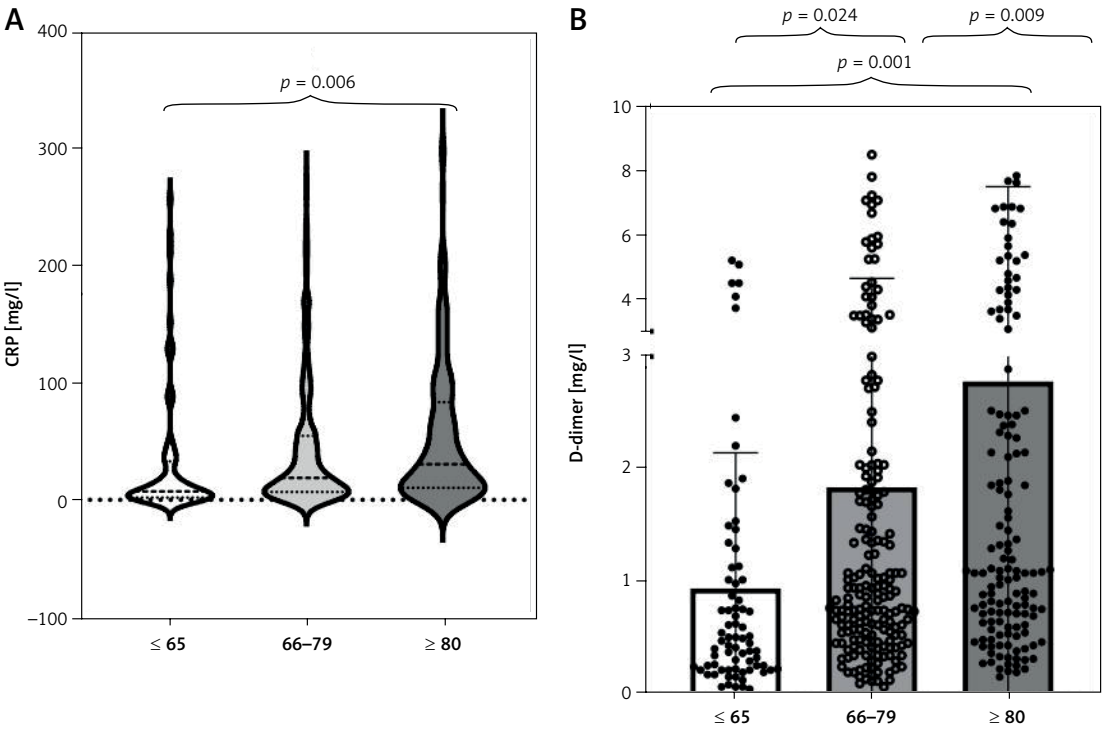

Figure 3. Systematic immune features of the 450 SARS-CoV-2/COVID-19 infected patients in different age groups. **A**, **B** – There was a steady increase of serum CRP expression and D-dimer level in patients aged 65 years and younger, 66 to 79 years old and aged 80 years and older

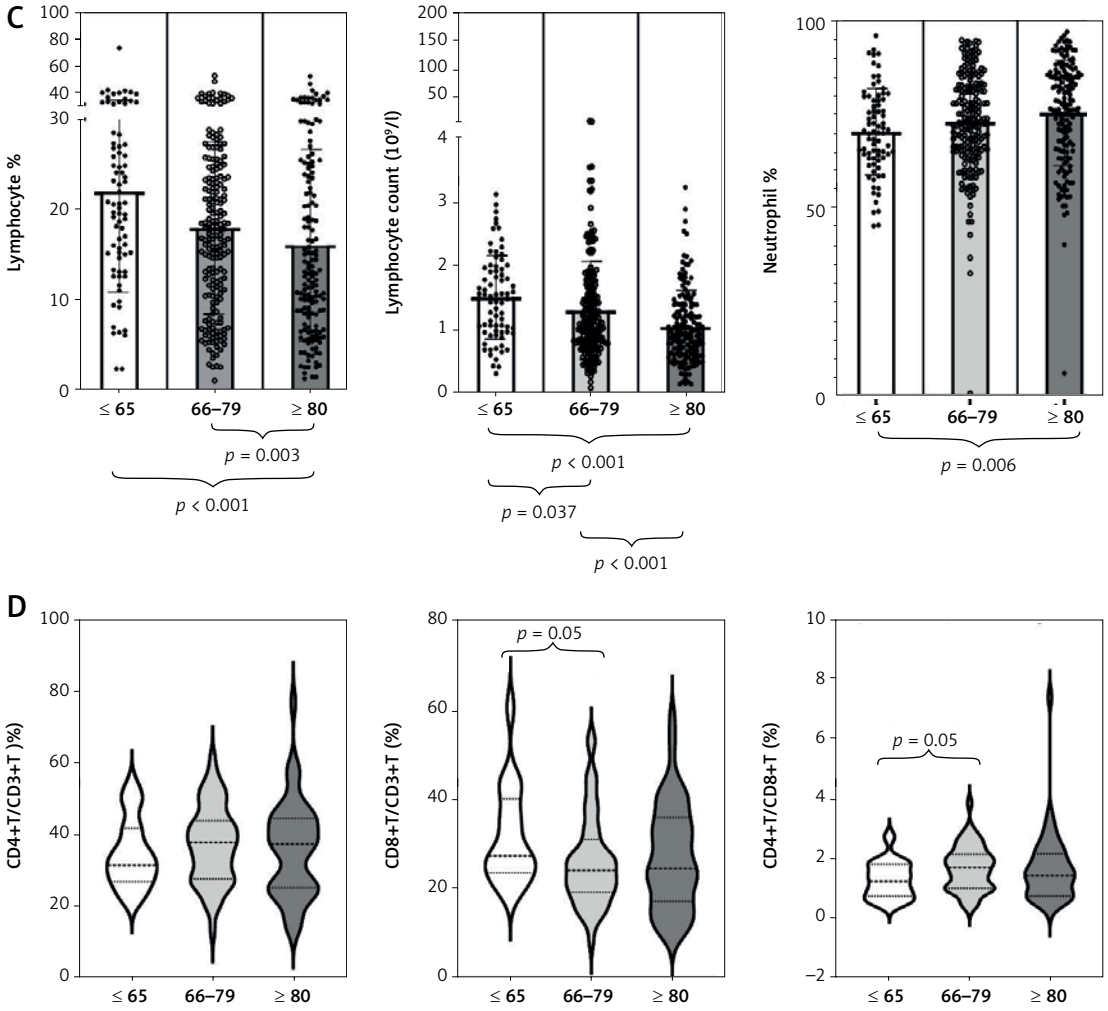

Figure 3. Cont. **C** – There was a significant decreasing trend of peripheral lymphocyte percentages, but a significant increasing trend of neutrophil percentages in patients aged 65 years and younger, 66 to 79 years old and aged 80 years and older. **D** – Patients aged 65 years and younger had a significantly higher peripheral CD8+T cell percentage and lower CD4+T/CD8+T ratio than patients who were 66 to 79 years old

IL-8, and MIP-1α [21–24]. As an essential component of the immune response, the inflammatory molecule IL-6 was widely monitored as a prognostic and treatment indicator in the clinic during the pandemic. In the present study, we therefore measured the serum IL-6 level of the studied patients. As shown in Figure 4 A, the serum IL-6 level was significantly decreased after treatment when patients were discharged ($p = 0.0006$). Importantly, the level of serum IL-6 was significantly higher in patients without underlying diseases compared with patients with hypertension, COPD, cancer and diabetes ($p < 0.001$) (Figure 4 B). Moreover, serum IL-6 level was significantly higher in patients who were 66–79 years old than that in patients aged 65 years and younger ($p = 0.036$) (Figures 4 C, D). These results suggest that patients with the acute stage of pneumonia that happened in the first week after onset of symptoms experienced an acute inflammatory storm, which can be significantly controlled by appropriate treatments and patient autoimmunity. Further, patients with preexisting commodities and patients aged 65 years and younger secreted a lower level of serum IL-6, implying that immune status may not be positively correlated with anti-virus responses.

Lung parenchyma involvement measured through computed tomography of patients with SARS-CoV-2/COVID-19 infection

The most commonly observed imaging abnormality of SARS-CoV-2/COVID-19 infection was ground-glass change. The mean involved ground-glass area of the lung of all studied 450 patients found by chest CT at the time of initial onset of symptoms was 35.71% (Figures 5 A, B). The acute stage of pneumonia happened in the first week after onset of symptoms, pneumonia started to recover in 2–3 weeks, and most patients steadily

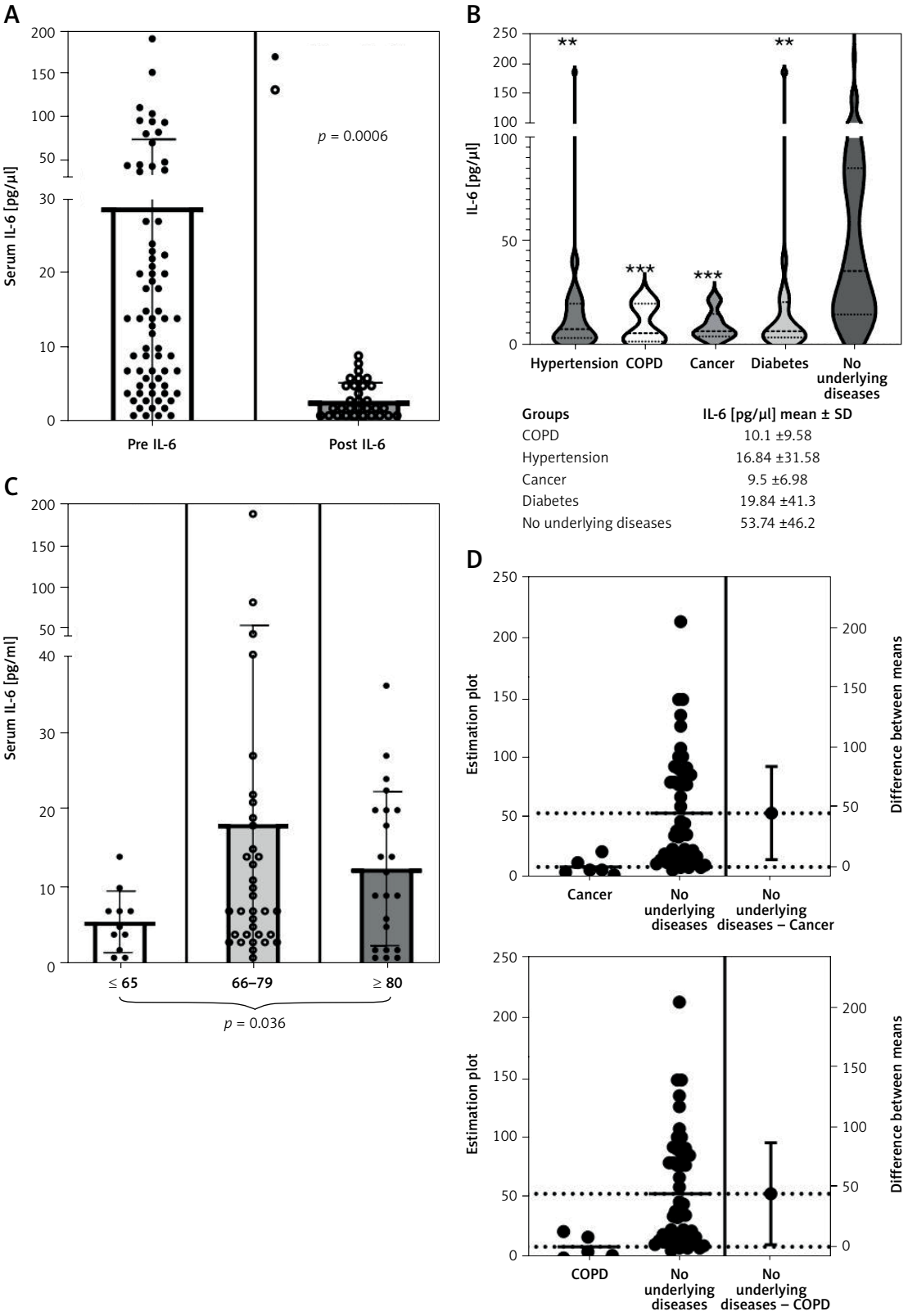

Figure 4. Interleukin-6 (IL-6) expression status of the studied patients with SARS-CoV-2/COVID-19 infection. **A** – The serum IL-6 level was significantly lower after treatment than when patients were discharged. **B** – Serum IL-6 expression was significantly higher in patients without underlying diseases than in patients with hypertension, COPD, cancer and diabetes. **C**, **D** – Serum IL-6 level was significantly higher in patients who were 66–79 years old than in patients aged 65 years and younger

continued to recover in 4–12 weeks (Figure 5 A). Involved ground-glass area of the lung of patients with diabetes or without underlying disease at the time of initial disease onset was significantly more severe than that in patients with COPD (p = 0.041 and p = 0.017, respectively) (Figures 6 A, C). Involved ground-glass area of the lung of patients aged 80 years and older was significantly more severe than that in patients aged 65 years and younger (p = 0.031) (Figures 6 B, D). Change over time of the lung pneumonia of each individual patient with different underlying diseases and ages is shown in Supplementary Figures S2 A-F, S3 A–C. There was no significant correlation between involved lung pneumonia area and systematic immune cell components, such as

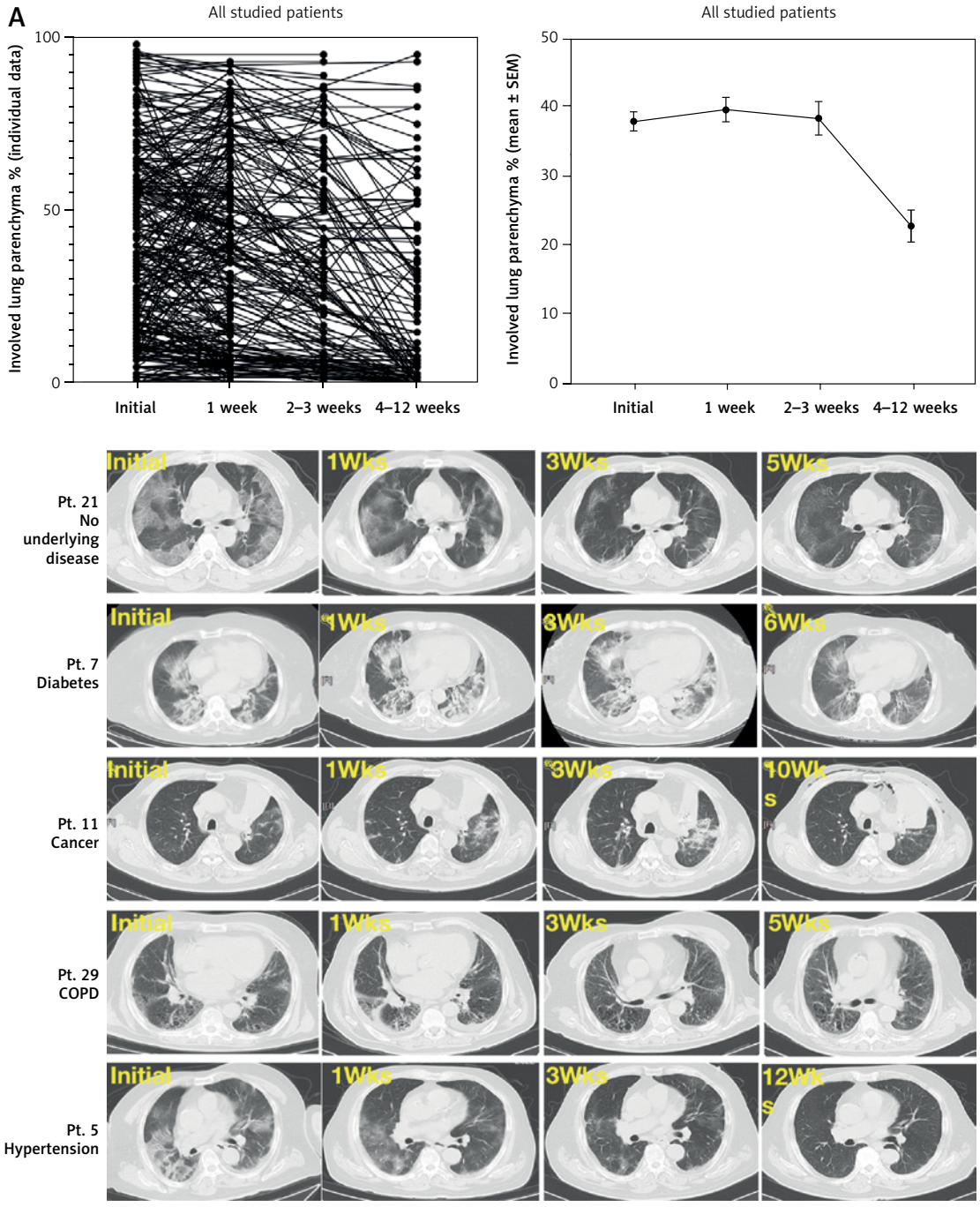

Figure 5. Lung parenchyma involvement measured through computed tomography (CT) of the 450 patients. **A** – The mean involved ground-glass area of the lung of all studied 450 patients found by chest computed tomography (CT) at the time of initial onset of symptoms was 35.71%, and decreased with disease recovery in the next few weeks. **B** – Representative chest CT scans of patients with different underlying diseases showing the ground-glass area change over time

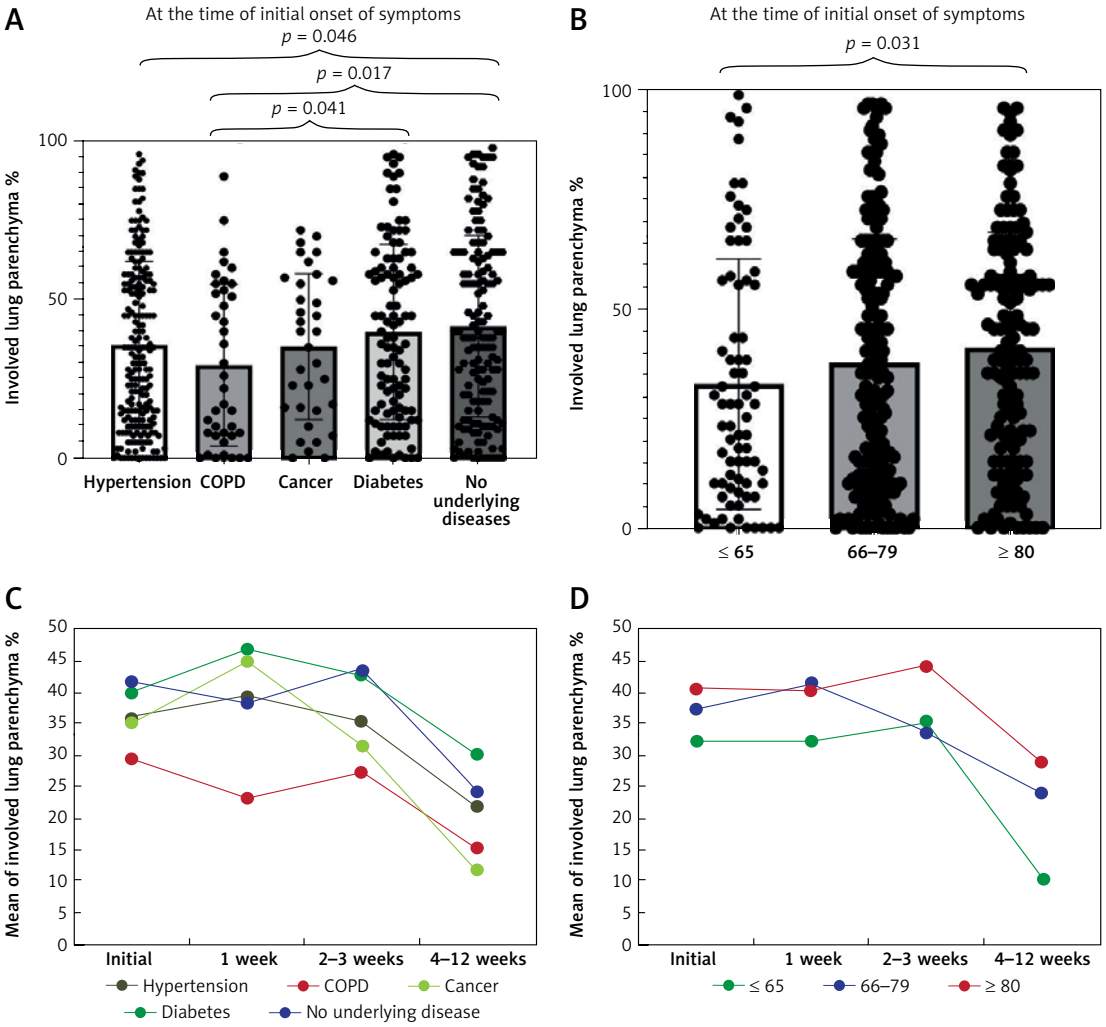

Figure 6. Post hoc analysis of the lung parenchyma involvement measured through computed tomography (CT) of the studied patients with different underlying diseases and age groups. **A**, **C** – Involved ground-glass area of the lung of patients with diabetes or without underlying disease at the time of initial disease onset was significantly more severe than that in patients with COPD. **B**, **D** – Involved ground-glass area of the lung of patients aged 80 years and older was significantly more severe than that in patients aged 65 years and younger

CD4+T, CD8+T percentages and neutrophil counts (Supplementary Figures S4 A–F). Fifty-seven out of 132 (43.2%) patients who had assessable CT scans in 4–12 weeks after infection completely recovered with no CT abnormality. A complete recovery of the lung pneumonia may take longer for a majority of patients, but there were no obvious clinical symptoms affecting daily life during the recovery.

Discussion

SARS-CoV-2/COVID-19 can actuate both adaptive and innate immune responses in humans. Virus-associated lung pneumonia was induced by blockade of adaptive immune function and uncontrolled inflammatory pathways. Although protein sub-unit-based vaccines have been developed to induce antiviral responses to prevent COVID-19-induced immunopathological changes such as Th2 immunopathology and antibody-dependent enhancement, lung tissue damage still occurred when there was rapid virus replication and virus overload in the body. It has been previously reported that significantly reduced counts of peripheral CD4+ T cells , CD8+ T cells, B cells, monocyte, and natural killer (NK) cells were found in patients infected with SARS-CoV-2/COVID-19 [25]. In the present study, we first analyzed the SARS-CoV-2 serological responses and characterization of immune analysis in blood of the most recently reported strain, Omicron XBB. We revealed that the peripheral CD3+T, CD4+T, and CD8+T cell counts and percentages of patients with Omicron XBB infection were similar to healthy humans [26]. The proportions of CD3+T, CD4+T, and CD8+T cells showed no significant differences in patients with different underlying diseases, but declined with aging (Figures 2 C, 3 C). These results imply that

the pathogenicity of the new strain Omicron XBB may significant decline with virus evolution. It is worth noting that the immune status strength of patients decreases with human aging, which can well explain why severe SARS-CoV-2/COVID-19 mainly occurred in elderly patients aged 80 years and older (Figure 3).

We also directly compared SARS-CoV-2/COVID-19 infection outcomes among multiple disease phenotype including hypertension, diabetes, COPD and cancer, which have not been reported elsewhere for the newly confirmed strains. Interestingly, we found that patients with preexisting diabetes experienced the most severe lung tissue damage and recovered more slowly, and patients with preexisting COPD showed the least lung pneumonia and recovered faster. We hypothesize that patients with diabetes may carry dysfunctional immune cells that cannot prevent SARS-CoV-2-induced immunopathology [27]. Previous research demonstrated that acute respiratory virus infection increases IFN-γ production, and it causes muscle insulin resistance in humans, which drives compensatory hyperinsulinaemia to maintain euglycaemia and in turn to boost antiviral CD8+ T cell immune responses [28, 29]. Further studies on the molecular mechanisms of the diabetic resistant immune response are urgently needed. Further, patients with COPD showed a lower level of lung tissue damage compared with patients with other underlying diseases in the present study, while some other studies have reported that preexisting COPD is associated with worse COVID-19 related clinical outcomes [30]. We propose that different SARS-CoV-2 strains may have different effects in COPD patients through various molecular mechanisms, which need to be further studied. To summarize, there are a few future research directions based on the results of the present study: 1) the molecular mechanisms by which IL-6 regulates the SARS-CoV-2 immune response; 2) why patients without underlying diseases experienced high IL-6 expression; 3) the molecular mechanisms behind the observation that COVID-19 patients with diabetes showed the most severe lung tissue damage; 4) why COVID-19 patients with COPD experience less lung pneumonia and recover better; 5) developing effective anti-virus drugs which can bind to the viral proteins to prevent virus-associated immune responses in already infected individuals; 6) the exact role of CD4+T and CD8+T in COVID-19 induced immune responses.

In conclusion, we performed a comprehensive analysis of 450 patients who were infected with Omicron XBB. These results revealed for the first time the clinical features and immunological characteristic of the most recent COVID strains. COVID-19 patients infected with Omicron XBB sub-variants of SARS-CoV-2 can recover well in 92% of cases in about a month. Patients aged 80 years and older who had a lower lymphocyte percentage experienced more severe pneumonia than patients aged 65 years and younger who had a higher lymphocyte percentage. The level of serum IL-6 can be a recovery indicator for these patients. These results will pave the way for future clinical management of respiratory virus infection, and enrich knowledge based on clinical observation for respiratory physicians.

Funding

Fenge Li and Yupeng Wang contributed equally.

This work is supported by the Tianjin Beichen Hospital (Beichen District Health System Technology Project, Funding No.: SHGY-2021006 and SHGY-2020024).

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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