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Alterations in Fecal Fungal Microbiome of Patients With COVID-19 During Time of Hospitalization until Discharge

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BACKGROUND & AIMS: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects intestinal cells, and might affect the intestinal microbiota. We investigated changes in the fecal fungal microbiomes (mycobiome) of patients with SARS-CoV-2 infection during hospitalization and on recovery.

METHODS: We performed deep shotgun metagenomic sequencing analysis of fecal samples from 30 patients with coronavirus disease 2019 (COVID-19) in Hong Kong, from February 5 through May 12, 2020. Fecal samples were collected 2 to 3 times per week from time of hospitalization until discharge. We compared fecal mycobiome compositions of patients with COVID-19 with those from 9 subjects with community-acquired pneumonia and 30 healthy individuals (controls). We assessed fecal mycobiome profiles throughout time of hospitalization until clearance of SARS-CoV-2 from nasopharyngeal samples. RESULTS: Patients with COVID-19 had significant alterations in their fecal mycobiomes compared with controls, characterized by enrichment of Candida albicans and a highly heterogeneous mycobiome configuration, at time of hospitalization. Although fecal mycobiomes of 22 patients with COVID-19 did not differ significantly from those of controls during times of hospitalization, 8 of 30 patients with COVID-19 had continued significant differences in fecal mycobiome composition, through the last sample collected. The diversity of the fecal mycobiome of the last sample collected from patients with COVID-19 was 2.5-fold higher than that of controls (P < .05). Samples collected at all timepoints from patients with COVID-19 had increased proportions of opportunistic fungal pathogens, Candida albicans, Candida auris, and Aspergillus flavus compared with controls. Two respiratory-associated fungal pathogens, A. flavus and

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Aspergillus niger, were detected in fecal samples from a subset of patients with COVID-19, even after clearance of SARS-CoV-2 from nasopharyngeal samples and resolution of respiratory symptoms. CONCLUSIONS: In a pilot study, we found heterogeneous configurations of the fecal mycobiome, with enrichment of fungal pathogens from the genera Candida and Aspergillus, during hospitalization of 30 patients with COVID-19 compared with controls. Unstable gut mycobiomes and prolonged dysbiosis persisted in a subset of patients with COVID-19 up to 12 days after nasopharyngeal clearance of SARS-CoV-2. Studies are needed to determine whether alterations in intestinal fungi contribute to or result from SARS-CoV-2 infection, and the effects of these changes in disease progression.

**Keywords:** Coronavirus; Microbe; Yeast; Intestine.

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), which primarily affects the respiratory system. Patients with COVID-19 present with variable disease symptoms and severity, some can be severe, resulting in hospitalization, respiratory failure, or even death. A recent meta-analysis of 35 COVID-19 studies reported that the pooled prevalence of digestive symptoms was 15% and pooled prevalence of digestive system comorbidities was 4%. Patients with gastrointestinal (GI) involvement tended to have a poor disease course. In addition, SARS-CoV-2 virus was detected in the feces and anal swabs in patients with COVID-19 and can infect human intestinal epithelium. Altogether these data suggest that the GI tract is an important extrapulmonary site for SARS-CoV-2 infection.

Bacterial and fungal infections are common complications of viral pneumonia, which may influence disease course and clinical manifestations, especially in critically ill patients. However, data regarding bacterial or fungal coinfections in viral pneumonia led by coronavirus are lacking. Our recent study showed that the gut bacterial microbiome was significantly altered in patients with COVID-19 with a significant expansion of opportunistic pathogens in the gut, which was associated with disease severity and fecal SARS-CoV-2 shedding. Beyond bacteria, the GI tract also harbors a large number of fungi, collectively known as the mycobiome. Intestinal fungi have been shown to be causally implicated in microbiome assembly and immune development. Accumulating findings highlighted that the gut mycobiota can strongly influence the host immune system and this interaction is linked to bacteria activities. Recent observations of the direct and indirect effects of fungal microbiota on various GI diseases have stimulated further investigation of the mycobiota composition and ways of regulating its diversity. Although the magnitude of the number of fungal cells is smaller than that of the bacterial microbiota, their impact on health is significant, especially as a reservoir for blooms of pathogenic microbes when the host is immunocompromised and as a cofactor in driving severe infectious diseases. It is unclear if the gut mycobiome is also altered and whether fungal pathogens cobloom in COVID-19 and underlie disease course.

In this pilot study, we hypothesize that the intestinal fungal microbiome (mycobiome) is altered in SARS-CoV-2 infection and COVID-19 is associated with blooms of certain fungi in the gut. We prospectively included 30 patients with COVID-19 (Table 1, Figure 1, Supplementary Figure 1), admitted between February 16, 2020, and April 13, 2020.

### Table 1. Clinical Characteristics of Study Subjects

| Variables                          | COVID-19 patients | Pneumonia patients | Healthy controls |
|-----------------------------------|-------------------|--------------------|-----------------|
| Number                            | 30                | 9                  | 30              |
| Male                              | 16 (53)           | 5 (56)             | 15 (50)         |
| Age, y                            | 46 (29, 63)       | 63 (47,69)         | 34 (23, 48)     |
| Comorbidities                     | 11 (37)           | 9 (100)            | 0 (0)           |
| Recent exposure history           |                   |                    |                 |
| Travel to Wuhan City              | 0 (0)             | 0 (0)              |                 |
| Travel to other cities of Hubei province | 1 (7)        | 0 (0)              |                 |
| Contact with person with COVID-19 | 9 (30)            | 0 (0)              |                 |
| Have family cluster outbreak      | 4 (13)            | 0 (0)              |                 |
| Symptoms at admission             |                   |                    |                 |
| Fever                             | 17 (57)           | 6 (67)             |                 |
| Gastrointestinal symptoms         |                   |                    |                 |
| Diarrhea                          | 4 (13)            | 2 (22)             |                 |
| Respiratory symptoms              |                   |                    |                 |
| Cough                             | 20 (67)           | 6 (67)             |                 |
| Sputum                            | 9 (30)            | 5 (56)             |                 |
| Sore throat                       | 4 (13)            | 0 (0)              |                 |
| Rhinorrhea                        | 5 (17)            | 1 (11)             |                 |
| Shortness of breath               | 4 (13)            | 3 (33)             |                 |
| Blood result                      |                   |                    |                 |
| Lymphocytes (x 10^9/L, normal range 1.1–2.9) | 1 (0.8, 1.375) | 1 (0.6, 1.2)     |                 |
| Antibiotics therapy               | 16 (53)           | 100 (100)          |                 |
| 1 type of antibiotics             | 6 (20)            | 2 (22)             |                 |
| 2 types of antibiotics            | 7 (23)            | 4 (44)             |                 |
| 3 types of antibiotics            | 3 (10)            | 3 (33)             |                 |
| Antiviral therapy                 | 20 (67)           | 0 (0)              |                 |
| Kaletra                           | 19 (63)           | 0 (0)              |                 |
| Ribavirin                         | 12 (40)           | 0 (0)              |                 |
| Interferon beta-1b                | 3 (10)            | 0 (0)              |                 |
| Death                             | 0 (0)             | 0 (0)              |                 |

Values are expressed in number (percentage) and median (interquartile range).

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**Abbreviations used in this paper:** COVID-19, coronavirus disease 2019; GI, gastrointestinal; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
1, 2020, in Hong Kong, China, followed from hospital admission until discharge. We investigated intestinal fungal compositions in patients with COVID-19 as compared with healthy individuals and patients with community-acquired pneumonia, and their temporal changes over time of hospitalization, via broad-target deep shotgun metagenomics sequencing.

Methods

Study Subject and Design

This prospective study involved 30 patients with COVID-19 hospitalized with laboratory-confirmed SARS-CoV-2 infection, 9 patients hospitalized with community-acquired pneumonia (pneumonia controls), and 30 healthy individuals (controls) (Table 1). Thirty hospitalized patients with COVID-19 were admitted between February 16, 2020, and April 1, 2020, in Hong Kong, China, and were followed from hospital admission until discharge (Figure 1). SARS-CoV-2 infection was confirmed by 2 consecutive reverse-transcriptase polymerase chain reaction (PCR) tests targeting different regions of the RdRp gene performed by the local hospital and Public Health Laboratory Service. Pneumonia controls were patients admitted with community-acquired pneumonia tested negative for SARS-CoV-2 PCR on 2 respiratory samples. Patients with COVID-19 and pneumonia controls were admitted to the Prince of Wales Hospital or the United Christian Hospital, Hong Kong. Controls were healthy individuals with no past medical history or history of antibiotic intake in the past 3 months recruited via advertisement from the general population and tested negative for SARS-CoV-2. Severity of COVID-19 infection was categorized as (1) mild, if there was no radiographic evidence of pneumonia; (2) moderate, if pneumonia was present along with fever and respiratory tract symptoms; (3) severe, if respiratory rate ≥30/min, oxygen saturation ≤93% when breathing ambient air, or PaO₂ / FiO₂ ≤300 mm Hg (1 mm Hg = 0.133 kPa); or (4) critical, if there was respiratory failure requiring mechanical ventilation, shock, or organ failure requiring intensive care. This study was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committees (2020.076). All patients provided informed consent to participate in this study. Data including demographics, laboratory results, imaging results and drug therapy were obtained from the electronic medical records in the Hong Kong Hospital Authority clinical management system. Fecal samples from patients with COVID-19 were collected serially 2 to 3 times per week until discharge. This study was conducted in accordance with the Declaration of Helsinki.

Fecal DNA Extraction

Approximately 0.1-g fecal sample was prewashed with 1 mL double-distilled H₂O and pelleted by centrifugation at 13,000g for 1 minute. The fecal DNA was subsequently extracted from the pellet using Maxwell RSC PureFood GMO and Authentication Kit (Promega, Madison, WI) following the manufacturer’s instructions. Briefly, the fecal pellet was added to 1 mL of CTAB buffer and vortexed for 30 seconds, then the sample was heated at 95°C for 5 minutes. After that, the samples were vortexed
The supernatant was then obtained by centrifuging at 13,000g for 5 minutes and was added to the Maxwell RSC machine for DNA extraction.

Statistical Analysis

Data on the relative abundance of fecal fungi was imported into R v3.5.1. Nonmetric multidimensional scaling analyses were performed on all baseline fecal mycobiomes between groups, and serial fecal mycobiomes in each COVID-19 case during the disease course, based on Bray-Curtis dissimilarities using vegan package (v2.5–3). Differential fungal taxa between patients with COVID-19 (at baseline or across all time points during hospitalization) and healthy controls were identified using LefSE.15

Temporal Changes in Gut Mycobiome Over Time of Hospitalization

We investigated longitudinal dynamics of the gut mycobiome in COVID-19 over time of hospitalization and explored whether recovery from SAR-CoV-2 infection was associated with restoration of gut mycobiome to a

Figure 2. Gut mycobiome (fungal community) alterations in patients with COVID-19. (A) Fecal mycobiome alterations in COVID-19, viewed by NMDS (nonmetric multidimensional scaling) plot based on Bray-Curtis dissimilarities. The fecal mycobiome was compared among healthy controls (n = 30), COVID-19 (n = 30), and pneumonia patient controls (n = 9). (B) Interindividual dissimilarities between fecal mycobiomes within each group. The mycobiome dissimilarity was calculated as Bray-Curtis dissimilarity. Between-group comparison was conducted by t test. (C) The relative abundance of Candida albicans in the fecal mycobiome. Between-group comparison was conducted by Wilcoxon rank sum test.
community similar to that of healthy individuals. The gut mycobiome in most (22 of 30) patients with COVID-19 was stable over the course of hospitalization and remained similar to that of healthy controls at the latest follow-up (Figure 3). However, fecal mycobiome of 8 of 30 patients (patients CoV3, 7, 8, 10, 11, 12, 17, and 23) showed drastic changes over the course of hospitalization and had a different fecal mycobiome composition compared with that of healthy controls at the last follow-up (Figure 3). The diversity of the fecal mycobiome did not differ between healthy controls and patients with COVID-19 at baseline (Figure 4A). In contrast, the diversity and richness of the gut mycobiome were both significantly higher in patients with community-acquired pneumonia than patients with COVID-19 at baseline (Figure 4A and B, $P < .05$ and < .01, respectively). At the last follow-up after hospitalization,
patients with COVID-19 showed a 2.5-fold higher diversity of the fecal mycobiome compared with healthy controls ($P < .05$, Figure 4A).

Overall, during disease course, the diversity of the fecal mycobiome showed constant changes in 53% (16 of 30) of patients with COVID-19 (Supplementary Figure 1). Altogether these data suggest that the gut mycobiome was unstable in a subset of patients with COVID-19 during the time of hospitalization. Patients CoV3, CoV10, and CoV11 who cleared SARS-CoV-2 virus from nasopharyngeal swab and had resolution of respiratory symptoms continued to display a different gut mycobiome composition with that of healthy controls in later time points up to the last follow-up (12, 0, and 5 days after nasopharyngeal clearance of SARS-CoV-2 respectively for patients CoV3, CoV10, and Cov11, Figure 3). These data indicate persistent gut fungal dysbiosis despite disease resolution in a subset of patients with COVID-19.

Across all time points during hospitalization, *C. albicans*, *Candida auris* and *Aspergillus flavus* were overrepresented in fecal samples of patients with COVID-19; these species however were absent in healthy controls (Figure 4C, Supplementary Figures 2 and 3, and Figure 5A). Patients (CoV6, 7, 8 and 11) who showed high fecal abundance of *C. albicans* (>50% in relative abundance) had a substantial decrease of *C. albicans* over time of hospitalization (Supplementary Figure 2A and B). Blooms of *C. albicans*, *C. auris*, and *A. flavus*, were also seen in patients with community-acquired pneumonia (Figures 2C and 5, and Supplementary Figures 2C and 3C).

Two fungal species from the genus *Aspergillus*, *A. flavus* and *Aspergillus niger*, known to cause pulmonary aspergillosis and respiratory illnesses (particularly cough), were detected in serial fecal samples of 6 and 4 patients with COVID-19, respectively, during hospitalization (Figure 5). All 6 patients presented with cough and varying degree of COVID-19 severity. Among the detected *Aspergillus* species, *A. flavus* was the most abundant and prevalent member (in 6/30 patients; relative abundance up to 2.28%, Figure 5A). *A. niger* was absent at baseline but showed a low relative abundance of <1% in 4 of 30 patients with COVID-19 over time of hospitalization (Figure 5B). Importantly, patients CoV15 and CoV19 who presented with a mild disease course showed presence of *A. flavus* and *A. niger* in fecal samples over time. *A. flavus* and *A. niger* were also detected at various time points after nasopharyngeal swab turned negative for SARS-CoV-2 in patients CoV3 and CoV15 (after 11 days and 4 days, respectively, Figure 5). These data indicate cobloom of opportunistic fungal pathogens, *Candida* species and *Aspergillus* species, in the gut of patients with COVID-19 over the disease course. Their presence after nasopharyngeal clearance of SARS-CoV-2 may pose a long-term threat to human health beyond SARS-CoV-2 infection.

**Discussion**

We showed for the first time that the gut mycobiome was disturbed in patients with COVID-19. Patients hospitalized with SARS-CoV-2 infection showed more heterogeneous gut mycobiome configurations (higher interindividual mycobiome dissimilarities) compared with healthy individuals. These data suggest that gut microbiota changes induced by SARS-CoV-2, might at least in part, be stochastic, therefore leading to transition from a stable to unstable microbial community state in COVID-19. In line with our findings in patients with COVID-19, a highly heterogeneous assembly of microbial community in response to disease...
stressors have been reported in the gut of patients with inflammatory bowel disease and in the lungs of patients with human immunodeficiency virus/AIDS. Human immunodeficiency virus/AIDS is associated with decreased CD4 T-cell counts, which increase an individual’s susceptibility to a wide range of bacterial, viral, and fungal opportunistic pathogens. Similarly, SARS-CoV-2 infection was associated with a significant reduction in the number of T cells, which could compromise host immune homeostasis and stability of the microbial communities residing in the human gut. In favor of this hypothesis, the overall gut mycobiome was unstable in a subset of patients with COVID-19 over time of hospitalization, and these individuals ended up with a different gut mycobiome composition compared with that of healthy individuals. In addition, gut mycobiome diversity of patients with COVID-19 at the last follow-up during hospitalization was significantly higher than that of healthy individuals. These data indicate expansion of fungi in the gut of patients with COVID-19 and SARS-CoV-2 infection may be associated with a persistent gut mycobiome dysbiosis in some patients.

Secondary fungal infection or coinfection in patients with COVID-19 during the disease course. Among them, C. albicans was overrepresented in COVID-19. C. albicans has been shown to impair holistic gut microbiome assembly in humans and mice. Moreover, gut colonization by C. albicans aggravated inflammation in the gut and non-gut tissues. Aspergillus infections were recently reported in respiratory tract secretions and tracheal aspirates in patients with COVID-19 from 2 studies (detection rate of 10% and 20%, respectively, in cohorts from China and France). Aspergillus is a genus of ubiquitous fungi that cause a variety of pulmonary and respiratory symptoms. Aspergillus may captivate on the immune-compromised host and affect the clinical features, disease course, and prognosis. To date, there are a lack of data on whether fungal pathogens exist in the gut of patients with COVID-19. In this case series, we provide the first evidence demonstrating the presence of opportunistic Aspergillus pathogens in the feces of patients with COVID-19; A. flavus were detected in the feces of 20% of patients with COVID-19 via metagenomics sequencing. Cough was previously reported to be more frequent in subjects infected by Aspergillus species than those who were not infected. All 6 patients with COVID-19 who had fecal A. flavus
presented with cough during hospitalization, suggestive of a systemic effect of *Aspergillus* infection and the intricate link between the GI and respiratory systems. Two of the 3 patients (CoV1 and 3) who had both fungal species *A. flavus* and *A. niger* in their feces presented with critical COVID-19 and were admitted to intensive care unit, and the third case (CoV7) had high fever and moderate COVID-19 severity. Patient CoV19 who had mild COVID-19 showed clearance of *A. flavus* and *A. niger* over time of hospitalization. Although the overall gut mycobiome structure in patients with COVID-19 gradually resembled that of healthy individuals over time of hospitalization (Figure 3), *Aspergillus* species continued to be present in a subset of patients with COVID-19 (CoV3 and CoV15) even after nasopharyngeal clearance of SARS-CoV-2 (Figure 5). The post-recovery existence of *Aspergillus* species underscores a potential prolonged detrimental effect of secondary fungal infection on host health after SARS-CoV-2 infection, cautioning on long-term monitoring of patients with COVID-19 after recovery.

Pneumonia is one of the leading infectious causes of death. Fungal coinfections in the respiratory tract and alterations in the lung mycobiome have been reported in pneumonia and pulmonary diseases. However, to our knowledge, changes in the gut mycobiome were not reported in patients with pneumonia to date. In the present study, we observed that patients with community-acquired pneumonia also showed a significant alteration in the gut mycobiome compared with healthy controls. Similar to patients with COVID-19, blooms of opportunistic fungal pathogens, *Candida* species and *Aspergillus* species, were also seen in patients with community-acquired pneumonia. In contrast, patients with community-acquired pneumonia showed more heterogeneous gut mycobiome configurations than patients with COVID-19, indicating that the gut mycobiome in community-acquired pneumonia may be more “dysbiotic” than that in COVID-19. This could in part relate to the use of antibiotics in these individuals. In addition, the diversity and richness of the gut mycobiome were both significantly lower in patients with COVID-19 than patients with community-acquired pneumonia. These data collectively suggest that patients with COVID-19 have a similar but less severe dysbiosis of gut mycobiome compared with patients with community-acquired pneumonia.

One limitation of this exploratory study is the modest sample size. Although assigning a causative relationship between COVID-19 and gut fungal dysbiosis requires larger validation studies, this pilot study presents the first to examine the influence of SARS-CoV-2 infection on gut mycobiome composition and dynamics. Stool collected after hospitalization for mycobiome analysis does not represent the bona fide baseline mycobiome at COVID-19 onset, nor the baseline mycobiome before disease onset. In addition, it is unclear whether blooms of gut fungi are a result of SARS-CoV-2 infection or of coinfection during hospitalization. The contribution of gut fungi in the pathogenesis and disease progression of COVID-19 is also unknown. Future studies should prospectively include asymptomatic SARS-CoV-2-infected subjects without hospitalization. In addition, patients with symptomatic SARS-CoV-2 infection should be followed from disease onset until after recovery to thoroughly delineate the role of gut fungi during SARS-CoV-2 infection and the effects of these changes in disease progression and long-term health.

In conclusion, our study provides evidence of numerous blooms of fungal species in the gut of patients with COVID-19. These data highlight an important role of gut mycobiome in COVID-19. The effects of gut fungi in disease pathogenesis and long-term health after recovery from SARS-CoV-2 infection warrant further investigation.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.06.048.

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Tao Zuo, PhD (Conceptualization: Lead; Formal analysis: Equal; Investigation: Lead; Methodology: Equal; Writing – original draft: Lead; Hui Zhan, PhD (Data curation; Lead; Formal analysis: Equal; Methodology: Lead; Writing – review & editing: Equal); Fen Zhang, PhD (Data curation: Supporting; Formal analysis: Supporting); Qin Liu, PhD (Data curation: Supporting; Formal analysis: Supporting); Eugene Y.K. Tso, MD (Resources: Lead); Grace Lui, Doctor (Resources: Equal); Nan Chen, Master (Methodology: Equal; Validation: Equal); Amy Li, NA (Data curation: Lead; Investigation: Equal); Wench Li, NA (Methodology: Equal); Francis K.L. Chan, MD (Investigation: Supporting; Project administration: Lead); Paul K.S. Chan, PhD (Resources: Supporting). Siew C Ng, PhD (Conceptualization: Supporting; Funding acquisition: Lead; Writing – original draft: Lead; Methodology: Equal; Writing – review & editing: Lead).

Conflict of interest
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Supplementary Figure 1. Temporal changes in the diversity of gut mycobiome (fungal) in COVID-19 patients over time of hospitalization.

Supplementary Figure 2. Temporal changes in the relative abundance of *Candida albicans* in the gut mycobiome of COVID-19 patients over time of hospitalization. (A) Longitudinal changes of *C. albicans* in each COVID-19 case. (B) Alteration in the relative abundance of *C. albicans* compared between baseline and the last follow-up; statistical comparison was conducted by paired Wilcoxon rank sum test. (C) The relative abundance of *C. albicans* across all time points in all patients with COVID-19 during hospitalization, as compared with healthy controls. Statistical comparison was conducted by paired Wilcoxon rank sum test.
Supplementary Figure 3. Temporal changes in the relative abundance of *Candida auris* in the gut mycobiome of COVID-19 patients over time of hospitalization. (A) Longitudinal changes of *C. auris* in each COVID-19 case. (B) Alteration in the relative abundance of *C. auris* compared between baseline and the last follow-up; statistical comparison was conducted by paired Wilcoxon rank sum test. (C) The relative abundance of *C. auris* across all time points in all patients with COVID-19 during hospitalization, as compared with healthy controls. Statistical comparison was conducted by paired Wilcoxon rank sum test.
## Supplementary Table 1. Clinical Characteristics of Patients With COVID-19

| Case | Sex | Age | Comorbidities | Recent exposure history | Symptoms at admission | Admitted to ICU | Medication | Blood routine lymphocytes | Chest radiograph findings | COVID-19 severity |
|------|-----|-----|---------------|-------------------------|-----------------------|-------------------|------------|--------------------------|--------------------------|---------------------|
| CoV1 | F   | 65  | Hypothyroidism, hypertension, Chronic hepatitis B carrier | None                   | Fever, runny nose     | No                | Yes        | Nil                      | Kaletra, ribavirin        | 1.0                   | Bilateral LZ haziness | Critical |
| CoV2 | F   | 55  | Contact with person with COVID-19 | Nil | Fever, cough, sputum | No                | No         | Nil                      | Kaletra                   | 1.2                   | Bilateral LZ haziness | Moderate |
| CoV3 | M   | 42  | Travel to Hubei province | Fever, cough | Sputum, shortness of breath | No | Nil | Daptomycin meropenem | Nil | 0.6 | Bilateral LZ haziness | Critical |
| CoV4 | M   | 70  | Hyperlipidemia, duodenal ulcer | No | Fever, cough | No | No | Augmentin, doxycycline | Kaletra | 0.6 | Bilateral lung haziness | Severe |
| CoV5 | M   | 58  | None | No | Fever, cough | No | No | Ceftriaxone, doxycycline | Kaletra, ribavirin | 0.9 | Slight Right LZ haziness | Moderate |
| CoV6 | M   | 71  | None | No | Fever, cough, shortness of breath | No | No | Augmentin | Kaletra, ribavirin | 1.0 | Bilateral lung infiltration | Severe |
| CoV7 | M   | 48  | Diabetes, hypertension, hyperlipidemia | No | Fever, cough | No | No | Ceftriaxone, doxycycline | Kaletra | 1.3 | Left LZ haziness | Moderate |
| CoV8 | F   | 38  | None | No | Fever, cough, sputum, runny nose | No | No | Ceftriaxone, piperacillin-tazobactam | Kaletra, ribavirin | 0.7 | Bilateral LZ infiltrates | Moderate |
| CoV9 | M   | 33  | Contact with person with COVID-19 | No | Cough | No | No | Doxycycline | Kaletra, ribavirin | 0.7 | Bilateral LZ haziness | Mild |
| CoV10| F   | 70  | Obesity, hypertension | No | Fever, cough, sputum, shortness of breath | No | No | Ceftriaxone, piperacillin-tazobactam Sulperazon, Ceftriaxone Disodium, Doxycycline hyclate Oseltamivir, Kaletra | Kaletra, ribavirin | 0.8 | Bilateral LZ haziness | Moderate |
| CoV11| M   | 62  | Diabetes, hyperlipidemia, left subclavian artery occlusion | No | Cough | No | No | Ceftriaxone, azithromycin | Kaletra, ribavirin | 0.9 | Bilateral lung infiltrates | Severe |
| CoV12| F   | 71  | Hypertension, renal impairment, hyperlipidemia | No | Cough | No | No | Kaletra, ribavirin | Kaletra, ribavirin | 2.2 | Bilateral LZ haziness | Moderate |
| Case | Sex | Age | Comorbidities | Recent exposure history | Symptoms at admission | Admitted to ICU | Medication | Blood routine lymphocytes⁴ | Chest radiograph findings | COVID-19 severity |
|------|-----|-----|---------------|-------------------------|-----------------------|-----------------|------------|--------------------------|--------------------------|-------------------|
| CoV13 | F | 47 | None | Contact with person with COVID-19 | Fever and respiratory Nil | Nil | Nil | Nil | No definite consolidation Nil | Moderate |
| CoV14 | F | 22 | None | Contact with person with COVID-19 | Fever, runny nose Cough, shortness of breath Nil | Nil | Augmentin | Kaletra, ribavirin, interferon beta-1b | Clear | Mild |
| CoV15 | F | 46 | None | Contact with person with COVID-19 | Cough, shortness of breath Nil | Nil | Augmentin, Azithromycin | Kaletra, Remdesivir | Left LZ haziness | Mild |
| CoV16 | M | 23 | Hypertension | Travel to Egypt | Fever, cough with white sputum Nil | Diarrhea | No | Augmentin, Azithromycin | Clear Right LL infiltrate | Severe |
| CoV17 | M | 67 | | Travel to UK | Fever, cough with white sputum Cough, shortness of breath, hoarseness, whitish sputum Nil | No | Augmentin | Ribavirin, Kaletra, Remdesivir | Clear Left LZ haziness | Mild |
| CoV18 | F | 34 | None | Travel to UK and Spain | Cough, yellowish sputum and whitish sputum, runny nose, sore throat Nil | No | Ribavirin, Kaletra | 0.7 Bilateral LZ haziness | Mild |
| CoV19 | M | 59 | Ankylosing spondylitis, Bilateral OA hip | Same building with person with COVID-19 | Cough, sore throat, hoarseness, whitish sputum Nil | No | Augmentin | Kaletra, Ribavirin, Interferon Beta-1B | 0.7 Bilateral LZ infiltrates | Moderate |
| CoV20 | F | 38 | None | No | Fever, cough with whitish sputum, runny nose | Nil | No | Ceftriaxone Disodium, Doxycycline hyclate Nil | Bilateral LZ haziness | Mild |
| CoV21 | F | 18 | | Travel to USA | Dry cough, loss of olfactory sensation | Nausea | No | Nil | Bilateral lung infiltrates | Severe |
| CoV22 | F | 38 | | | | | | | | |
| CoV23 | F | 63 | None | Contact with person with COVID-19 | Fever, dry cough | Nil | No | Ceftriaxone Disodium | Bilateral LZ haziness | Mild |
## Supplementary Table 1. Continued

| Case | Sex | Age | Comorbidities | Recent exposure history | Symptoms at admission | Admitted to ICU | Medication | Blood routine lymphocytes | Chest radiograph findings | COVID-19 severity |
|------|-----|-----|---------------|-------------------------|-----------------------|-----------------|------------|--------------------------|--------------------------|-----------------|
| CoV24 | M   | 15  | None          | Travel to UK            | Sore throat, cough with yellowish sputum Nil | No             | Nil         | Nil | Nil | 1.0 | Clear | Asymptomatic |
| CoV25 | M   | 28  | None          | Travel to South Africa, Russia, and transit in UK | Nil | Nil | No | Nil | Nil | 1.4 | Clear | Mild |
| CoV26 | M   | 66  | Hypertension, hepatoma | Travel to Sydney, contact with Person with COVID-19 | throat discomfort | Diarrhea | No | Piperacillin+ Tazobactam injection Nil | Nil | 0.8 | Mild left LZ infiltrates | Moderate |
| CoV27 | M   | 63  | Cervical radiculopathy, bilateral varicose vein with bilateral Trendelenburg operation | Travel to Egypt | Fever | Nil | No | Interferon Beta-1B, Ribavirin, Kaletra Nil | Nil | 1.3 | Clear | Mild |
| CoV28 | F   | 16  | None          | Travel to UK            | Nil | Abdominal pain, nausea, diarrhea | No | Nil | Nil | 1.5 | No pneumonic changes | Mild |
| CoV29 | M   | 27  | None          | Travel to UK            | Fever | Nil | No | Augmentin | Nil | 0.7 | No consolidation | Mild |
| CoV30 | M   | 19  | Eczema        | Travel to France and Austria, contacted with person with COVID-19 | dry cough, nasal congestion | Nil | No | Nil | Nil | 1.2 | Clear | Mild |

COVID-19, coronavirus disease 2019; GI, gastrointestinal; ICU, intensive care unit; LZ, Lower Zone; LL, Lower Lobe; MZ, Middle Zone

*Value in x 10⁹/L, normal range 1.1–2.9.*