Clinical Features and Risk Factors for Secondary Infection in Critically Ill Patients With COVID-19

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Abstract

Background: To analyze the clinical features and the possible risk factors of secondary infection, and explore their impact on prognosis of COVID-19.

Methods: A total of 165 severe and critical hospitalized patients diagnosed with COVID-19 were included. The clinical characteristics, laboratory tests, imaging data, secondary infections and outcomes were analyzed.

Results: The mean age of total patients was (57.3±15.2) years, of which 111 were males (67.3%). 108 cases were with basic diseases (65.5%), and 1 death (0.6%). The secondary infection rate in critical patients was significantly higher than in severe patients (P <0.05). The secondary infections were mainly lung infections. The pathogens were principally Burkholderia multivorans, Stenotrophomonas maltophilia, Acinetobacter baumannii and Klebsiella pneumoniae. The recovery rate of 28 days in the infected group was significantly lower than that in the non-infected group (p < 0.001).The utilization rate and usage time of invasive ventilator, and deep vein catheterization, catheter indwelling and ECMO were the risk factors for the secondary infected patients.

Conclusion: Secondary infection is an extremely common complication in critically ill patients and a trigger point for exacerbation of the disease. An effective control on the secondary infection will do good to the prognosis of COVID-19 patients.

1. Introduction

In December 2019, a cluster of pneumonia cases of unknown origins emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia[1]. In January 2020, Chinese Center for Disease Prevention and Control (CDC) revealed a novel betacoronavirus that resembled severe acute respiratory syndrome coronavirus (SARS-CoV) (which shared about 79% of the genetic sequence) by high-throughput sequencing analysis from lower respiratory tract samples. Therefore, it named SARS-CoV-2 by the World Health Organization (WHO), and this disease was named COVID-19 (Corona Virus Disease 2019) [2, 3].

As of September 22, 2020, COVID-19 has spread across more than 200 countries, with more than 30 million confirmed cases and nearly one million deaths. Scientists, researchers and governments all over the world are actively and urgently seeking for an antidote. However, there is still no specific drug for COVID-19, and active antiviral and symptomatic treatment is still available. Compared with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), the COVID-19 had the stronger transmission speed and infectivity, while had a relatively lower fatality rate[2, 4]. Most of patients with COVID-19 had mild symptoms and good prognosis, but some of them were still in critical condition, with severe pneumonia, pulmonary edema, ARDS or secondary infection, and even multiple organ failure and death[5]. It has been reported that the mortality of critically ill patients is as high as 22–62%[6, 7], and

secondary infection is one of the important factors of death (accounts for 50% in the death cases). Secondary bacterial infection such as pneumonia, sepsis, meningitis and so on may be one of the important factors that aggravate the illness and lead to the death of the COVID-19 patient. Reduced lymphocyte production, higher doses of glucocorticoids, duration of hospitalization in intensive care units, and mechanical ventilation are all high risk factors for secondary infection[8–10], while the possible risk factors of secondary infection in critically ill patients with COVID-19 has few been reported.

Wenzhou, Zhejiang, China, became the city with the highest number of COVID-19 cases next to Wuhan due to economic cooperation and communication between both cities. We collected datas from six designated hospitals in Wenzhou to analyze the epidemiological, clinical, laboratory characteristics and the impact of secondary infection on the prognosis of SARS-CoV-2 pneumonia, and explore possible risk factors of secondary infection. We hope our study findings will help to reduce the secondary infection rate of patients with COVID-19 and improve their prognosis.

2. Methods

2.1 Patients

This study was conducted from January 25, 2020, to February 16, 2020, in six designated hospitals of Wenzhou and the final date of follow-up was February 29, 2020. Written informed consent was waived in light of the urgent need to collect clinical data.

2.2 Definitions

A confirmed case with COVID-19 was defined as a positive result to real-time fluorescent quantitative PCR assay for pharyngeal swab specimens. Severe and critical cases of COVID-19 infection were defined based on the guidelines for the diagnosis and treatment of novel coronavirus disease (version 6). Secondary infection was diagnosed when patients showed clinical signs or symptoms of pneumonia or bacteraemia and a positive culture of a new pathogen excluding colonization and contamination after admission[12].

2.3 Data collection

Epidemiological, demographic, clinical, laboratory, radiological, treatment and prognosis data were extracted from electronic medical records. Laboratory assessments consisted of blood routine examination, blood biochemistry detection, blood gas analysis, urine routine examination, C-reactive protein, culture results of pathogen and so on. Radiologic assessments included chest X-ray and computed tomography. All enrolled patients (n = 165) were divided into the severe subtype and the critical subtype based on the severity of COVID-19. The seventeen patients with critical subtype were divided into infected group and non-infected group according to whether they were complicated with infection during hospitalization. The study was approved by the First Affiliated Hospital of Wenzhou Medical University

Ethics Committee (KY-2020-06.01). All patients provided signed informed consent. The privacy rights of human subjects must always be observed.

2.4 Statistical analysis

All statistical analyses were conducted using SPSS version 22.0 (SPSS, Chicago, IL). Data were expressed as numbers (percentages) for categorical variables, as mean ± standard deviation for normally distributed continuous variables and median (inter-quartile range) for skewed distributed continuous variables. Student's t-test or Wilcoxon rank-sum tests were applied to continuous variables, Pearson $\chi 2$ or Fisher's exact test were used for categorical variables as appropriate. *P*-value of < 0.05 was considered to be statistically significant.

3. Results

3.1 Demographic and clinical characteristics

A total of 165 COVID-19 patients with ages ranging from 17 to 93 years (57.3 ± 15.2) were enrolled, including 114 cases of severe subtype, 51 cases of critical subtype, 111 cases of males (67.3%) and 54 cases of females (32.7%). There were 108 patients with basic diseases (65.5%) (hypertension, diabetes and heart disease in the majority). The main clinical signs and symptoms were fever, cough and short breath, and some patients had gastrointestinal symptoms such as diarrhea. Compared with the severe subtype, the patients with critical subtype was older ((54.5 ± 14.2) vs (63.5 ± 16.0), $P = 0.041$). And there was a significant difference in smoking history *(*$P = 0.026$*)*, however, there was no significant difference in the gender, basic diseases and contact history between the two subtypes (Table 1).

Table 1
Baseline characteristics of patients with COVID-19 infection.

	Severe subtype ***n*** **= 114**	**Critical subtype** ***n*** **= 51**	**All patients** ***n*** **= 165**	***P-value***
Age (years)	54.5 ± 14.2	63.5 ± 16.0	57.3 ± 15.2	**0.041**
Gender (n, %)				0.786
Male	78 (68.4)	33 (64.7)	111 (67.3)	
Female	36 (31.5)	18 (35.3)	54 (32.7)	
Contact history (n, %)				
Contact to epidemic area	36 (31.6)	15 (29.4)	51 (30.9)	0.781
Contact to confirmed cases	42 (36.8)	26 (51)	68 (41.2)	0.089
Smoking history (n, %)	15 (13.2)	16 (31.4)	31 (18.8)	**0.006**
Basic diseases (n, %)				
Hypertension	30 (26.3)	27 (52.9)	57 (34.5)	0.055
Diabetes	21 (18.4)	15 (29.4)	36 (21.8)	0.576
Coronary heart disease	4 (3.5)	0	4 (2.4)	1.000
Cerebral Infarction	3 (2.6)	3 (5.9)	6 (3.6)	0.527
Malignant Tumor	0	2[a] (3.9)	2[a] (1.2)	1.000
Signs and symptoms (n, %)				
Fever	108 (94.7)	51 (100)	159 (96.4)	1.000
Cough	81 (71.1)	51 (100)	132 (80)	**0.034**
Short breath	69 (60.5)	51 (100)	120 (72.7)	**0.007**
Pharyngodynia	12 (10.5)	7 (13.7)	19 (11.5)	0.553
Diarrhea	18 (15.8)	10 (19.6)	28 (17.0)	0.547

Data are expressed as numbers (percentages) for categorical variables. [a]: Two cases were leukemia and prostate cancer respectively.

3.2 Complications and treatment

During hospital admission, the most common complication was acute respiratory distress syndrome (ARDS) (72.7%), followed by hepatic insufficiency (70.9%) and secondary infection (18.2%) (including 27 cases of hospital-acquired pneumonia, 9 cases of urinary tract infection, 3 cases of septicemia). Critical

cases yielded significantly higher rates of secondary infection as compared with severe cases (47.1% v.s. 5.2%, $P = 0.001$). All patients were isolated and treated with antiviral therapy (including alpha-interferon, lopinavir (Kaletra) and Arbidol). Systemic corticosteroid and immunoglobulin were given to 91 cases (55.2%) and 82 cases (49.7%) respectively, and both more so in the critical subtype than the severe subtype (94.1% v.s. 36.8%, $p < 0.001$; 76.5% v.s. 36.8%, $p = 0.007$, respectively). And antibiotic therapy was given to 153 cases (92.7%). By the end of the final date of follow-up, there was only one case died of multiple organ failure associated with secondary infection. Among the critical subtype cases that did not get better within twenty-eight days from illness onset, 15 cases accepted extracorporeal membrane oxygenation (ECMO) treatment, 6 cases undertook continuous renal replacement therapy (CRRT) due to renal failure and 9 cases were treated with artificial liver supporting systems (ALSS)(Table 2). And they were all treated with hyperensort and had difficulties in tracheal intubation and extubation.

Table 2
Complications and treatments of patients with COVID-19 infection.

	Severe subtype *n* **= 114**	**Critical subtype** *n* **= 51**	**All patients** *n* **= 165**	***P-value***
Complications (n, **%)**				
Acute respiratory distress syndrome	69 (60.5)	51 (100)	120 (72.7)	**0.007**
Acute kidney injury	3 (2.6)	6 (11.8)	18 (10.9)	0.223
Hepatic insufficiency	75 (65.8)	42 (82.4)	117 (70.9)	0.353
Secondary infection	6 (5.2)	24 (47.1)	30 (18.2)	**0.001**
Hospital-acquired pneumonia	3 (2.6)	24 (47.1)	27 (16.5)	**< 0.001**
Urinary tract infection	3 (2.6)	6 (11.8)	9 (5.5)	0.223
Septicemia	0	3 (5.9)	3 (1.8)	0.309
Shock	0	18 (35.3)	18 (10.9)	**0.001**
Treatments (n, **%)**				
HFNC	21 (18.4)	38 (74.5)	59 (35.8)	**< 0.001**
Mechanical ventilation	0	51 (100)	51 (30.9)	**< 0.001**
ECMO	0	15 (29.4)	15 (9.1)	**0.003**
CRRT	0	6 (11.8)	6 (3.6)	0.169
Hyperensort	0	21 (41.2)	21 (12.7)	**< 0.001**
ALSS	0	9 (17.6)	9 (5.5)	**0.043**
Antibiotic therapy	102 (89.5)	51 (100)	153 (92.7)	0.165
Glucocorticoid	42 (36.8)	49 (96.1)	91 (55.2)	**< 0.001**
Immunoglobulin	42 (36.8)	40 (78.4)	82 (49.7)	**< 0.001**

Data are expressed as numbers (percentages) for categorical variables.
Abbreviations: HFNC=high-flow nasal cannula oxygen therapy, ECMO=extracorporeal membrane oxygenation, CRRT=continuous renal replacement therapy, ALSS=artificial liver supporting systems.

3.3 Risk factors of secondary infection in critical subtype

In the seventeen critical subtype cases, the non-infected group got better after twenty-eight days from illness onset and had a higher improved rate than the infected group (100% v.s. 12.5%, $p < 0.001$). Overall,

the utilization of invasive ventilator, deep vein catheterization, catheter indwelling and ECMO in the infected group were significantly higher than those in the non-infected group (p = 0.002, 0.002, 0.029, 0.009, respectively). While the days from illness onset to admission, age, gender, APACHE Ⅱ score, SOFA score, and related laboratory parameters had no obvious difference in the two groups (Table 3).

Table 3. The possible risk factors of secondary infection in critically ill COVID-19 patients.

	Infected group *n*=24	Non-infected group *n*=27	*P-value*
Days from illness onset to admission (days)	4.3 ± 2.2	4.0 ± 2.1	0.815
Improvement after 28 days from illness onset (*n*, %)	3 (12.5)	27 (100)	**<0.001**
Demographic parameters			
Age (years)	66.9 ± 18.3	60.6 ± 13.9	0.433
Gender (*n*, %)			0.620
Male	18 (75)	15 (55.6)	
Female	6 (25)	12 (44.4)	
Basic diseases (*n*, %)			
Two or more comorbidities	6 (25)	12 (44.4)	0.620
Oxygenation index (mmHg)	140.4 ± 36.9	192.4 ± 75.4	0.098
APACHE Ⅱ score	7.4 ± 3.9	6.7 ± 3.8	0.710
SOFA score	3.4 ± 1.5	2.2 ± 1.4	0.122
Laboratory parameters			
Leukocyte count (×10^9/L)	7.85 ± 4.07	7.28 ± 2.54[a]	0.741
Neutrophil count (×10^9/L)	6.43 ± 4.04	5.97 ± 2.40[a]	0.758
Lymphocyte count (×10^9/L)	0.80 ± 0.40	0.84 ± 0.43[a]	0.850
Neutrophil to lymphocyte ratio	7.72 (3.2 - 10.9)	8.38[a] (4.0 - 13.2)	0.834
CD4(+) T cells (/uL)	241.6 ± 166.9	279.5 ± 152.5[a]	0.671
CD8(+) T cells (/uL)	167.5 ± 103.1	180.8 ± 104.9[a]	0.816
CD4(+) / CD8(+)	1.6 ± 0.6	1.7 ± 1.0[a]	0.674
B lymphocytes (/uL)	196.6 ± 70.7	141.3 ± 77.4[a]	0.189
Blood platelet count (×10^9/L)	152.0 ± 61.2	199.1 ± 117.5	0.326
Mechanical ventilation			
Non-invasive ventilator (*n*, %)	18 (75)	27 (100)	0.206
Usage time of non-invasive ventilator (days)	6.8 ± 5.0	5.2 ± 2.4	0.491

Invasive ventilator (*n*, %)	24 (100)	6 (22.2)	**0.002**
Usage time of invasive ventilator (days)	18.1 ± 5.9	6.5 ± 0.7	**0.028**
Deep vein catheterization (*n*, %)	24 (100)	24 (22.2)	**0.002**
Catheter indwelling (*n*, %)	24 (100)	12 (44.4)	**0.029**
CRRT (*n*, %)	6 (25)	0	0.206
ALSS (*n*, %)	9 (37.5)	0	0.082
ECMO (*n*, %)	15 (62.5)	0	**0.009**

Data are expressed as numbers (percentages) for categorical variables, as means ± SD for normally distributed continuous variables and medians (interquartile ranges) for skewed distributed continuous variables. [a]: *n*=24, One case of leukemia was excluded.

Abbreviations: APACHE=acute physiology and chronic health evaluation, SOFA=sequential organ failure assessment, ECMO=extracorporeal membrane oxygenation, CRRT=continuous renal replacement therapy, ALSS=artificial liver supporting systems.

3.4 Culture results of pathogen

Among the severe subtype cases (n=114), there were six positive cultures of new pathogens including three positive sputum culture of Klebsiella pneumoniae and three positive urine culture of Candida albicans. Among the critical subtype cases (n=51), there were 24 positive cultures of new pathogens (excluding colonization and contamination). The most common secondary infectious agent (excluding the repeated strains isolated from the same part of the same patient) were mainly Burkholderia multivorans (37.5%) and Stenotrophomonas maltophilia (37.5%), followed by Acinetobacter baumannii (25%), Ralstonia mannitolilytica (25%), Candida albicans (25%) and Klebsiella pneumoniae, Enterobacter aerogenes, Corynebacterium accolens, Hospital acinetobacter, Staphylococcus aureus, Enterococcus faecalis, Candida glabrata and Aspergillus niger.

3.5 A brief case of secondary infection

The initial chest imaging findings from a middle-aged male patient of critical subtype with the history of contacting to the epidemic area and hypertension and diabetes, showed bilateral multiple small flaky and patchy ground-glass opacity (Figure 1). The invasive ventilator and deep vein catheterization were given due to the rapid deterioration after admission. After the symptomatic treatments such as antiviral therapy, he got better for some time but got worse again. Repeated blood and sputum cultures showed multidrug-resistant Acinetobacter baumannii and Klebsiella pneumoniae. Ductal culture and bronchoalveolar lavage fluid were detected multidrug-resistant Klebsiella pneumoniae and Ralstonia mannitolilytica

respectively. Meanwhile, significantly elevated inflammatory markers and more bilateral pulmonary infiltration on chest radiograph (Figure 2b) suggested secondary infection. With the antibiotic therapy, the patient's condition and chest radiograph findings (Figure 2c) were better than before.

4. Discussion

Some studies suggest that secondary infection is a risk factor for death of viral pneumonia[13]. Our study retrospectively analyzed the clinical characteristics of 165 patients diagnosed with severe and critical COVID-19, and focused on the risk factors of secondary infection and prognosis. Herein, the critical subtype had a higher incidence of secondary infection than the severe subtype (47.1% v.s. 5.2%). In the critical subtype, non-infected group had a higher improved rate after 28 days from onset than the infected group, suggesting secondary infection is associated with disease severity and prognosis. In our study, the secondary infections were mainly lung infections, accounting for about 90%, and pathogens were mainly Gram-negative bacteria, principally Burkholderia multivorans, Stenotrophomonas maltophilia, Acinetobacter baumannii, Klebsiella pneumoniae followed by Candida albicans and Aspergillus flavus, which is similar to the previoys report[2, 14].

The pathogenesis of SARS-CoV-2 combined with bacterial and fungal infections is complex that involving interreaction between viruses, bacterial virulence factors and host immune system which damages to all organs, especially the respiratory system. The possible mechanisms of secondary pulmonary infection of COVID-19 are as follows: First, like other SARS coronaviruses, SARS-COV-2 targets the invasion of alveolar epithelial cells and type II alveolar cells by binding the SARS spike protein to the angiotensin-converting enzyme 2(ACE2) receptor. Second, we found that those with no improvement after 28 days from illness onset had lower CD4(+) T cells and CD8(+) T cells, and the higher incidence of respiratory distress syndrome (RDS) and secondary infection, suggesting that T lymphocyte injury is the negative factor leading to the exacerbations of the patient, which is consistent with previous reports[2]. Lymphocytopenia is the typical feature of severe patients with SARS-CoV and MERS-CoV because coronavirus consumes many immune cells and inhibits the body's cellular immune function[[6]]. And the early rapid replication of the virus leads to many epithelial and endothelial cells apoptosis and vascular leakage, which triggers the release of numerous pro-inflammatory cytokines and chemokines, such as IL-2R、IL-6、IL-10、TNF-α, induces a cytokine storm in the body, generates a series of immune responses and causes changes in peripheral white blood cells and immune cells such as lymphocytes[2]. Third, the release of risk-related molecular patterns (DAMps), which serve as endogenous danger signals to promote and exacerbate immune and inflammatory responses that lead to lung injury, and the DAMP/ receptor axis of late glycosylation end-products have been found to integrate with toll-like receptors (TLRs), amplifying bacterial fungal inflammatory responses[15, 16].

Previous studies have suggested that secondary infection, especially Gram-negative bacteria infection, may be associated with hormone use, severe basic diseases, and frequent invasive operations[17]. Most of severe and critical patients are male middle-aged and elderly population which may be associated with

chronic basic diseases and weakened immune system. If infected with SARS-CoV-2, elderly male patients with chronic basic diseases, such as cardio-cerebrovascular diseases, are more likely to develop into critical subtype and have a higher risk of death[4]. According to one study, the fatality rate of COVID-19 in diabetic patients is 35.4%. Diabetic patients are more likely to suffer from multiple organ dysfunction, secondary infection and poor prognosis[18]. Moreover, We found that the utilization of invasive ventilator, deep vein catheterization, catheter indwelling and ECMO in the infected group were significantly higher than those in the non-infected group, identifying the invasive operation is related to secondary infection. Using invasive ventilator for long time leads the upper respiratory tract to lose the filtration and humidification of the inhaled air, destroys upper respiratory barrier function and airway mucosa. Plus, the mechanical ventilation makes it easy for pathogens to multiply in the respiratory tract, suppresses the ciliary system of the lower respiratory tract, impacts the fluent respiratory tract and clearance function, thus which increased frequency of sputum aspiration, resulting in damage to the airway mucosa. Because the patients' physiological reflexes such as swallowing and coughing, protease, complement and inflammatory factors can be released to increase the permeability of pulmonary capillaries, aggravate the diffusion of inflammation and tissue damage, and eventually cause pulmonary infection[19]. Therefore, timely assessment of the necessity of mechanical ventilation, prompt removal of the ventilator, and tracheotomy for the long-term ventilator-dependent patient, reduce the incidence of ventilator-related lung infection. Studies have shown that prolonged arteriovenous catheterization is a risk factor for catheter-related bloodstream infections[20]. Our study had only one case of bloodstream infection, which may be related to the early usage of antibiotics therapy and strict aseptic operation, or small samples and the short follow-up time.

As shown in the *A brief case of secondary infection*, it is of great importance for the improvement of the prognosis and survival rate to detect the secondary infection as early as possible and to select appropriate antimicrobial agents in combination with drug sensitivity results in time.

Our study focused on the effect of secondary bacterial and fungal infection on the prognosis of SARS-CoV-2 infection and analyzed infection-related risk factors to reduce COVID-19 mortality and improve disease outcomes. We suggest that preventive measures for co-infection include strict aseptic operation, less number of invasive operations, shortening the time of the indwelling catheter, early appropriate empirical antibiotic therapy and so on.

Our study has some limitations. The incidence of secondary infections may be underestimated due to the usage of the empirical antibiotic therapy and uncertainty of sensitivity and specificity of specimen culture. Besides, some cases didn’t undertake different parts of the pathogen culture. According to clinical manifestations, laboratory examination and radiography cannot completely distinguish viral infection from secondary infection. Due to small samples, it was not possible to assess the independent correlation of risk factors for secondary infection. What’s more, we did not focus on the details of antibiotic therapy because different drugs may also affect prognosis.

5. Conclusions

COVID-19 has a relatively low fatality rate but also has fatal complication like ARDS, hepatic failure, multiple organ failure and even septicopyemia. Secondary infection is an extremely common complication in critically ill patients and a trigger point for exacerbation of the disease. Invasive operations such as the use of invasive ventilator, deep vein catheterization and indwelling catheter are high risk factors for secondary infection. The improvement of COVID-19 patients' prognosis needs to take related preventive measures, strengthen the control of hospital infection and reduce the secondary infection.

Abbreviations

CDC = Chinese Center for Disease Prevention and Control

SARS-CoV = severe acute respiratory syndrome coronavirus

WHO = World Health Organization

COVID-19 = Corona Virus Disease 2019

SARS = severe acute respiratory syndrome

MERS = Middle East respiratory syndrome

HFNC = high-flow nasal cannula oxygen therapy

ECMO = extracorporeal membrane oxygenation

CRRT = continuous renal replacement therapy

ALSS = artificial liver supporting systems.

APACHE = acute physiology and chronic health evaluation

SOFA = sequential organ failure assessment

Declarations

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Conflicts of interest

The authors declare that they have no competing interests.

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Figures

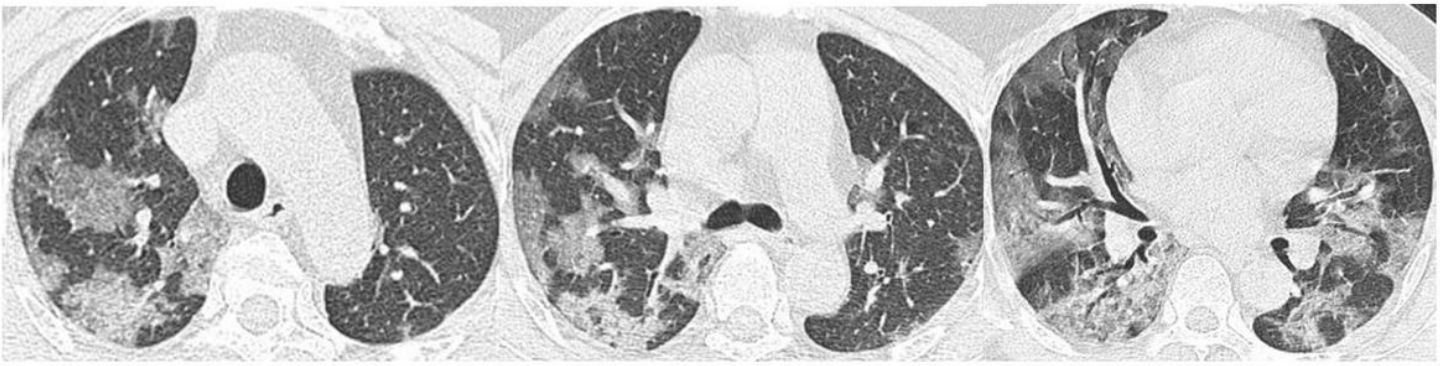

Figure 1

One case of chest CT images in critically ill COVID-19 patients. The chest CT images showed bilateral multiple small flaky and patchy ground-glass opacity.

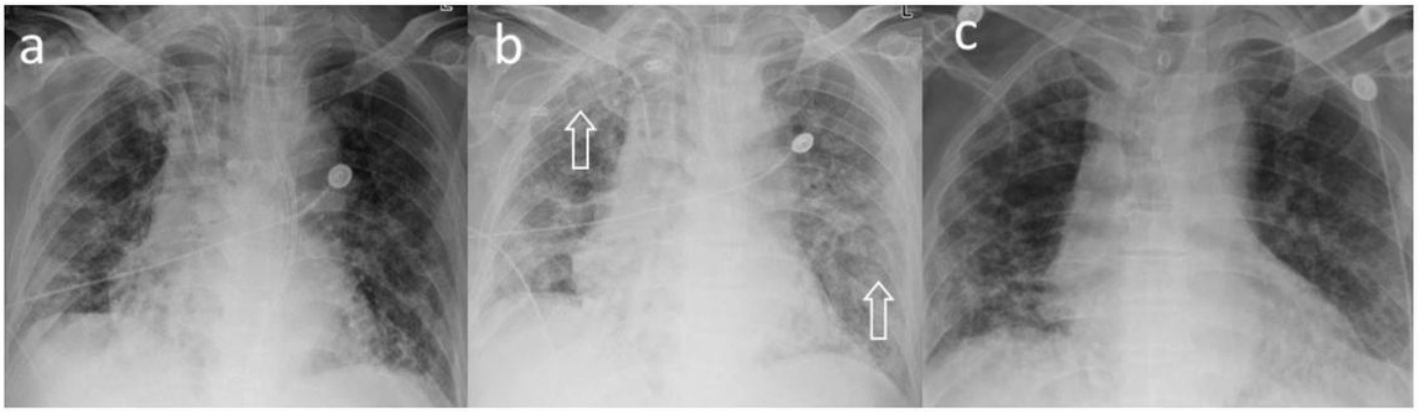

Figure 2

One case of chest radiograph images in critically ill COVID-19 patients before and after secondary infection. a. Before secondary infection: little bilateral pulmonary infiltration. b. After secondary infection: bilateral multiple patchy hyperdense shadow with infiltration and more lesion. c. The three weeks after antimicrobial therapy: scattered bilateral pulmonary infiltration and more absorption of lung lesions than before.