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Effect of a previous history of antiretroviral treatment on the clinical picture of patients with co-infection of SARS-CoV-2 and HIV:

A preliminary study

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ABSTRACT

Objectives: We explored the effect of antiretroviral treatment (ART) history on clinical characteristics of patients with SARS-CoV-2 and HIV co-infection.

Methods: We retrospectively reviewed 20 patients with laboratory-confirmed co-infection of SARS-CoV-2 and HIV in a designated hospital. Patients were divided into medicine (n = 12) and non-medicine (n = 8) groups according to previous ART history before SARS-CoV-2 infection.

Results: The median age was 46.5 years and 15 (75%) were female. Ten patients had initial negative RT-PCR on admission, five of which had normal computed tomography (CT) appearance and four were asymptomatic. Lymphocytes were low in nine patients (45%); CD4 cell count and CD4/CD8 were low in all patients. The predominant CT features in 19 patients were multiple (42%) ground-glass opacities (58%) and consolidations (32%). Erythrocyte sedimentation rate was significantly lower in the medicine than the non-medicine group [median (interquartile range, IQR): 14.0 (10.0–34.0) vs 51.0 (35.8–62.0), $P = 0.005$]. Nineteen patients (95%) were discharged with a median hospital stay of 30 days (IQR 26–30). **Conclusions:** Most patients with SARS-CoV-2 and HIV co-infection exhibited mild to moderate symptoms. The milder inflammatory response to SARS-CoV-2 infection might be associated with a previous history of ART in HIV-infected patients.

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19) was caused by a type of beta coronavirus (Zhou et al., 2020), named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on February 11, 2020. The disease quickly spread across China and beyond. As of July 31, 2020, over 17.1 million confirmed cases including 668,910 deaths were reported worldwide (World Health Organization, 2020a). At present, the diagnosis depends on reverse transcription-polymerase chain reaction (RT-PCR) or gene sequencing from throat swab, sputum, or lower respiratory tract secretion (Li et al., 2020a, b). Due to false-negative results of PCR by insufficient sampling or low viral load (Zhang et al., 2020), the

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specific antibody response to SARS-CoV-2 can be helpful for diagnosis.

The respiratory system is one of the most frequently affected organ systems in HIV-infected patients (Benito et al., 2012). HIV patients with immunocompromised status seem to be more susceptible to viral infection than healthy individuals. Several reports on co-infection of SARS-CoV-2 and HIV have been published, therefore there is some initial understanding of the clinical manifestation in this population (Blanco et al., 2020; Gervasoni et al., 2020; Harter et al., 2020; Maggiolo et al., 2020; Vizcarra et al., 2020; Zhu et al., 2020). It remains controversial whether HIV patients are at higher risk of severe disease or death (Gervasoni et al., 2020; Maggiolo et al., 2020).

The aim of this retrospective study was to report the clinical characteristics of a case series of HIV and SARS-CoV-2 co-infected patients in Wuhan, and to explore the effect of previous antiretroviral treatment (ART) before SARS-CoV-2 infection on clinical manifestation.

Methods

Study design and participants

Between February 25 and April 4, 2020, we retrospectively reviewed 20 patients with laboratory-confirmed co-infection of SARS-CoV-2 and HIV from Jinyintan Hospital, a designated hospital specializing in infectious diseases. All included patients were diagnosed with COVID-19 according to the interim guidance from the World Health Organization and the guidelines for the diagnosis and treatment of COVID-19 (seventh edition) published by China National Health Commission (General Office of the National Health Committee of China, 2020a; World Health Organization, 2020b). The immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies against SARS-CoV-2 were also tested on admission. One patient with negative RT-PCR but positive IgM and IgG, as well as another patient with typical symptoms (fever and cough) lasting for 29 days and a positive IgG result, were diagnosed according to the China National Health Commission guidelines.

Demographics and epidemiological data, symptoms and signs, laboratory results, medical treatment of HIV infection before admission, as well as COVID-19 treatment and outcome data were obtained from the electronic medical records of the patients. The clinical endpoint in this study was death or discharge. Disease severity was classified into two categories (non-severe and severe) at the time of admission as used in a previous study published by the China Medical Treatment Expert Group for COVID-19 (Guan et al., 2020). Patients were discharged from hospital once the results of RT-PCR tests for SARS-CoV-2 turned negative on two occasions (at least 24 h apart) (General Office of the National Health Committee of China, 2020a).

Imaging acquisition and analysis

Concerning chest computed tomography (CT) data, one 77-year-old severe patient underwent a chest CT scan in another hospital and died the day after admission, and so we failed to obtain his CT data. All other patients underwent non-contrast enhanced chest CT in Jinyintan Hospital. All images were analyzed independently by two chest radiologists (JL and YKC) with 5–7 years of experience, and final decisions were reached by consensus. The imaging analysis mainly focused on the lesion features of each patient, such as distribution pattern and important CT signs of COVID-19 pneumonia. The extent of lesion involvement was categorized as focal, multifocal, or diffuse. Lesion location was categorized as peripheral, central, or peripheral and central. We also quantified the CT images using a previously published method (Ooi et al., 2004). We defined the evolution of lesions as an increase in size or density, and the improvement as decrease in lesion size or resorption of the ground-glass opacities and consolidation.

This was a retrospective, single-center case series study and no patients were involved in the study design. This study was approved by the institutional review board of Wuhan Jinyintan Hospital. All participants remained anonymous and written informed consent was waived by the ethics commission for rapid emerging infectious diseases.

Table 1
Demographics, baseline characteristics, treatment, and outcomes of patients with co-infection of SARS-CoV-2 and HIV.

Characteristics	Patients (n = 20)	Characteristics	Patients (n = 20)
Age, median (IQR), years	46.5 (39.3–50.5)	Sore throat	1 (5%)
Sex		Diarrhea	1 (5%)
Male	5 (25%)	Abdominal pain	1 (5%)
Female	15 (75%)	Dizziness	1 (5%)
Exposure history	16 (76%)	Anorexia	1 (5%)
Exposure to Huanan Seafood Market	1 (5%)	Clinical classification	
Exposure to infected patients	15 (75%)	Non-severe	17 (85%)
Unknown exposure	4 (20%)	Severe	3 (15%)
Comorbidities	15 (75%)	ART before SARS-CoV-2 infection	12 (60%)
Hepatitis C	8 (40%)	NRTIs	12/12 (100%)
Syphilis	4 (20%)	Non-NRTIs	6/12 (50%)
Other chronic liver disease	3 (15%)	PI	8/12 (67%)
Hypertension	3 (15%)	Treatment during hospitalization	
CHD	1 (5%)	Antiviral	19 (95%)
Diabetes	1 (5%)	ART	19 (95%)
Hepatitis B	1 (5%)	Corticosteroids	1 (5%)
COPD	1 (5%)	Chinese herbals	4 (20%)
Psychosis	1 (5%)	Oxygen therapy	3 (15%)
Signs and symptoms		Immunoglobulin	2 (10%)
Cough	13 (65%)	ICU admission	0
Fever	9 (45%)	Outcome	
Expectoration	5 (25%)	Discharged	19 (95%)
Shortness of breath	4 (20%)	Died	1 (5%)
Fatigue	2 (10%)		

Abbreviations: IQR, interquartile range; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; NRTIs, nucleoside reverse transcriptase inhibitors; Non-NRTIs, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; ART, antiretroviral therapy; ICU, intensive care unit.

Statistical analysis

We presented the continuous measurements as median (interquartile range, IQR) and categorical variables as frequency (percentage). For laboratory results, we assessed whether the measurements were within or outside the normal range. According to the history of ART before SARS-CoV-2 infection, we divided the patients into medicine and non-medicine groups. Laboratory results and radiologic features were compared between the two groups using Mann–Whitney *U* test for continuous variables and chi-squared test for categorical data. Here, we need to point out that when comparing radiologic features between two groups, the non-medicine group contained only seven patients. The data were analyzed using IBM SPSS version 22 (SPSS Inc, Chicago, IL, USA) and GraphPad Prism version 7.00 (GraphPad Software, La Jolla, CA, USA).

Results

Demographics, baseline characteristics, treatment, and outcomes

Demographics, baseline characteristics, treatment, and outcomes of the patients are shown in Table 1. Twenty patients were included in the study with a median age of 46.5 years (IQR 39.3–50.5) and most cases were female (15 [75%]). Twelve of 20 patients were on ART at the time of COVID-19 diagnosis. Antiretroviral regimens included nucleoside reverse transcriptase inhibitors (NRTIs, *n* = 12), protease inhibitors (PI, *n* = 8), and non-NRTIs (*n* = 6). The NRTIs were mainly lamivudine (*n* = 12), tenofovir disoproxil fumarate (*n* = 9), and zidovudine (*n* = 2). The PI was mainly kaletra (lopinavir/ritonavir) and non-NRTI was mainly efavirenz.

The clinical course of the patients as well as the results of IgM/IgG antibodies obtained on admission are shown in Figure 1. On admission, the total seropositive rate for IgM and IgG was 20% (4/20) and 55% (11/20), respectively. Ten patients had initial negative RT-PCR on admission, of whom eight showed positive

results of RT-PCR four days later, five showed normal CT appearance, and four were asymptomatic cases. After admission, one severe patient, a 77-year-old male with several combined diseases [chronic obstructive pulmonary disease (COPD) and alcoholic liver disease], died the day after admission due to septic shock and multiple organ failure. The remaining patients received antiviral treatment and ART after admission, and were discharged with a median hospital stay of 30 days (IQR 26–30). None of the patients were admitted to intensive care units (ICUs).

Laboratory and radiologic findings

Laboratory and radiologic findings are summarized in Tables 2 and 3, respectively. On admission, leukocytes were below the normal range in five patients (25%). Lymphocytes were low in nine patients (45%). Only one of the severe patients had high serum levels of myoglobin (786 ng/mL), procalcitonin (31.8 ng/mL), and high-sensitivity C-reactive protein (hsCRP > 160.0 mg/L).

The mean interval from symptom onset to the first CT scan was 25.8 days (standard deviation 21.8). Of 19 patients with chest CT scans, eight non-severe patients showed normal chest CT appearance of both lungs. The predominant CT features were multiple [8 (42%)] ground-glass opacities [11 (58%)] and consolidations [6 (32%)] (Figure 2). Fibrotic streaks were seen in five patients (26%). Pleural effusion and enlarged lymph nodes were not present.

The erythrocyte sedimentation rate (ESR) was significantly lower in the medicine than in the non-medicine group (*P* = 0.005). The hsCRP was also lower in the medicine compared with the non-medicine group [median (IQR): 0.5 (0.2–1.3) vs 2.1 (0.4–5.9)], but the difference was not significant (*P* = 0.074). Other laboratory parameters and all CT features showed no significant difference (*P* > 0.05) between the two groups.

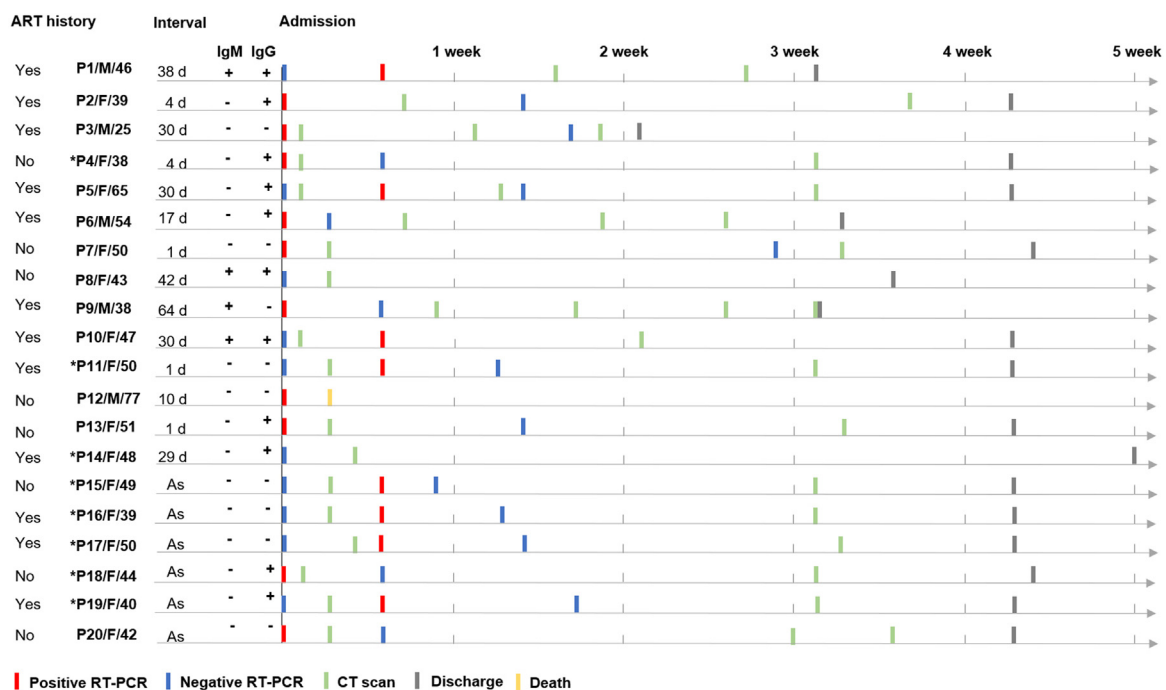


Figure 1. Chart of the clinical courses in 20 patients with co-infection of SARS-CoV-2 and HIV. ART, antiretroviral therapy; Interval, time interval between symptoms onset and admission; As, asymptomatic; F, female; M, male. *patient with normal CT appearance.

Table 2
Laboratory results of patients with co-infection of SARS-CoV-2 and HIV on admission.

Variables	Normal range	Total (n = 20)			Medicine group (n = 12)	Non-medicine group (n = 8)	P-value
		Median (IQR)	Increased	Decreased			
Leukocytes ($\times 10^9/L$)	3.5–9.5	4.4 (3.5–5.3)		5 (25%)	4.5 (3.9–5.3)	3.7 (3.0–5.8)	0.343
Neutrophils ($\times 10^9/L$)	1.8–6.3	2.5 (2.2–3.2)		2 (10%)	2.5 (2.2–3.2)	2.5 (2.0–3.9)	0.970
Lymphocytes ($\times 10^9/L$)	1.1–3.2	1.1 (0.9–1.9)		9 (45%)	1.3 (1.0–1.9)	1.1 (0.7–1.9)	0.545
Hemoglobin (g/L)	110.0–150.0 (female) 120.0–160.0 (male)	117.0 (106.0–128.0)		6 (30%)	120.0 (109.0–131.0)	114.5 (98.5–121.5)	0.238
Platelets ($\times 10^9/L$)	125.0–350.0	168.5 (135.8–196.3)	1 (5%)	2 (10%)	165.0 (134.0–193.0)	180.0 (134.0–198.0)	0.681
D-dimer ($\mu g/L$)	0.0–1.5	0.4 (0.3–0.5)	2 (10%)		0.4 (0.3–0.5)	0.4 (0.3–0.8)	0.805
Albumin (g/L)	40.0–55.0	37.7 (32.9–40.4)		13 (65%)	37.5 (33.0–41.3)	37.8 (28.8–40.1)	0.791
Glucose (mmol/L)	3.9–6.1	5.4 (4.6–6.4)	7 (35%)		5.2 (4.4–6.4)	6.2 (4.7–7.8)	0.417
CK (U/L)	50.0–310.0	56.0 (50.0–77.0)	1 (5%)	4 (20%)	56.0 (42.0–77.0)	57.5 (53.5–76.5)	0.657
LDH (U/L)	120.0–250.0	191.0 (176.0–310.0)	5 (25%)		191.0 (162.0–207.0)	188.0 (177.5–313.5)	0.717
Myoglobin (ng/mL)	0.0–146.9	25.2 (19.1–41.9)	1 (5%)		29.9 (12.9)	23.5 (14.5–53.1)	0.805
AST (U/L)	15.0–40.0	33.5 (26.0–57.8)	8 (40%)		33.0 (26.0–56.0)	34.0 (26.0–63.0)	0.860
ALT (U/L)	9.0–50.0	27.5 (12.5–55.0)	4 (20%)		17.0 (11.0–73.0)	36.0 (26.0–49.0)	0.328
Serum creatinine ($\mu mol/L$)	57.0–111.0	56.3 (50.3–63.9)	1 (5%)	10 (50%)	60.9 (50.3–65.7)	53.6 (49.0–59.2)	0.408
Procalcitonin (ng/mL)	0.0–5.0	< 0.05 (< 0.05–0.06)	1 (5%)				
IL-6 (pg/mL)	0.0–7.0	6.7 (5.5–8.0)	8 (40%)		6.6 (5.6–7.9)	6.7 (5.5–8.3)	0.711
ESR (mm/h)	0.0–15.0	34.0 (13.0–53.0)	14 (70%)		14.0 (10.0–34.0)	51.0 (35.8–62.0)	0.005*
Serum ferritin (ng/mL)	21.0–274.7	163.5 (52.8–607.2)	6 (30%)	2 (10%)	174.7 (56.5–532.6)	78.1 (47.2–150.1)	0.351
hsCRP (mg/L)	0.8–8	0.6 (0.4–2.4)	1 (5%)		0.5 (0.2–1.3)	2.1 (0.4–5.9)	0.074
CD4 cell count	500–1500	237.0 (142.5–346.8)		20 (100%)	249.0 (117.0–424.0)	195.0 (143.0–290.0)	0.791
CD4/CD8	1.4–2.0	0.4 (0.2–0.6)		20 (100%)	0.5 (0.3–0.6)	0.4 (0.2–0.5)	0.536

Abbreviations: IQR, interquartile range; CK, creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IL-6, Interleukin-6; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein.

* $P < 0.05$.

Table 3
Findings on initial chest CT scan in 19 patients with co-infection of SARS-CoV-2 and HIV.

CT features	Total (n = 19)	Medicine group (n = 12)	Non-medicine group (n = 7)	P-value
Normal/abnormal	8/11 (42%/58%)	5/7	3/4	0.960
Extent				
Focal	2 (11%)	2	0	0.253
Multifocal	8 (42%)	3	4	0.161
Diffuse	2 (11%)	2	0	0.253
Location				
Peripheral	8 (42%)	4	4	0.311
Central	0			
Peripheral and central	4 (21%)	3	0	0.149
CT features				
Ground-glass opacities	11 (58%)	6	4	0.764
Consolidations	6 (32%)	3	2	0.865
Mixed pattern	1 (5%)	1	0	0.433
Fibrotic streaks	5 (26%)	3	2	0.865
Subpleural transparent line	1 (5%)	1	0	0.433
Air bronchogram	3 (16%)	2	0	0.253
Bronchial distortion	2 (11%)	2	0	0.253
Pleural retraction	3 (16%)	1	0	0.433
Pleural effusion	0	–	–	–
Enlarged lymph nodes	0	–	–	–
CT score	Mean 4.7 (Min–Max 0–20)	Mean 5.2 (Min–Max 0–20)	Mean 2.2 (Min–Max 0–5)	0.892

Abbreviation: Min–Max, minimum value to maximum value.

The dynamic profile of chest CT images

Seventeen patients underwent several follow-up CT scans with a median of two times. The median interval between the initial and second CT scans was 20 days (IQR 8–21). Five patients (26%) showed improvement on the second CT scan, while two patients (11%) showed worsening (Figure 3). Eight patients with initial normal CT scan remained normal on the follow-up chest CT scans.

Discussion

COVID-19 is a severe infectious disease with a capability of human–human transmission (Li et al., 2020a, b; Lu et al., 2020), which has caused a large number of deaths around the world. Patients included in our study were diagnosed using a combination of viral RNA RT-PCR and IgM/IgG antibody test according to the seventh edition of China National Health Commission guidelines for diagnosis and treatment of COVID-19 pneumonia (General Office of the National Health Committee of China, 2020a). As previously reported, the test of IgM/IgG antibodies against

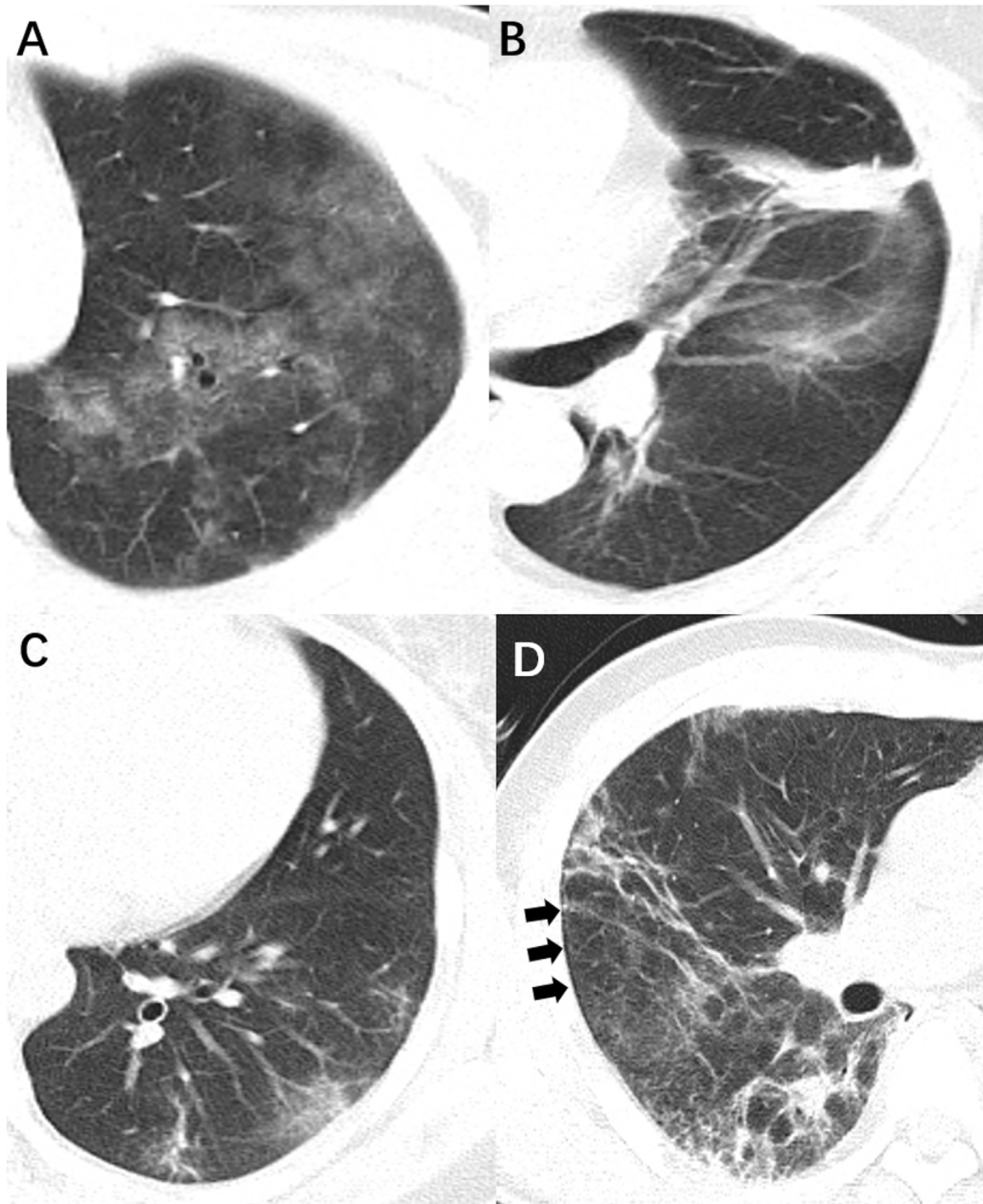


Figure 2. CT features in patients with co-infection of SARS-CoV-2 and HIV.

(A) Diffuse ground-glass opacities; (B) Patchy consolidation; (C) Fibrotic streak; (D) Subpleural transparent line (arrows).

SARS-CoV-2 provides important immunological evidence and can be an effective supplementary indicator in diagnosing the suspected cases with no detectable viral RNA (Gao et al., 2020).

In our study, some patients tested negative for RT-PCR nucleic acid and IgM/IgG antibodies on admission, and the results of the viral RNA test turned positive a few days later. Several reasons may contribute to this phenomenon. Firstly, some patients were initially isolated in the compartment hospital and, when admitted to Jinyintan Hospital, they were at a stage with a low RNA positive rate and a high IgM negative and IgG positive rate, indicating a late stage of the infection. Secondly, some asymptomatic cases sought

medical treatment in the early stage due to a history of close contact with infected patients, in whom temporal negative results may have been present because of a low viral load.

The predominant gender in our study was female (75%), in contrast to findings in previous studies (Gervasoni et al., 2020; Harter et al., 2020; Vizcarra et al., 2020). Such a discrepancy may be due to the different risk behavior between study populations. As the priority was to initiate timely treatment for COVID-19 patients, clinicians were not aware of the risk behavior concerning HIV infection. Most patients (75%) were infected by close contact with confirmed patients, which is reported to be the current main

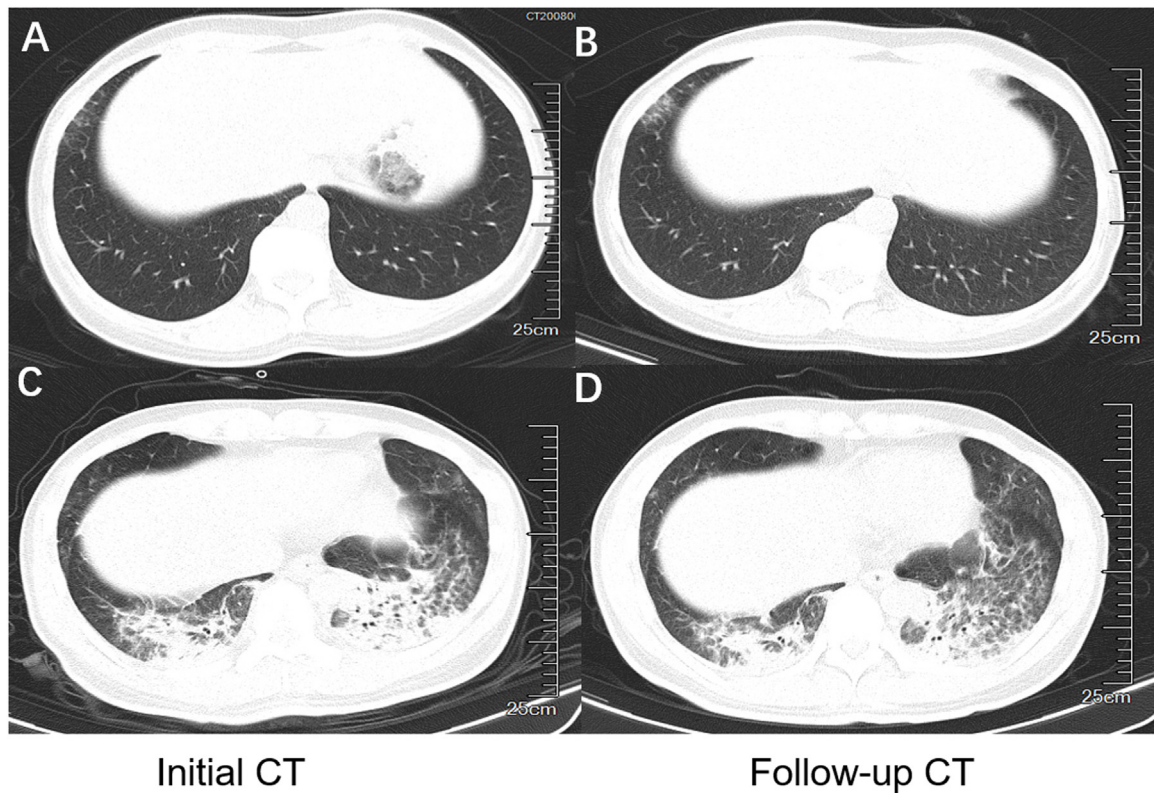


Figure 3. Dynamic changes of CT images in patients with co-infection of SARS-CoV-2 and HIV. (A and B) 50-year-old female, non-severe type. Follow-up CT scan showed increased density of the ground-glass opacity in the right lower lobe 21 days after initial scan. (C and D) 38-year-old male, severe type. Follow-up CT scan showed partial resorption of consolidation in the left lower lobe 8 days after initial scan.

source of infection (Chen et al., 2020a, b). The clinical characteristics in patients co-infected with SARS-CoV-2 and HIV were similar to those in the general population. Except for three severe cases, the patients (17/20) exhibited mild or moderate symptoms, with predominant presentation of cough and fever. Laboratory tests revealed low peripheral blood leukocyte (25%) and lymphocyte (45%) counts. This finding is consistent with previous studies (Chen et al., 2020a, b; Guan et al., 2020), which suggests that COVID-19 mainly acts on lymphocytes, especially T lymphocytes. However, the extent of lymphocyte decrease in our study (mean 1.3; standard deviation 0.6) was relatively small compared with that of a previous study published by the China Medical Treatment Expert Group for COVID-19 (median 1.0; IQR 0.7–1.3) (Guan et al., 2020).

In terms of radiologic findings, we summarized the features of 19 patients who underwent chest CT scans after admission. The predominant CT findings on the first scan were multifocal ground-glass opacities, which were linked to variable histopathologic changes, such as diffuse alveolar damage or interstitial inflammatory cell infiltration (Kanne et al., 2007). Consolidation was also a typical finding in our case series, occasionally combined with air bronchogram. Fibrotic changes were apparent in five patients, which is often seen as a form of chronic change during the remission stage. Xiong et al. (2020) reported that most patients (83%) exhibited a progressive process in follow-up CT scans. In our study, abnormal CT appearance in most patients remained unchanged or improved in the second scan. Normal CT appearance was seen in eight patients, accounting for nearly half of the patients. Previous studies also reported cases with normal CT scans (Chung et al., 2020; Wu et al., 2020), which may be related to the relatively weak immune response in HIV patients. Additionally, it suggests that we cannot reliably fully exclude cases by normal

imaging studies. Patients showing initially negative for SARS-CoV-2 nucleic acid test can also have abnormal CT findings (Ai et al., 2020). Given the sensitivity of chest CT, a clinical diagnostic standard based on typical CT characteristics was adopted in the revised 5th edition of the Guideline of Diagnosis and Treatment, which was only applicable in Hubei Province, China (General Office of the National Health Committee of China, 2020b). Therefore, chest imaging still plays an important role in the diagnosis and assessment of the patient's condition.

In our study, ESR of patients who had received ART before SARS-CoV-2 infection was significantly lower than that of patients without ART ($P = 0.005$). In addition, hsCRP was also lower in patients with a previous history of ART than in patients without ART history [median (IQR): 0.5 (0.2–1.3) vs 2.1 (0.4–5.9)], but the difference was not significant ($P = 0.074$). Another important inflammatory marker, Interleukin-6 (IL-6), showed no difference between the two groups. A previous study revealed that ART can reduce the systemic inflammation and immune activation in HIV patients (Hileman and Funderburg, 2017). We propose that the inflammatory response lasted longer in patients without a history of ART, so an elevated ESR level (which can help monitor chronic inflammation) may be observed in the chronic/recovery stage of the infection. The extent of the inflammatory response may be minimized by a previous history of ART in HIV-infected patients. Further large-scale studies are warranted to clarify and explain the effect of ART use on the inflammatory response to SARS-CoV-2 infection.

The laboratory test results and radiologic findings both showed that most patients experienced mild illness. As reported, in an immunocompromised population, the host response to the virus may be an important contributor to the disease process (D'Antiga, 2020). When infection occurs in an immunocompromised

population who have some persistent immune activity, they may be protected by a weaker immune response against the pathogen. As a result, the SARS-CoV-2 infection may not progress to a severe cytokine storm in this population (Hileman and Funderburg, 2017). In the last two outbreaks of coronavirus (SARS and MERS), patients with immunocompromised status did not show an increased risk of severe pulmonary involvement, complications, or a poorer prognosis (Hui et al., 2018; D'Antiga, 2020). Another possibility in regard to mild manifestation of symptoms, laboratory results, and chest CT scans in our study could be the early admission and early intervention. Some asymptomatic patients sought medical advice once they were aware of a suspicious contact history. The HIV patients might have a greater opportunity for being tested for SARS-CoV-2 infection even in mild or moderate cases, given that they are usually considered at high risk of infection, especially in an epidemic outbreak.

In our study, one severe patient (a 77-year-old male with several comorbidities) died the day after admission due to septic shock and multiple organ failure. The other 19 patients were discharged after corresponding treatment. Up to now, no specific drug has been confirmed effective for the treatment of patients with COVID-19. Due to the unique sample, except for one severe patient who deceased after admission, all of the patients received ART during hospitalization (they had their usual ART, and some of them modified the regimen to include lopinavir/ritonavir); therefore both antiretroviral and anti-SARS-CoV-2 effects were expected (Choy et al., 2020). Our study showed a low proportion of individuals with severe disease ($n = 3$) and ICU admission ($n = 0$), which were lower than in previous studies (Harter et al., 2020; Vizcarra et al., 2020). Vizcarra et al. (2020) pointed out that in a HIV population, severe COVID-19 disease, ICU admission, low nadir CD4 cell counts, and comorbidities could help identify individuals with delayed viral clearance even after clinical improvement. Current data suggest that the main mortality risk factors are linked to older age and multimorbidity, not particularly to HIV (Mirzaei et al., 2020; World Health Organization, 2020b).

Our study had some limitations. This single-center study was limited by its retrospective nature and small sample size. The HIV viral load was not measured because of the great pressure on the medical supplies and staff regarding COVID-19 treatment at that time, and the dynamic changes of IgM/IgG antibodies during hospitalization were not evaluated due to the limited number of patients with multiple tests of antibodies.

In conclusion, compared with the SARS-CoV-2 infected general population, patients with HIV co-infection mostly had milder clinical presentation. A single test of viral RNA test and antibodies against SARS-CoV-2 might be insufficient to exclude COVID-19 infection in patients with HIV. The lesser extent of inflammatory response to SARS-CoV-2 infection might be associated with a previous history of ART in HIV-infected patients. The association between inflammatory response to SARS-CoV-2 and history of ART use requires further assessment in large-scale studies.

Author contributions

Heshui Shi, Yanqing Fan, and Fan Yang conceived the study. Jia Liu, Wenjuan Zeng, and Yukun Cao participated in the study design. Yue Cui and Yumin Li collected the data. Osamah Alwalid and Sheng Yao performed the statistical analysis. Jia Liu and Wenjuan Zeng drafted the manuscript. All authors contributed to the study and have read and approved the final manuscript.

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Conflict of interest

All authors declared that there were no competing interests.

Ethics approval and consent to participate

This study was approved by the institutional review board of Wuhan Jinyintan Hospital. All participants remained anonymous and written informed consent was waived by the ethics commission for rapid emerging infectious diseases.

References

- Ai T, Yang ZL, Hou HY, Zhan CN, Chen C, Lv WZ, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology* 2020;200642.
- Benito N, Moreno A, Miro JM, Torres A. Pulmonary infections in HIV-infected patients: an update in the 21st century. *Eur Respir J* 2012;39(3):730–45.
- Blanco JL, Ambrosioni J, Garcia F, Martínez E, Soriano A, Mallolas J, et al. COVID-19 in patients with HIV: clinical case series. *Lancet HIV* 2020;7(5):e314–6.
- Chen NS, Zhou M, Dong X, Qu JM, Gong FY, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020a;395(10223):507–13.
- Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World J Pediatr* 2020b;16(3):240–6.
- Choy KT, Wong AYL, Kaewpreedee P, Sia SF, Chen D, Hui KPY, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res* 2020;178:104786.
- Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology* 2020;295(1):202–7.
- D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transplant* 2020;26(6):832–4.
- Gao Y, Yuan Y, Li TT, Wang XW, Li XY, Li A, et al. Evaluation of the auxiliary diagnostic value of antibody assays for the detection of novel coronavirus (SARS-CoV-2). *J Med Virol* 2020; (accepted article).
- General Office of the National Health Committee of China. China Traditional Chinese Medicine Administration Office. Diagnosis and Treatment Plan of Novel Coronavirus Pneumonia (seventh trial edition). 2020 Available from: <http://www.satcm.gov.cn/d/file/p/2020/03-04/ddfd72721be1d510657c1c-b0a42cb045.pdf#%3Ece6945832a438eae415350a8ce964.pdf#4.37%20MB>. [Accessed 3 March 2020].
- General Office of the National Health Committee of China. Notice on the Issuance of a Program for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infected Pneumonia (trial revised fifth edition). 2020 Available from: <http://www.nhc.gov.cn/yzygj/s7653p/202002/3b09b894ac9-b4204a79db5b8912d4440.shtml> [Accessed 4 February 2020].
- Gervasoni C, Meraviglia P, Riva A, Giacomelli A, Oreni L, Minisci D, et al. Clinical features and outcomes of HIV patients with coronavirus disease 2019. *Clin Infect Dis* 2020; ciae579.
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708–20.
- Harter G, Spinner CD, Roeder J, Bickel M, Krznaric I, Grunwald S, et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. *Infection* 2020;1–6.
- Hileman CO, Funderburg NT. Inflammation, immune activation, and antiretroviral therapy in HIV. *Curr HIV/AIDS Rep* 2017;14(3):93–100.
- Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect Dis* 2018;18(8):e217–27.
- Kanne JP, Godwin JD, Franquet T, Escuissato DL, Müller NL. Viral pneumonia after hematopoietic stem cell transplantation: high resolution CT findings. *J Thorac Imaging* 2007;22(3):292–9.
- Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. *J Med Virol* 2020a;92(4):424–32.
- Li Q, Guan XH, Wu P, Wang XY, Zhou L, Tong YQ, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020b;382(13):1199–207.

- Lu RJ, Zhao X, Li J, Niu PH, Yang B, Wu HL, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395(10224):565–74.
- Maggiolo F, Zoboli F, Arosio M, Valenti D, Guarneri D, Sangiorgio L, et al. SARS-CoV-2 infection in persons living with HIV: a single center prospective cohort. *J Med Virol* 2020; (accepted article).
- Mirzaei H, McFarland W, Karamouzian M, Sharifi H. COVID-19 among people living with HIV: a systematic review. *AIDS Behav* 2020;30:1–8.
- Ooi GC, Khong PL, Müller NL, Yiu WC, Zhou LJ, Ho JC, et al. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. *Radiology* 2004;230(3):836–44.
- Vizcarra P, Perez-Elias MJ, Quereda C, Moreno A, Vivancos MJ, Drona F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. *Lancet HIV* 2020; (accepted article).
- World Health Organization. Coronavirus Disease (COVID-2019) Situation Reports. 2020 Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>. [Accessed 31 July 2020].
- World Health Organization. Clinical Management of Severe Acute Respiratory Infection When Novel Coronavirus (nCoV) Infection is Suspected: Interim Guidance. 2020 Available from: [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected). [Accessed 27 May 2020].
- Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, et al. Clinical characteristics of imported cases of COVID-19 in Jiangsu Province: a multicenter descriptive study. *Clin Infect Dis* 2020; ciaa199.
- Xiong Y, Sun D, Liu Y, Fan YQ, Zhao LY, Li XM, et al. Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes. *Invest Radiol* 2020;55(6):332–9.
- Zhang W, Du RH, Li B, Zheng X, Yang XS, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect* 2020;9(1):386–9.
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579(7798):270–3.
- Zhu F, Cao Y, Xu Sy, Zhou M. Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China. *J Med Virol* 2020; (accepted article).