

Imaging Progression Under Low Respiratory Viral Load of SARS-CoV-2 Omicron Variant Infection: A Retrospective Study in China

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Purpose: To investigate the computed tomography (CT) findings of SARS-CoV-2 Omicron variant in relation to respiratory viral loads determined by cycle threshold values in reverse-transcription polymerase chain reaction (RT-PCR).

Materials and Methods: From October 2022 to November 2022, 74 hospitalized patients with Omicron were included in this retrospective study. The radiological features, CT involvement scores in relation to the respiratory viral load, and factors associated with imaging progression (IP) after the RT-PCR results turned negative were analyzed.

Results: The most common CT patterns of Omicron were multiple round-like or patchy ground-glass opacity (GGO) or mixed GGO in the peripheral or diffuse areas. The grading of CT involvement scores exhibited an inverse pattern compared to viral loads from day 1 to day 8 and from day 13 to day 20 after diagnosis. Among the 65 patients with complete imaging data, 45 (69.23%) showed IP with clinical warning indicators of disease exacerbation negative in 34 and positive in 11. Patients with IP were older than those with non-IP (NIP); the erythrocyte sedimentation rates, procalcitonin levels, and D-dimer levels on admission of patients with IP were significantly higher than those of patients with NIP, whereas the immunoglobulin (Ig) G antibody level on admission and CT involvement score on initial CT of patients with IP were significantly lower than those of patients with NIP (all $P < 0.05$).

Conclusion: For patients with Omicron, the IP of lung abnormalities is common when the viral load decreases. Under these circumstances, paying attention to clinical warning indicators of disease progression may contribute to better patient management and the mitigation of severe pneumonia.

Keywords: severe acute respiratory syndrome coronavirus-2, Omicron, pneumonia, computed tomography, viral load

Introduction

Since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first reported in 2019, it has spread rapidly around the world via some common routes, such as aerosol transmission, and direct transmission.¹ The pandemic posed a serious threat to human health, and many people suffered from post-COVID-19 syndrome.² SARS-CoV-2 constantly evolves during replication, and many variants have appeared through the pandemic. Omicron, a SARS-CoV-2 variant that was first detected in South Africa's Gauteng province in mid-November 2021, became the dominant SARS-CoV-2 strain (after the Delta variant) in most countries by 2022.^{3,4} This variant, which is characterized by multiple mutations, rapid spread, and the ability to infect people with naturally acquired or vaccine-induced immunity against previous variants, causes significant increments in infection rates.⁵⁻⁷

According to the current diagnostic criteria, reverse-transcription polymerase chain reaction (RT-PCR) has become a standard and routine assessment for the diagnosis of the SARS-CoV-2 infection. Different viral target genes have been

used for the detection of SARS-CoV-2, including spike (S), nucleocapsid (N), RNA-dependent RNA polymerase (RdRp), open reading frame 1ab (ORF1ab), and envelope (E). Cycle threshold (Ct) values in RT-PCR have been used to determine the dynamics of the SARS-CoV-2 viral load by measuring the amplification required for the target viral gene to cross the threshold and are inversely related to the viral load.⁸

Chest computed tomography (CT) plays a key role in the diagnosis and management of hospitalized patients with SARS-CoV-2 infection. Multiple studies have indicated a correlation between disease severity and the degree of parenchymal involvement on CT scans.^{9–12} Several semiquantitative CT scores have been developed to evaluate the extent of pulmonary involvement and objectively monitor the disease course.^{9–12} In our clinical practice, we found that many patients infected with Omicron demonstrated imaging progression (IP) even after their RT-PCR results had become negative for SARS-CoV-2. In particular, a few patients progressed to severe disease because of inadequate attention to symptom aggravation. However, this topic is poorly reported.

Therefore, we aimed to investigate the chest CT findings of the SARS-CoV-2 Omicron variant infection in relation to respiratory viral loads determined by Ct values in RT-PCR.

Materials and Methods

Patients

This study was conducted according to the principles of the Declaration of Helsinki and posed no risks to patients. It was approved by the Ethics Committee of Chongqing University Three Gorges Hospital, and informed consent was obtained from all individual participants included in the study. We included all consecutive patients with SARS-CoV-2 infection admitted to a large referral center in Chongqing, China, from October 2022 to November 2022, when the Omicron variant was predominant in this city. Our inclusion criteria were as follows: 1) positive RT-PCR results for SARS-CoV-2 from respiratory samples (pharyngeal swab) on admission; 2) sequential RT-PCR tests for SARS-CoV-2 nucleic acid once every 1–3 days during hospitalization; 3) two or more available CT scans, with at least one of them showing positive results for viral pneumonia; and 4) negative RT-PCR results for influenza virus pneumonia, prevalent in the current season, from respiratory samples. Exclusion criteria were as follows: 1) poor imaging quality due to obvious respiratory motion artifacts and 2) the presence of diffused lesions that would influence the evaluation of pneumonia on CT images.

CT Protocols

All chest CT examinations were performed on a uCT960+ scanner (United Imaging Healthcare). All patients underwent noncontrast-enhanced scanning in the supine position. The imaging parameters were as follows: tube voltage: 110–120 kVp; tube current: 50–250 mAs (automatic tube current modulation technology); and scanning slice thickness/interval: 5 mm/5 mm. All images were reconstructed with a section thickness and slice interval of 1 mm each for analysis.

CT Image Analysis

Axial images with a 1-mm slice thickness were interpreted by two radiologists with >10 years of experience with chest imaging. These radiologists were blinded to the related clinical data and used workstations and multiplanar reconstruction images to aid their analysis. Any disagreement was resolved via discussions to reach a consensus. The lung and mediastinal windows were set as follows: window width: 1600 HU, window level: –600 HU and window width: 400 HU, window level: 40 HU, respectively. For patients with SARS-CoV-2 infection, the following data were carefully analyzed: lobar involvement (single lobe/unilateral multiple lobes/bilateral multiple lobes), distribution (peripheral/central/both central and peripheral), density (GGO/mixed GGO [GGO mixed with consolidation]/consolidation) and shapes of lung opacities (round-like/patchy/linear), and other findings (crazy-paving pattern/vascular enlargement pattern/bronchodilation/interlobular septal thickening/tree-in-bud pattern/pleural effusion/thoracic lymphadenopathy). A semiquantitative scoring method was designed to assess the degree of involvement of each lung lobe:⁹ score 0, no involvement; score 1, less than 5% involvement; score 2, 5% to less than 25% involvement; score 3, 25% to less than 50% involvement; score 4, 50% to less than 75% involvement; and score 5, at least 75% involvement. The total involvement score was obtained by summing the individual scores of five lung lobes, which ranged from 0 to 25 points. According to CT involvement

scores, the degree of lung involvement was divided into four grades: grade I (low degree: scores ≤ 5), grade II (mild degree: $5 < \text{scores} \leq 10$), grade III (moderate degree: $10 < \text{scores} \leq 15$), or grade IV (severe degree: $15 < \text{scores} \leq 25$). IP was defined as an increase in the total involvement score of follow-up CT relative to the previous score.

RT-PCR and Variant Status

Virological tests for SARS-CoV-2 RNA detection were performed via pharyngeal sampling using swabs. A single sample was obtained per patient. Viral RNA was extracted using the SARS-CoV-2 nucleic acid detection kit (BioGerm, Shanghai, China and Medeasy, Wuhan, China). The ORF1ab and N genes were simultaneously amplified and tested using RT-PCR. A positive result was observed when both targets showed positive amplification (Ct value < 40), whereas a negative result was observed when both targets showed negative amplification (Ct value ≥ 40). Based on the Ct values of both N and ORF1ab genes, the viral load was classified into four grades: grade I (low viral load: CT values > 35), grade II (mild viral load: $30 < \text{CT values} \leq 35$), grade III (moderate viral load: $25 < \text{CT values} \leq 30$), or grade IV (high viral load: CT values ≤ 25).

Clinical Classification for Disease Severity

Disease severity was divided into four categories according to the Guidelines for the Diagnosis and Treatment of SARS-CoV-2 issued by the National Health Commission (7th edition; China):¹³ 1) mild type: mild clinical symptoms without pneumonia on CT imaging; 2) moderate type: fever and respiratory infection symptoms, among others (note: a miniscule number of patients may be asymptomatic) with pneumonia on CT imaging; 3) severe type: a. respiratory distress with a respiratory rate $\geq 30/\text{min}$, b. oxygen saturation $\leq 93\%$ in a resting state, c. arterial partial pressure of oxygen/oxygen concentration $\leq 300 \text{ mmHg}$ ($1 \text{ mmHg} = 0.133 \text{ kPa}$), and/or d. patients with $>50\%$ lesion progression within 48 hours in lung imaging; and 4) critical type: a. respiratory failure requiring mechanical ventilation, b. shock, and/or c. the patient required intensive care unit monitoring and treatment because of other organ failure.

Clinical Warning Indicators of Severe-Critical Type

The disease might worsen from mild-moderate type to severe-critical type when patients met any of the following criteria:¹³ 1) peripheral blood lymphocytes progressively decreased; 2) peripheral inflammatory factors such as interleukin-6 and C-reactive protein progressively increased; 3) lactic acid progressively increased; and 4) clinical symptoms such as fever and respiratory tract symptoms progressively aggravated.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 19.0; IBM Corp., Armonk, NY). Quantitative data were expressed as medians (25 and 75% quartiles). The two independent-samples Student's *t*-test or the Mann-Whitney *U*-test was used to determine differences in variables between groups. Categorical data were expressed as counts and percentages, and the Chi-square test was used to determine differences in these variables between groups. A two-tailed $P < 0.05$ indicated statistical significance.

Results

Demographics and Clinical Characteristics of Patients

After excluding 3 patients with poor imaging and 8 patients with diffused lesions, 74 patients (median age, 54 [49, 62]; range, 23–92 years) infected with SARS-CoV-2 were included in this study. Figure 1 shows the flowchart of the patient inclusion process. The demographics and clinical characteristics of our study participants are summarized in Table 1. Forty-nine (66.22%) patients were women and 25 (33.78%) were men. Sixty-seven (90.54%) patients had clinical symptoms and seven patients (9.46%) were asymptomatic during hospitalization. Thirty-one (41.89%) patients had comorbidities, whereas 43 (58.11%) did not have them. For laboratory test results, the most common abnormalities included decreased lymphocyte counts as well as elevated interleukin-6 levels, highly sensitive C-reactive protein levels, erythrocyte sedimentation rates, procalcitonin levels, and immunoglobulin (Ig) G and Ig M antibody titers. In our cohort,

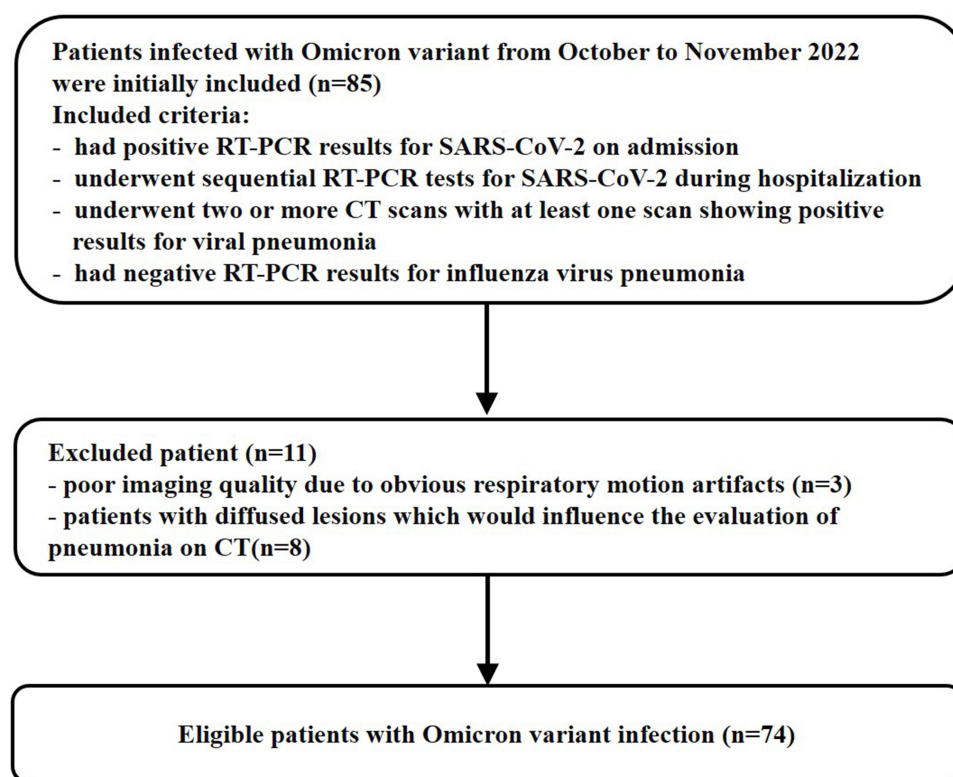


Figure 1 Flowchart of the patient inclusion process.

72 (97.30%) patients were vaccinated and only 2 (2.70%) were unvaccinated. The infection duration at the time of the initial CT scan was 1.00 (1.00, 2.00) days, ranging from one day to 13 days. For the clinical classification for disease severity on initial CT, 59 (79.73%) patients were divided into mild type, 10 (13.51%) were moderate type, three (4.05%) were severe type, and two (2.70%) were critical type.

Table 1 Demographics and Clinical Characteristics of the Patients Infected with Omicron

Characteristics	Results
Age (years)	
Average	54 (49, 62)
Range	23–92
Sex	
Male	25 (33.78%)
Female	49 (66.22%)
Clinical symptoms *	
Presence	67 (90.54%)
Absence	7 (9.46%)
Comorbidities**	
Presence	31 (41.89%)
Absence	43 (58.11%)

(Continued)

Table 1 (Continued).

Characteristics	Results
Laboratory tests on admission	
Leukocyte count ($\times 10^9/L$)	4.74 (3.85, 5.72)
Neutrophil count ($\times 10^9/L$)	3.14 (2.30, 4.21)
Lymphocyte count ($\times 10^9/L$)	0.94 (0.63, 1.31)
Interleukin-6 (pg/mL)	6.56 (1.61, 12.88)
Highly sensitive C-reactive protein (mg/L)	4.90 (2.20, 13.20)
Erythrocyte sedimentation rate (mm/H)	19.00 (6.50, 32.25)
Procalcitonin (ng/mL)	0.03 (0.02, 0.06)
Virus-specific IgG antibody (S/CO)	4.45 (1.40, 13.71)
Virus-specific IgM antibody (S/CO)	0.14 (0.08, 0.41)
Vaccination status	
Unvaccinated	2 (2.70%)
Single or double vaccinated	10 (13.51%)
Booster vaccinated	62 (83.78%)
Infection duration at the time of initial CT scan (days)***	
Average	1.00 (1.00, 2.00)
Range	1.00–13.00
Clinical classification for disease severity on initial CT	
Mild type	59 (79.73%)
Moderate type	10 (13.51%)
Severe type	3 (4.05%)
Critical type	2 (2.70%)

Notes: *Clinical symptoms included fever, fatigue, cough, expectoration, chest pain, shortness of breath, muscle pain, sore throat, diarrhea, loss of appetite, parageusia, heterosmia, headache, and abdominal pain.

Comorbidities included cardiovascular or cerebrovascular disease, diabetes mellitus, immunocompromised status, and chronic lung, liver, or renal disease. *Infection duration at the time of initial CT scan, days from initial positive RT-PCR for SARS-CoV-2 to initial CT scan.

Abbreviation: CT, computed tomography.

Chest CT Findings with Lung Abnormalities Upon Initial Presentation

Of all 74 patients, the CT findings with high suspicion of SARS-CoV-2 pneumonia upon initial presentation are shown in Table 2. The most frequent CT patterns were round-like or patchy ground-glass opacity (GGO) or mixed GGO in the peripheral or diffuse areas of both lungs, usually accompanied by vascular enlargement patterns, crazy-paving

Table 2 CT Findings of Omicron Pneumonia at Initial Present

CT Features	Results
Lobar involvement	
Single lobe	13 (17.57%)
Right upper lobe	6
Right middle lobe	0
Right lower lobe	5
Left upper lobe	1
Left lower lobe	1
Unilateral multiple lobes	3 (4.05%)
Bilateral multiple lobes	58 (78.38%)

(Continued)

Table 2 (Continued).

CT Features	Results
Distribution	
Peripheral	31 (41.89%)
Central	6 (8.11%)
Diffuse	37 (50.00%)
Density of lesions	
Only GGO	27 (36.49%)
Mixed GGO with consolidation	45 (60.81%)
Only consolidation	2 (2.70%)
Morphology	
Round-like shadowing	68 (91.89%)
Patchy shadowing	45 (60.81%)
Linear shadowing	2 (2.70%)
Other findings	
Crazy-paving pattern	16 (21.62%)
Vascular enlargement pattern	32 (43.24%)
Bronchodilation	6 (8.11%)
Interlobular septal thickening	14 (18.92%)
Tree-in-bud pattern	2 (2.70%)
Pleural effusion	2 (2.70%)
Thoracic lymphadenopathy	1 (1.35%)

Abbreviations: CT, computed tomography; GGO, ground-glass opacity.

patterns, and interlobular septal thickening (Figure 2). Seven (9.46%) patients were asymptomatic during hospitalization but displayed abnormal chest CT results, revealing multifocal GGO or mixed GGO, which resolved rapidly during follow-up CT.

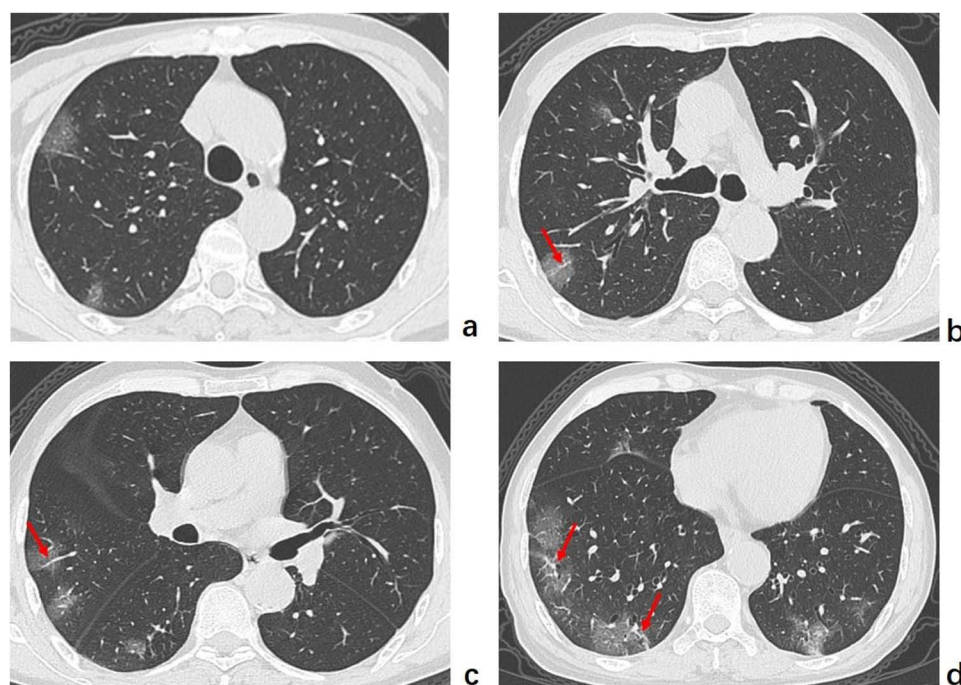


Figure 2 Typical chest computed tomography manifestations of a 67-year-old man infected with the Omicron variant. (a–d) Axial computed tomography images show round-like and patchy ground-glass opacity in the peripheral areas of both lungs accompanied by vascular enlargement patterns (red arrow).

CT Involvement Scores in Relation to Respiratory Viral Loads

Out of 74 patients, 18 underwent two CT scans, 39 underwent three CT scans, 12 underwent four CT scans, and 5 underwent five CT scans to monitor their condition. In total, 226 CT examinations were performed at an interval of 3–14 days. For all CT scans, the median CT involvement score of both lungs was 3.00 (0.00, 6.00) (range: 0.00–20.00); the median scores in the right upper, right middle, right lower, left upper, and left lower lobes were 0.00 (0.00, 2.00), 0.00 (0.00, 1.00), 1.00 (0.00, 2.00), 0.00 (0.00, 1.00), 1.00 (0.00, 2.00), respectively. For the grading of lung involvement degrees, the number of CT scans in grades I, II, III, and IV were 166, 49, 6, and 5, respectively. In total, 684 RT-PCR tests for all patients were performed at an interval of 1–3 days. All patients had positive RT-PCR results for SARS-CoV-2 on admission. For the grading of N gene Ct values (ranging from 13.69 to ≥ 40), the number of RT-PCR tests in grades I, II, III, and IV was 246, 171, 156, and 111, respectively. For the grading of ORF1ab gene Ct values (ranging from 13.82 to ≥ 40), the number of RT-PCR tests in grades I, II, III, and IV was 272, 177, 137, and 98, respectively. The dynamics of the grading of CT involvement scores and respiratory viral loads according to the time from diagnosis (ie, the initial positive result of RT-PCR) (0–20 days) are shown in Figure 3. The grading of lung involvement degrees on CT exhibited a reversed tendency compared with that of viral loads from the 1st day to the 8th day and from the 13th day to the 20th day, respectively.

Associated Factors with IP After RT-PCR Results Negative for SARS-CoV-2

Sixty-five of our study participants underwent multiple CT scans on admission and after obtaining two consecutive negative RT-PCR results, with an interval of >24 hours. The average interval from initial positive RT-PCR results to the time of two consecutive negative results at an interval of >24 hours was 11 days (range: 5–18 days). Among the 65 patients, 20 (30.77%) showed imaging absorption or stabilization after the negative RT-PCR results for SARS-CoV-2, whereas 45 (69.23%) showed IP (Figure 4). Of the 45 patients with IP, 11 had positive clinical warning indicators of severe-critical type and 3 of the 11 patients with IP transformed from mild-moderate type to severe-critical type on the 10th, 14th, and 15th days, respectively, after their diagnosis, despite their RT-PCR results being negative (Figure 4). Meanwhile, significant increments in virus-specific immunoglobulin (Ig) G levels (76.03, 111.14, and 240.43[S/CO], respectively) in the three patients were observed after disease aggravation. After corticosteroids and immunoglobulin therapy, their condition improved and they were subsequently discharged from the hospital.

As shown in Table 3, patients in the IP group were older than those in the non-IP (NIP) group ($P < 0.05$). The erythrocyte sedimentation rate, procalcitonin level, and D-dimer level of the patients in the IP group were significantly higher than those of the patients in the NIP group, whereas the IgG antibody levels and CT involvement scores on initial CT in the IP group were significantly lower than those in the NIP group (all $P < 0.05$).

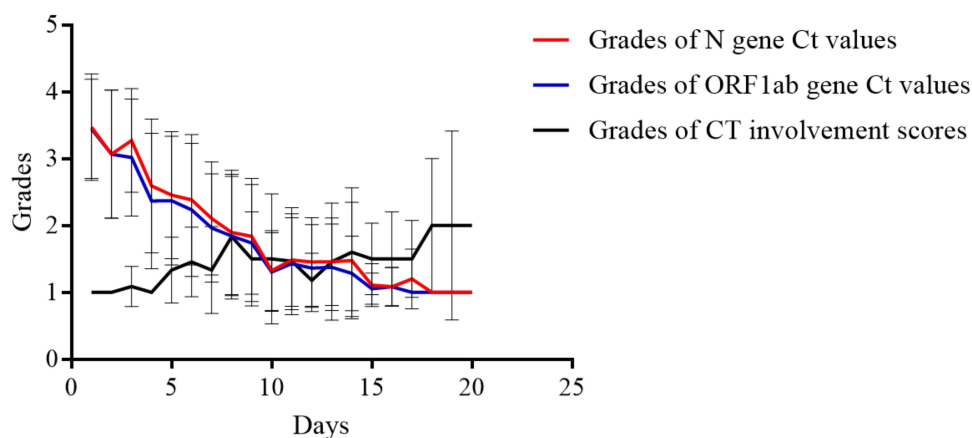


Figure 3 Dynamics of the grades of computed tomography involvement scores and respiratory viral loads according to the time from the initial positive reverse-transcription polymerase chain reaction. From the 1st to the 8th day, the grade of the viral load decreases gradually, whereas the grade of the computed tomography involvement scores increases. From the 8th to 13th day, the grade of the computed tomography involvement scores and respiratory viral loads are maintained at similar levels. From the 13th to 20th day, the grade of the computed tomography involvement scores increases continuously, whereas that of the viral loads declines to a low level.

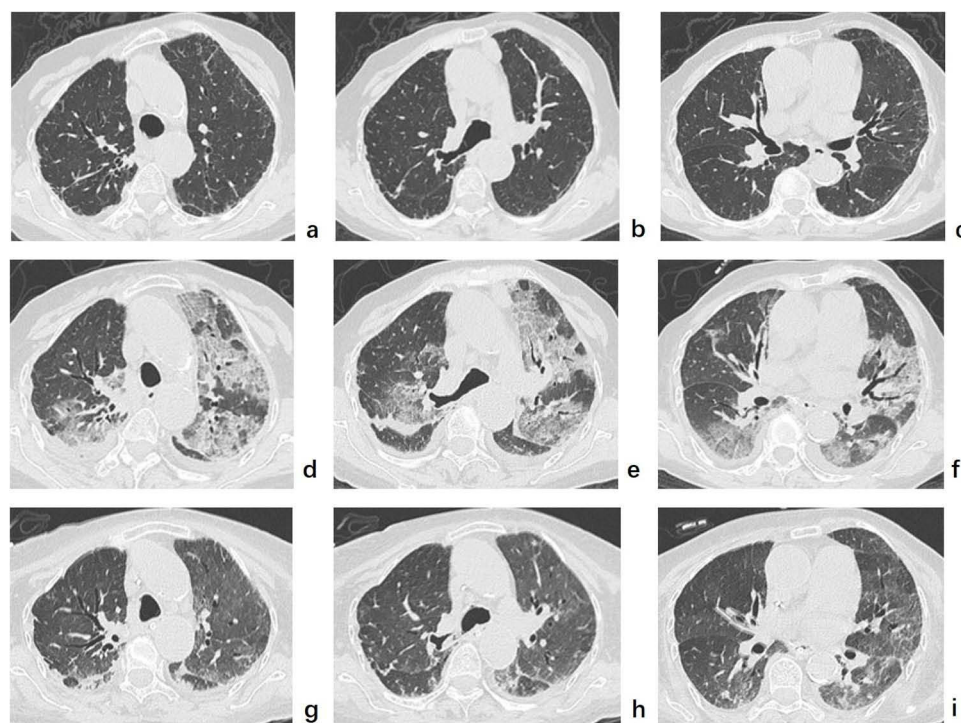


Figure 4 Sequential chest computed tomographic images of an 87-year-old woman infected with the Omicron variant. (a–c) Initial computed tomography images show a few peripheral ground-glass opacities (GGOs) and linear shadows in both lungs on the 2nd day after diagnosis. (d–f) Twelve days later when the reverse-transcription polymerase chain reaction results became negative, the follow-up computed tomography images revealed imaging progress with bilateral multi-patchy GGO displaying crazy-paving patterns, intralobular lines, vascular enlargement patterns, and pleural effusion. (g–i) After another seven days, follow-up computed tomography images demonstrated an obvious absorption of lung abnormalities after corticosteroids and immunoglobulin therapy.

Discussion

During the last few months of 2022, when the Omicron variant was predominant in our country, frequent PCR and CT examinations were routinely performed to closely assess the changes in the condition of the patients after short-term treatment in most referral centers. In the current study, we retrospectively observed a group of 74 hospitalized patients with laboratory-confirmed SARS-CoV-2 pneumonia during the Omicron pandemic and analyzed the radiological

Table 3 Factors Related to Imaging Progression at Minimal Viral Load Condition

Characteristics	Non-Progression Group (n=20)	Progression Group (n=45)	P value
Age (years)			0.022
Average	52 (48,56)	56 (50,69)	
Range	30–65	34–92	
Sex			0.929
Male	6 (30.00%)	14 (31.11%)	
Female	14 (70.00%)	31 (68.89%)	
Initial symptoms*			0.377
Presence	12 (60.00%)	32 (71.11%)	
Absence	8 (40.00%)	13 (28.89%)	
Comorbidities**			0.706
Presence	9 (45.00%)	18 (40.00%)	
Absence	11 (55.00%)	27 (60.00%)	

(Continued)

Table 3 (Continued).

Characteristics	Non-Progression Group (n=20)	Progression Group (n=45)	P value
Laboratory tests on admission			
Leukocyte count (×10 ⁹ /L)	4.62 (3.63,5.84)	4.78 (3.91,5.73)	0.738
Neutrophil count (×10 ⁹ /L)	2.54 (2.28,4.51)	3.18 (2.29,4.21)	0.760
Lymphocyte count (×10 ⁹ /L)	1.02 (0.58,1.70)	0.94 (0.66,1.29)	0.604
Highly sensitive C-reactive protein (mg/L)	3.00 (1.00,12.78)	4.90 (3.15,12.55)	0.191
Erythrocyte sedimentation rate (mm/H)	12.00 (4.75,22.00)	21.5 (8.00,43.00)	0.046
Interleukin-6 (pg/mL)	3.14 (0,10.60)	5.98 (2.04,12.73)	0.461
Procalcitonin (ng/mL)	0.02 (0.01,0.04)	0.03 (0.02,0.07)	0.039
D-dimer level (mg/L)	0.18 (0.08,0.34)	0.45 (0.27,0.53)	0.004
Virus-specific IgG antibody (S/CO)	9.24 (2.01,58.65)	2.47 (0.93,5.95)	0.006
Virus-specific IgM antibody (S/CO)	0.26 (0.09,0.54)	0.11 (0.07,0.33)	0.455
Vaccination status			0.863
Unvaccinated	1 (5.00%)	1 (2.22%)	
Single or double vaccinated	3 (15.00%)	7 (15.56%)	
Booster vaccinated	16 (80.00%)	37 (82.22%)	
Initial RT-PCR test at admission			
Ct values of ORF1ab gene	23.64 (18.74,29.29)	22.87 (20.46,28.06)	0.957
Ct values of N gene	21.61 (18.33,26.92)	22.78 (17.63,28.31)	0.896
Infection duration at the time of initial CT scan (days)***			0.571
Average	1.00 (1.00,3.00)	1.00 (1.00,1.00)	
Range	1.00–13.00	1.00–6.00	
CT involvement scores on initial CT			0.012
Average	0.00 (0.00,3.50)	0.00 (0.00,0.00)	
Range	0.00–17.00	0.00–8.00	

Notes: *Symptoms included fever, fatigue, cough, expectoration, chest pain (chest tightness), shortness of breath, muscle pain, sore throat, diarrhea, loss of appetite, headache, and abdominal pain. **Comorbidities included cardiovascular or cerebrovascular disease, diabetes mellitus, immunocompromised status, and chronic lung, liver, or renal disease. ***Infection duration at the time of initial CT scan, days from initial positive RT-PCR for COVID-19 to first CT scan.

Abbreviations: RT-PCR, reverse-transcription polymerase chain reaction; ORF1ab, open reading frame 1ab; N, nucleocapsid; CT, computed tomography.

changes, the lung involvement degree on CT in relation to the respiratory viral load, and factors associated with IP after the viral load decreased to a low level.

In terms of CT features, this study revealed that the most common CT manifestations were round-like/patchy GGO or mixed GGO involving the peripheral or diffuse regions of both lungs. These manifestations were usually accompanied by vascular enlargement patterns, crazy-paving patterns, and interlobular septal thickening. These results are similar to those of some previous reports.^{14,15} An interesting observation was that asymptomatic patients could also present with pneumonia on CT, and lung severity was generally mild. Our results showed that patients with Omicron infection had a low median CT involvement score, with the lower lobes predominantly involved; this finding is consistent with the reduced severity of Omicron, probably due to its lower replication competence in human lungs.^{7,16,17}

This study found that the grading of CT involvement scores and viral loads exhibited opposite trends from the 1st day to the 8th day and from the 13th day to the 20th day after diagnosis, while both were maintained at similar grades from the 8th day to the 13th day. After SARS-CoV-2 infection, a series of immune changes against viruses are induced, including innate immune responses, T- and B-cell immunity, and antiviral-neutralizing antibody responses.^{18,19} Some previous studies have shown an increase in virus-specific IgM and IgA in the acute phase (usually within the first week after symptom onset), followed by an increase in virus-specific IgG titers at later phases (about two weeks following symptoms) in the course of the SARS-CoV-2 infection.^{20,21} We speculated that the direct damage caused by viral invasion plays a key role in lung injury and elevated CT scores at the early stage, particularly when the viral load is high. As the virus-specific IgM is developed against the virus, a gradual decline in viral load occurs, resulting in similar grades to CT scores. Later, with the increase in virus-specific IgG levels, the viral load decreases further or becomes negative, but the CT scores continuously increased during this period. For

patients with IP under conditions of low viral load, our results showed that most patients were absent of clinical warning indication of severe and critical cases. This finding might be related to a slow absorption rate of pneumonia caused by Omicron or a longer duration of follow-up CTs, thereby suggesting that the imaging changes were not carefully evaluated. Therefore, IP with negative clinical warning indicators might not be associated with an exacerbation of patients' condition. Furthermore, a few patients with clinical warning indicators positive at low viral loads were also observed in this study. We hypothesize that such aggravation might stem from an immune-mediated lung injury due to immune dysregulation.^{18,22,23} Notably, the conditions of three patients in our cohort progressed to severe disease with remarkable increments in virus-specific IgG titers when their PT-PCR results turned negative. Fortunately, their conditions improved after timely immune regulation therapy. Therefore, although the nucleic acid test results could be negative, it is also important for the affected individuals to pay attention to these warning indicators of disease progression. For example, if the symptoms are aggravated or new symptoms occur (eg, persistent cough, shortness of breath, and fever), follow-up CTs might be necessary. For patients with IP, immunotherapeutic strategies targeting dysfunctional immune responses should be considered to prevent the development of severe disease.^{24–27} Moreover, some complications such as lung embolism or secondary infection may be alternative explanations for the clinical worsening under low viral load.

Furthermore, this study indicated that patients with IP who tested negative in nucleic acid test were older than those without IP. This suggests that age is a risk factor for progression in imaging. Some laboratory parameters, including higher erythrocyte sedimentation rates, procalcitonin levels, and D-dimer levels as well as lower virus-specific IgG titers on admission, were noted in patients with IP, which is similar to the findings of some studies.^{28,29} As a result, abnormalities in the aforementioned indicators were suggested as predictive biomarkers for potential disease progression; thus, such abnormalities should alert physicians to identify patients with exacerbations in a timely manner. In addition, the present study found that patients in the IP group had lower CT involvement scores on initial CT than those in the NIP group, indicating that patients with less lung involvement on admission may tend to exhibit IP at a later stage and that imaging monitoring should be performed for patients with worse clinical symptoms.

This study has several limitations. First, this study only evaluated the lung involvement degrees in relation to respiratory viral loads of Omicron due to insufficient data on other SARS-Cov-2 variants. We wonder if the finding that IP under low respiratory viral load is specific to Omicron; therefore, we are planning to compare this characteristic between Omicron variants and non-Omicron variants. Second, the present study lacked pathological evidence for possible immune-mediated lung diseases after exacerbation with a low viral load. Third, some clinical indicators such as oxygen saturation, treatment methods and complications of patients were not evaluated in this study due to the absence of complete data. Future studies are needed to substantiate our findings.

Overall, for patients with the Omicron variant, the IP of lung abnormalities is frequently observed when the viral load declines to a low level. Under these circumstances, focusing on clinical warning indicators of disease exacerbation may enhance the management of infected patients and mitigate severe pneumonia.

Abbreviations

Ct, cycle threshold; E, envelope; GGO, ground-glass opacity; Ig, immunoglobulin; IP, imaging progression; N, nucleocapsid; ORF1ab, open reading frame 1ab; RdRp, RNA-dependent RNA polymerase; RT-PCR, reverse-transcription polymerase chain reaction; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Data Sharing Statement

Data supporting the results reported in the manuscript can be found by contacting the correspondence author with email (GUOSL_999@163.com).

Ethics Approval and Informed Consent

Chongqing University Three Gorges Hospital's institutional review board approved this study, and informed consent was obtained from all individual participants included in the study. This retrospective study complies with the Declaration of Helsinki and abides by the principle of confidentiality, ensuring non-disclosure of patient information.

Consent for Publication

The details of any images, recordings, and figures can be published, and the persons providing consent have been shown the article contents to be published.

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Disclosure

The authors report no conflicts of interest in this work.

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