Clinical Features of Patients Without Fever Infected by SARS-CoV-2: an Observational Study

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Research

Keywords: Severe Acute Respiratory Syndrome Coronavirus-2, Coronavirus Disease 2019, fever

Posted Date: June 2nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-570387/v1

Abstract

Objective: A large number of patients had infected by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). We aimed to clarify the clinical features of the patients without fever infected by SARS-CoV-2.

Methods: This is a retrospective and single-center study. We collected and analyzed the data of demographic, clinical presentation, laboratory tests, radiological results, treatment, and complications. The patients with fever and without fever were compared.

Results: 113 patients were enrolled in the study, 36 (31.9%) patients without fever on admission. Among the patients without fever, the mean age was 41 years (IQR, 30-53; Range, 8-82years) and 18 (50%) were male. The median from the onset of illness to the first admission was 3.0 days. None of the patients without fever had complications and received high-flow oxygen therapy or invasive ventilation. As of Feb 22, 2020, 8 patients (22.2%) were discharged, and the remaining patients were still hospitalized.

Conclusions: Out of 113 patients with SARS-COV-2 infection, patients without fever accounted for 31.9% in total. The clinical prognosis of patients without fever may be better than those of patients with fever on admission.

Introduction

In December 2019, a series of cases of pneumonia with unknown causes were found in Wuhan city, Hubei province, which were identified as 2019-nCoV[1−4]. On February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) renamed it as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which was a new strain of RNA virus that had not been discovered in animals or humans so far5. Additionally, the SARS-CoV-2 infected disease was named as coronavirus disease 2019 (COVID-19) by WHO. By Jan 10, 2021, confirmed SARS-CoV-2 cases had occurred in 223 countries, areas or territories[5]. Globally, 88,828,387 cases have been diagnosed with COVID-19, while in China, this value was 97,625. Unfortunately, overall, 1,926,625 patients died because of COVID-19[5]. Therefore, the global cooperation between governments, health workers, and the public are vital to prevent its spread[6].

Thus far, many published scientific studies mainly focused on the epidemiology and clinical features of COVID-19[1,2,6−10]. However, the difference in clinical characteristics of cases without fever has not been reported. By Jan 23, 2020, three studies of 99 patients, 41 patients, and 138 patients respectively with laboratory-confirmed in the Wuhan area indicating 3%, 2%, and 1.4 % of patients without fever, respectively[1,6,7]. Xu et al[9] suggested that 23 % (62) of the patients without fever and the atypical symptoms of patients in Zhejiang province were significantly larger than the patients in Wuhan. An observation study of 1099 laboratory-confirmed cases including 483 (43.95%) patients of Wuhan from 30 hospitals in China suggested that 12.1% of patients without fever[10]. Meanwhile, due to the precautions

taken and management implemented quickly by the Chinese government, more patients without fever have been diagnosed with COVID-19 before their symptoms getting worse or during the incubation period.

In this study, we retrospectively collected and analyzed detailed clinical data of patients with laboratory-confirmed SARS-CoV-2 infection in a hospital of Changsha, Hunan province. We concluded clinical manifestations and prognostic characteristics of COVID-19 patients without fever in order to direct clinical treatment and provide further guidance on patient management.

Methods

Study design and participants

This study used a retrospective design. Patients with COVID-19 admitted to the Changsha Public Health Center from Jan 30 to Feb 22, 2020, were included. All the enrolled patients were diagnosed with SARS-CoV-2 infection on the basis of the WHO interim guidance[11]. The clinical outcome was monitored up to Feb 22, 2020, the final date of follow-up. This study was approved by the institutional ethics board of the Second Xiangya Hospital, Central South University. As an urgent retrospective study, informed consent was waived by the ethics board.

Data collection

The medical information of patients with SARS-CoV-2 infection was collected, including age, gender, history of Hubei exposure in two weeks, days from illness onset, physical examination, comorbidities, signs and symptoms, laboratory findings, and chest radiography at admission. The treatment, complications, oxygen support, and prognosis were recorded during hospitalization. Laboratory findings were collected for each patient, including complete blood count, coagulation test, liver and renal function, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, lactate dehydrogenase and creatine kinase. All data were collected by two physicians (ND and FT). Laboratory-confirmation of SARS-CoV-2 was done in the designated hospital. The SARS-CoV-2 RNA extraction procedure was performed with the Viral Nucleic Acid Isolation Kit according to the manufacturer's instructions.

Definitions

Fever was defined as an elevated body temperature and presence of axillary temperature ≥37.0°C[12]. Assessment of body temperatures (axillary) with admission was performed by using mercury thermometers. Patients who reported any fever history during the time from the onset symptom to admission were categorized into the fever group. Acute respiratory distress syndrome (ARDS), according to the Berlin definition, referred to a decrease in the PaO2/FiO2 index below 300 mmHg [13]. Acute kidney injury (AKI) was identified and classified based on the highest serum creatinine level or urine output criteria according to the kidney disease improving global outcomes classification[14].

Statistical analysis

As the difference onset of illness, we divided the cohort into patients with symptoms of fever and those without fever. Characteristics are expressed as mean ± standard deviation or median (IQR) for continuous variables and a percentage or frequency for categorical variables. Continuous variables were compared using Student's t-test (normal distribution) or Mann–Whitney U-test (Skewed distribution), and categorical variables were compared using Fisher's exact test or Chi-square analysis. All analyses were carried out using R (http://www.R-project.org). Two-sided P values <0.05 were considered statistically significant.

Results

Demographics and clinical characteristics

By 22 Feb 2020, 113 patients with SARS-CoV-2 infection were included in the study, including 36 (31.9%) patients without fever and 77 (68.1%) patients with fever on admission. In total, 75 (64%) patients had a history of Hubei exposure and all 113 patients had been exposed to people infected by SARS-CoV-2. There was no difference in the history of Hubei exposure between without fever and fever patients. Of these patients, the median age was 45 years (IQR, 35–60; Range, 8-83years) and 62 (54.9%) were male (Table 1). Compared with fever patients, the patients without fever were younger (median, 41vs 50 years) and were more likely to admission early (median, 3 vs 5 days, $P = 0.032$). The underlying comorbidities between patients without fever and fever patients were significant differences. Only 5 (13.9%) patients without fever had the underlying disease, less than those in fever patients (26[33.8%], $P = 0.027$). Hypertension (17[15.0%]), diabetes (6[5.2%]), cardiovascular disease (3[2.7%]) were the most common underlying diseases.

Table 1
Clinical characteristics of 113 patients infected by SARS-CoV-2

	All patients(n = 113)	Non-fever(n = 36)	Fever(n = 77)	P-value
Characteristics				
Age, years, IQR	45 (35.0, 60.0)	41 (30.0, 53.5)	50 (37.0,64.0)	0.104
< 18	7 (6.2%)	4 (11.1%)	3 (3.9%)	0.253
18–40	33 (29.2%)	13 (36.1%)	20 (26.0%)	
40–65	53 (46.9%)	14 (38.9%)	39 (50.7%)	
≥ 65	20 (17.7%)	5 (13.9%)	15 (19.5%)	
Gender				0.477
Male	62 (54.9%)	18 (50.0%)	44 (57.1%)	
Female	51 (45.1%)	18 (50.0%)	33 (42.9%)	
Hubei exposure	75 (66.4%)	23 (63.9%)	52 (67.5%)	0.702
Current smoking	11 (9.7%)	3 (8.3%)	8 (10.4%)	0.731
Drinking	2 (1.8%)	0 (0.0%)	2 (2.6%)	0.329
Any comorbidity	31(27.4%)	5(13.9%)	26(33.8%)	0.027
Hypertension	17 (15.0%)	3 (8.3%)	14 (18.2%)	0.172
Cardiovascular disease	3 (2.7%)	0 (0.0%)	3 (3.9%)	0.230
Diabetes	6 (5.3%)	2 (5.6%)	4 (5.2%)	0.936
Cerebrovascular disease	1 (0.9%)	0 (0.0%)	1 (1.3%)	0.492
Chronic obstructive pulmonary disease	1 (0.9%)	0 (0.0%)	1 (1.3%)	0.498
Chronic liver disease	2 (1.8%)	0 (0.0%)	2 (2.6%)	0.329
Malignant tumor	1 (0.9%)	0 (0.0%)	1 (1.3%)	0.498
Signs and symptoms				

Data are n (%) unless specified otherwise. IQR, interquartile range.

	All patients(n = 113)	Non-fever(n = 36)	Fever(n = 77)	P-value
Cough	61 (5.0%)	13 (36.1%)	48 (62.3%)	0.009
Fatigue	37 (32.7%)	5 (13.9%)	32 (41.6%)	0.003
Myalgia	11 (9.7%)	3 (8.3%)	8 (10.4%)	0.731
Expectoration	33 (29.2%)	13 (36.1%)	20 (26.0%)	0.270
Anorexia	3 (2.7%)	1 (2.8%)	2 (2.6%)	0.956
Headache	7 (6.2%)	0 (0.0%)	7 (9.1%)	0.062
Dyspnea	13 (11.5%)	2 (5.6%)	11 (14.3%)	0.175
Diarrhea	3 (2.7%)	0 (0.0%)	3 (3.9%)	0.230
Sore throat	12 (10.6%)	7 (19.4%)	5 (6.5%)	0.037
Nausea	1 (0.9%)	0 (0.0%)	1 (1.3%)	0.492
Dizziness	2 (1.8%)	0 (0.0%)	2 (2.6%)	0.329
Days from illness onset to first hospital admission (days), IQR	4 (3.0, 7.0)	3 (2.0, 5.0)	5 (3.0, 7.0)	0.032
Systolic pressure, mmHg, Mean (SD)	124.9 ± 12.9	125.7 ± 15.0	124.5 ± 11.9	0.640
Diastolic pressure, mmHg, Mean (SD)	78.8 ± 9.2	80.0 ± 9.6	78.3 ± 9.0	0.359
Respiratory rate > 24 breaths per min	3 (2.9%)	0 (0.0%)	3 (4.0%)	0.227
Heart rate > 100 beats per min	30 (26.6%)	5 (13.9%)	25 (32.5%)	0.037
Data are n (%) unless specified otherwise. IQR, interquartile range.				

Among the patients without fever, the most common symptoms at onset were cough (13[36.1%]), expectoration (13[36.1%]), sore throat (7[19.4%]), and fatigue (5[13.9%]). Among patients in the fever group, followed by cough (48[62.3%]), fatigue (32[41.6%]), and expectoration (20[26%]). The symptom of sore throat in patients without fever were more in frequency than the fever group ($P = 0.037$).

Laboratory testing and vital signs

On admission, there were more cases in fever patients of fast heart rate (> 100 bpm) when compared with this in patients without fever (32% vs 13.9, $P = 0.037$). There was no difference between fever and

patients without fever on respiratory rate, systolic pressure and diastolic pressure (Table 1). Of all patients' admission recordings, 37.2% and 10.6% of patients had leucopenia and thrombocytopenia, respectively. Moreover, the levels of white blood cell count, lymphocyte count, monocyte count, and platelet count in patients without fever were higher than fever patients ($P < 0.05$). However, the levels of lactate dehydrogenase, C-reactive protein, and erythrocyte sedimentation rate in patients without fever were lower than those in patients with fever ($P < 0.05$) (Table 2). All of the 36 patients without fever had received the chest CT scan, 5 (13.9%) of them showed unilateral pneumonia, 29 (80.6%) of them showed Bilateral pneumonia (Fig. 1).

Table 2
Laboratory and chest radiography findings in patients infected by SARS-CoV-2

	All patients(n = 113)	Non-fever(n = 36)	Fever(n = 77)	P-value
White blood cell count, × 10⁹/L, IQR	4.6 (3.5, 5.7)	5.4 (4.4, 6.2)	4.1 (3.4, 5.4)	0.012
Neutrophil count, × 10⁹/L, IQR	2.9 (2.2, 3.5)	3.0 (2.3, 3.7)	2.9 (2.2, 3.4)	0.802
Lymphocyte count, × 10⁹/L, IQR	1.2 (0.8, 1.7)	1.70 (1.2, 2.4)	1 (0.7, 1.4)	< 0.001
Hemoglobin, g/L, IQR	131(121.0, 144.0)	130.5(123.5, 141.3)	131 (121.0, 145.0)	0.753
Monocyte count, × 10⁹/L, IQR	0.4 (0.3, 0.4)	0.4(0.3, 0.5)	0.3 (0.2, 0.4)	0.009
Platelet count, × 10⁹/L, IQR	163(139.0, 228.0)	216(169.5, 268.3)	158 (131.0, 184.0)	0.032
Prothrombin time, s, IQR	12 (11.1, 12.5)	11.6 (11.1, 12.3)	12(11.1, 12.5)	0.087
Activated partial thromboplastin time, s, IQR	32.8 (30.3, 35.0)	31.8 (30.1, 35.7)	32.9 (30.6, 34.9)	0.520
D-dimer, ug/mL, IQR	0.2 (0.1, 0.4)	0.2(0.1, 0.4)	0.2 (0.1, 0.4)	0.728
Albumin, g/L, IQR	38.3(35.5, 41.5)	41 (38.8, 43.1)	37 (34.7, 39.1)	0.854
Alanine aminotransferase, U/L, IQR	20(14.61, 27.80)	15.7 (11.81, 25.25)	21.8 (17.0, 29.0)	0.014
Aspartate aminotransferase, U/L, IQR	25 (20.0, 33.0)	24.4 (17.1, 28.0)	26 (21.0, 33.0)	0.067
Total bilirubin, mmol/L, IQR	11 (8.6, 15.4)	10 (7.2, 14.4)	11.3 (9.2, 15.4)	0.337
Direct bilirubin, mmol/L, IQR	4 (2.8, 5.5)	3.5 (2.4, 5.0)	4 (3.1, 5.6)	0.224
Creatinine, μmol/L, IQR	53 (40.7, 66.1)	51.5(41.8, 65.9)	54 (40.7, 67.0)	0.690
Lactate dehydrogenase, U/L, IQR	172(145.0, 208.0)	151 (124.8,176.3)	184.3 (150.0,235.0)	0.001
Creatine kinase, U/L, IQR	76(52.0, 113.0)	73.5 (45.7, 87.2)	76 (53.0, 124.0)	0.086
C-reactive protein, mg/L, Mean (SD)	13.2 (4.2, 35.0)	4 (1.1, 13.0)	19.8(8.6, 39.)	< 0.001
Procalcitonin, ng/mL, IQR	0.05 (0.05, 0.05)	0.05 (0.05, 0.05)	0.05 (0.05, 0.05)	0.862

Data are n (%) unless specified otherwise. IQR, interquartile range.

	All patients(n = 113)	Non-fever(n = 36)	Fever(n = 77)	P-value
Erythrocyte sedimentation rate, mm/h, IQR	42(16.0, 70.0)	23 (11.0, 59.50)	48 (27.0, 72.0)	0.014
Unilateral pneumonia	11 (9.7%)	5 (13.9%)	6 (7.8%)	0.518
Bilateral pneumonia	93 (82.3%)	29 (80.6%)	64 (83.1%)	
Data are n (%) unless specified otherwise. IQR, interquartile range.				

Complications and treatment

During hospitalization, 14 (12.4%) of patients developed into ARDS and one (0.9%) patients developed into AKI. None of the patients without fever developed into ARDS or AKI compared with fever patients (0% vs 18.2%, $P = 0.006$) (Table 3). For the patients without fever, all of them received the oxygen support of the nasal cannula. In 14 fever patients with ARDS, 10 of them received high flow high-flow nasal cannula oxygen, and 3 of them received invasive ventilation (1patient was given extracorporeal membrane oxygenation). Most of the cases were given antiviral treatment and traditional Chinese medicine treatment in both patients without fever and fever patients. 12 (33.4%) patients without fever received antibiotic treatment which was less than 51(66.2%) of fever patients ($P = 0.001$). Additionally, systematic corticosteroid and gamma globulin treatment were less used in patients without fever compared with fever patients ($P < 0.001$).

Table 3
Treatments and outcomes in patients infected by SARS-CoV-2

	All patients(n = 113)	Non-fever(n = 36)	Fever(n = 77)	P-value
Complications				
Acute respiratory distress syndrome	14 (12.4%)	0 (0.0%)	14 (18.2%)	0.006
Acute kidney injury	1 (0.9%)	0 (0.0%)	1 (1.3%)	0.492
Treatment				
Antiviral therapy	104 (92.0%)	32 (89.0%)	72 (93.5%)	0.398
Antibiotic therapy	63 (55.8%)	12 (33.4%)	51 (66.2%)	0.001
Use of corticosteroid	42 (37.2%)	3 (8.3%)	39 (50.7%)	< 0.001
Gamma globulin	38 (33.6%)	3 (8.3%)	35 (45.5%)	< 0.001
Continuous renal replacement therapy	1 (0.9%)	0 (0.0%)	1 (1.3%)	0.492
Traditional Chinese medicine treatment	109 (96.5%)	36 (100.0%)	73 (94.8%)	0.164
Oxygen support				
Nasal cannula	100 (88.5%)	36 (100.0%)	64 (83.1%)	0.009
High-flow nasal cannula	10 (8.9%)	0 (0.0%)	10 (13.0%)	0.024
Non-invasive ventilation	1 (0.9%)	0 (0.0%)	1 (1.3%)	0.492
Invasive mechanical ventilation	2 (1.8%)	0 (0.0%)	2 (2.6%)	0.329
Invasive mechanical ventilation and ECMO	1 (0.9%)	0 (0.0%)	1 (1.3%)	0.492
Prognosis				0.834
Hospitalization	83 (73.5%)	28 (77.8%)	55 (71.4%)	
Discharge	28 (24.8%)	8 (22.2%)	20 (26.0%)	
Death	2 (1.8%)	0 (0.0%)	2 (2.6%)	

Data are n (%) unless specified otherwise. ECMO, extracorporeal membrane oxygenation.

Outcomes

As of Feb 22, 2020, 28 patients have been discharged and two patients died (1.8%). A total of 83 patients are still hospitalized. Although two of the fever patients were dead, the prognosis between without fever and fever patients had no difference follow up to Feb 22, 2020. Discharge health is based on fever reduction for at least three days, and there is better evidence that chest X-rays and the virus clear samples from the lower respiratory tract.

Discussion

To our knowledge, this is the first study reported the clinical features of patients without fever on admission. Previous studies had reported that fever was the most common symptom of patients with COVID-19, whereas the symptoms without fever were in a minority in Wuhan[6,7]. Recently, several studies suggested that the symptoms of patients without fever were increasing outside Wuhan[9,10]. In this study, the percentage of patients without fever was more than in previous studies. The reason for this may be related to the early screen for SARS-CoV-2 infection in the large scales of individuals during the incubation period and the local government's comprehensive management. Moreover, recent study[7] showed that one reason for the rapid spread may be also associated with the atypical symptoms in the initial stage in cases with SARS-CoV-2 infection, including patients without fever.

In our study, the days of onset illness to admission in patients without fever were shorter than those in fever patients, which suggested that the time of confirmed diagnosis with SARS-CoV-2 infection in patients without fever was earlier than in fever patients. An observation study suggested that days onset of symptoms to hospital admission of COVID-19 were shorter in non-ICU patients than in ICU patients, and the age and complications were the risk factors of worse clinical outcome[7]. Our data demonstrated that the fever patients were more tend to develop into ARDS compared with patients without fever, and the clinical characteristic of patients with fever was more severe than those without fever. That could be explained by that the patients without fever were younger and rarely had underlying disease than fever patients, which was also consistent with the previous studies[7,8].

Patients with any underlying disease were more likely to have a bacterial infection due to impaired immune function[15]. Evidence illuminated that lymphocytes, especially T lymphocytes, were the main targets by SARS-CoV-2 as well as SARS-CoV[6]. Compared with patients without fever, the percentage of white blood cell count ($\leq 4\times10^{9}$/l) and lymphocyte count($< 1\times10^{9}$/l) were slightly lower in fever patients. The decrease of lymphocyte count was related to the progress of the disease[15]. In addition, C-reactive protein and erythrocyte sedimentation rate were associated with inflammation reactions, which were significantly higher in severe patients. Therefore, compared with patients without fever, more patients with fever were given antibiotic therapy. To date, no specific treatment of COVID-19 has been recommended except for symptomatic supportive treatment[7,9]. In our study, some patients were also given corticosteroid or gamma globulin on the basis of the difference in the severity of the disease. However, further research needs to assess whether systemic corticosteroid and gamma globulin therapy are beneficial for patients with COVID-19.

There are several limitations to our study. First, we just selected 113 patients. Due to the continuous admission of patients, we only collected data from most patients during this period. Secondly in this study, data on the treatment and outcome of these patients have not been finalized, as most of them are still hospitalized. Third, since the patients were all from Changsha, the clinical characteristics of COVID-19 may be different from other areas, which may result in biases of observation. Finally, we cannot get the specific Ct value of SARS-CoV-2 test, so we do not know that the viral value can affect these patients' symptom of fever or non-fever.

Conclusions

In this single-center retrospective study, out of 113 patients with SARS-CoV-2 infection, patients without fever accounted for 31.9% in total. Compared with the onset of illness symptoms of patients without fever, more complications may be developed with fever patients in Changsha. The clinical prognosis of patients without fever may be better than those of patients with fever on admission.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University (Changsha, China) (NO. LYF2020044) and informed consent was waived due to its retrospective nature.

Consent for publication

All authors have read the manuscript and have approved the publication on the European Journal of Medical Research.

Availability of data and materials

The datasets used and/or analyzed during the present study were availed by the corresponding author on reasonable request.

Competing interests

None

Funding

This work was supported by Special Emergency Treatment for Novel Coronavirus Pneumonia, Science and Technology Projects of Hunan province, China. (2020SK3004 to Dr. Chai)

Authors' contributions

N.D., C.G, and F.T collected epidemiological and clinical data. T. Guo is responsible for summarizing all data related to the virus. N. Ding, Y. Zhou, G. Yang and X. Chai take responsibility for the accuracy of the data analysis. N. Ding, Y. Zhou and G. Yang contributed equally and share the second authorship. Y. Zhou drafted the manuscript. G. Yang revised the final manuscript. X.C. is responsible for summarizing all epidemiological and clinical data.

Acknowledgments

We thank all the patients involved in the study.

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Figures

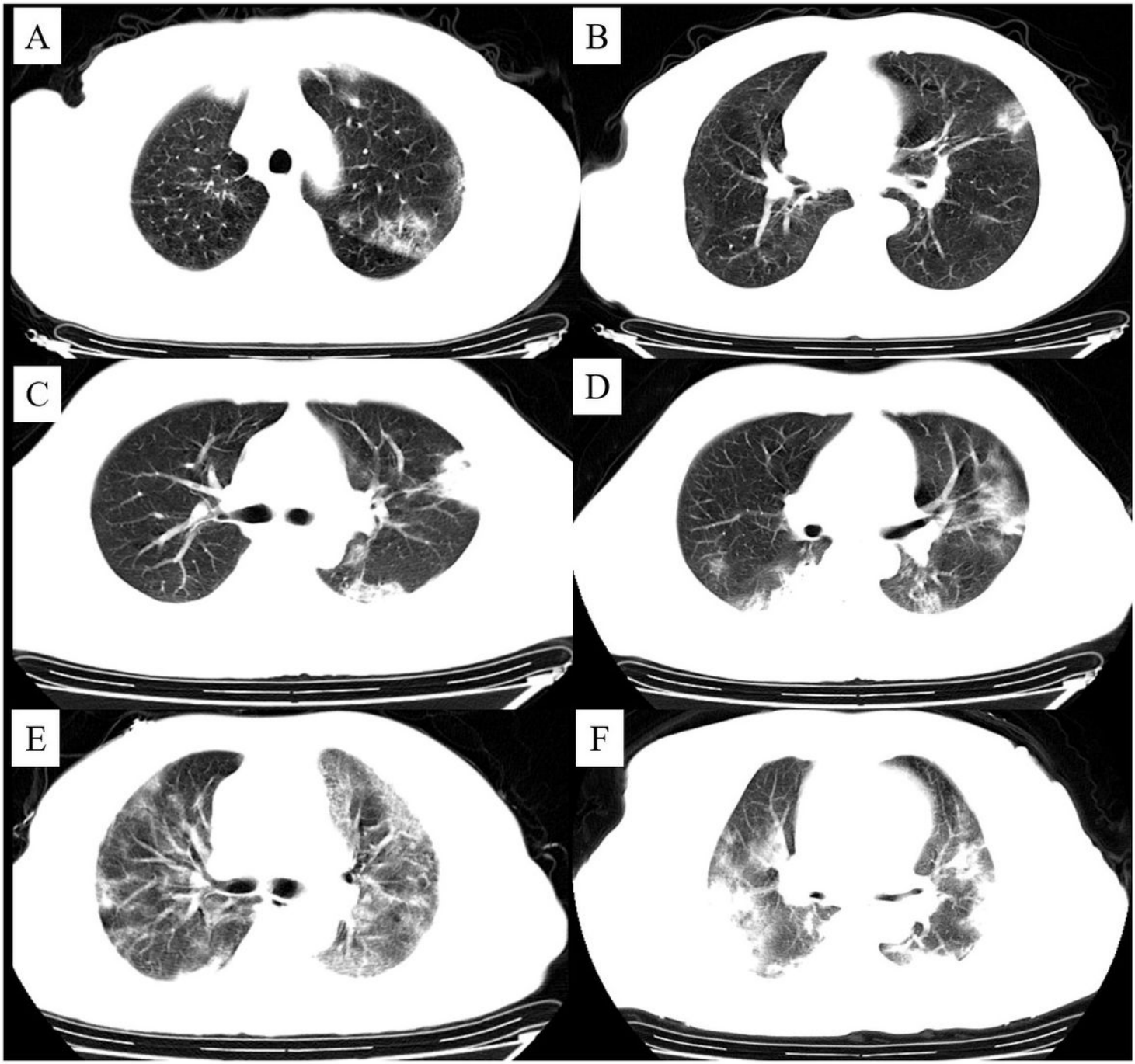

Figure 1

Chest images of patients infected by SARS-CoV-2 on admission. (A) and (B) CTs from 72 years old man without fever, showing patchy ground-glass opacity. (C) and (D) CTs from 41 years old woman with fever, showing multiple mottling ground-glass opacities. (E) and (F) CTs from 70 years old woman and 67 years old women with ARDS, showing multiple mottling ground-glass opacities and consolidation, especially around the peripheral parts.