Clinical Infectious Diseases

MAJOR ARTICLE

Clinical Characteristics of Refractory Coronavirus Disease 2019 in Wuhan, China

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Background. Since December 2019, coronavirus disease 2019 (COVID-19), caused by severe adult respiratory syndrome coronavirus 2, occurred in Wuhan, and rapidly spread throughout China. This study aimed to clarify the characteristics of patients with refractory COVID-19.

Methods. In this retrospective single-center study, we included 155 consecutive patients with confirmed COVID-19 in Zhongnan Hospital of Wuhan University from 1 January to 5 February. The cases were divided into general and refractory COVID-19 groups according to the clinical efficacy of treatment after hospitalization, and the differences between groups were compared.

Results. Compared with patients with general COVID-19 (45.2%), those with refractory disease were older, were more likely to be male, and had more underlying comorbid conditions, a lower incidence of fever, higher maximum temperatures among patients with fever, higher incidences of shortness of breath and anorexia, more severe disease assessment at admission, higher neutrophil, aspartate aminotransferase, lactate dehydrogenase, and C-reactive protein levels, lower platelet counts and albumin levels, and higher incidences of bilateral pneumonia and pleural effusion ($P < .05$). Patients with refractory COVID-19 were more likely to receive oxygen, mechanical ventilation, expectorant, and adjunctive treatment, including corticosteroids, antiviral drugs, and immune enhancers ($P < .05$). Considering the factors of disease severity at admission, mechanical ventilation, and intensive care unit transfer, patients with refractory COVID-19 were also more likely to be male, have manifestations of anorexia on admission, and receive oxygen, expectorant, and adjunctive agents ($P < .05$).

Conclusion. In nearly 50% of patients with COVID-19 obvious clinical and radiological remission was not achieved within 10 days after hospitalization. Male, anorexia, and no fever at admission was predictive of poor treatment efficacy.

Keywords. COVID-19; SARS–CoV-2; clinical efficacy; predictors.

Since December 2019, an outbreak of pneumonia of unknown cause occurred in Wuhan, China and rapidly spread throughout the country [1–3]. The pathogen was confirmed to be a distinct clade from the β-coronaviruses associated with the Middle East syndrome (MERS) and severe acute respiratory syndrome (SARS) [4, 5]. The novel virus was officially named SARS coronavirus 2 (SARS–CoV-2), with the disease termed coronavirus disease 2019 (COVID-19) [6]. Epidemiological data demonstrated person-to-person transmission in hospital and family settings [7, 8] The high infectivity of COVID-19 resulted in a rapid increase of new cases and a worldwide outbreak [9, 10].

Up to now, no antiviral drug with definite effects has been found, and a focus on symptomatic support has been the main therapeutic strategy. In some patients, treatment efficacy after hospitalization was poor, with ensuing development of severe pneumonia, pulmonary edema, acute respiratory distress syndrome, or multiple organ failure. At present, information regarding the clinical characteristics of refractory COVID-19 was scarce. In the study, we aimed to clarify the characteristics of patients with refractory COVID-19.

METHODS

Study Design and Participants

This retrospective study was approved by the ethics committee of Zhongnan Hospital of Wuhan University (no. 2020011). All consecutive patients with confirmed COVID-19 admitted to Zhongnan Hospital of Wuhan University from 1 January to 5 February were enrolled, and written or oral informed consent was obtained.

Definitions

COVID-19 was confirmed by detecting SARS–CoV-2 RNA in throat swab samples using a virus nucleic acid detection kit according to the manufacturer's protocol (Shanghai BioGerm

Received 11 February 2020; editorial decision 9 March 2020; published online 16 March 2020.

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Clinical Infectious Diseases® 2021;73(11):e4208–13

DOI: 10.1093/cid/ciaa270

Medical Biotechnology). For hospitalized patients, general COVID-19 was defined according to following criteria: (1) obvious alleviation of respiratory symptoms (eg, cough, respiratory distress, and shortness of breath) after treatment, (2) maintenance of normal body temperature for ≥3 days without the use of corticosteroid or antipyretics, (3) improvement in radiological abnormalities seem with chest computed tomography (CT) or radiography after treatment, and (4) a hospital stay of ≤10 days. Otherwise, it was classified as refractory COVID-19. Figure 1 shows the chest CT findings in a patient with refractory COVID-19.

In severity assessment at admission, illness was considered serious if ≥1 of the following criteria was met: (1) respirations ≥30/min; (2) pulse oximeter oxygen saturation ≤93% at rest; (3) ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ≤300 mm Hg (1 mm Hg = 0.133 kPa); it was considered critical illness if ≥1 of the following criteria was met: (1) respiratory failure with receipt of mechanical ventilation; (2) shock; (3) combined with failure of other organs and receipt of care in the intensive care unit (ICU).

Data Collection

A COVID-19 case report form was designed to document primary data regarding demographic, clinical, laboratory, radiological, and therapeutic characteristics from electronic medical records. The following information was extracted for each patient: age, sex, medical history, COVID-19–related exposure history, symptoms, signs, severity assessment at admission, laboratory findings, chest CT or radiographic findings, and treatment (eg, antivirals, corticosteroids, and respiratory support).

Statistical Analysis

Categorical data were recorded as percentages, and continuous data as medians with interquartile ranges (IQRs). Nonparametric comparative tests were used for continuous data and χ^2 tests for categorical data to compare variables between groups. Differences were considered statistically significant at $P < .05$. The variables identified by means of univariate analysis ($P < .05$) were analyzed using multivariate analysis, in which these variables were adjusted by 3 main factors (disease severity at admission, mechanical ventilation, and ICU transfer). All statistical analyses were performed using SPSS Statistics software, version 21.0.

RESULTS

Baseline Characteristics

A total of 155 patients with COVID-19 pneumonia were included in the current study (Table 1). The median (IQR) age was 54 (42–66) years, and 86 patients (55.5%) were male. Six patients (3.9%) were current smokers, and 37 (23.9%) had a history of exposure to source transmission (Huanan seafood market or infected individuals). Seventy-one patients (45.8%) had ≥1 comorbid conditions, including hypertension (23.9%), diabetes (9.7%), and cardiovascular diseases (9.7%). Fever (81.3%), fatigue (73.2%), cough (62.6%), and myalgia/arthralgia (61.0%) were the most common symptoms, whereas digestive symptoms were rare. At admission, 55 (35.5%) and 37 (23.9%) of the patients were categorized as having serious and critical illness, respectively.

After hospitalization, 70 patients (45.2%) reached obvious clinical and radiological remission within 10 days. Compared with patients with general COVID-19, those with refractory disease were significantly older ($P < .001$) and more likely to be male ($P = .01$). Meanwhile, with patients refractory COVID-19 have more underlying comorbid conditions ($P < .001$,) including diabetes ($P = .04$), cardiovascular diseases ($P = .002$), and cerebrovascular diseases ($P = .04$), a lower incidence of fever ($P = .01$), higher levels of maximum temperature among patients with fever ($P = .005$), higher incidence of shortness of breath ($P = .009$) and anorexia ($P = .005$), and more severe disease assessment at admission ($P < .001$).

Laboratory and Radiological Findings

At admission, the majority of patients had lymphopenia and abnormalities of neutrophils, platelets, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase (LDH), and inflammatory biomarkers, as shown in Table 2. Chest CT or radiography showed bilateral pneumonia in 143 patients (92.3%), and pleural effusion in 16 (10.3%).

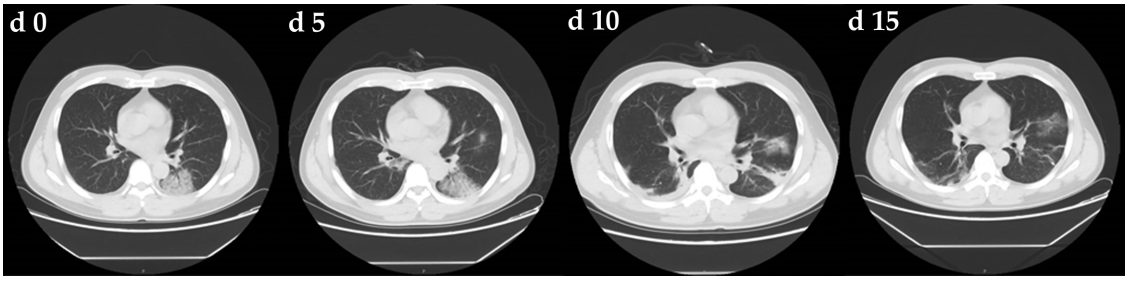

Figure 1. Chest computed tomographic images of a 42-year-old patient with refractory coronavirus disease 2019 pneumonia, obtained on 19 January (day 0), 24 January (day 5), 29 January (day 10), and 3 February (day 15) 2020. The patient reached remission on day 15.

Table 1. Baseline Characteristics of Patients with Refractory Coronavirus Disease 2019

Characteristic	Patients, No. (%)[a]			*P* Value
	Total (n = 155)	General COVID-19 (n = 70)	Refractory COVID-19 (n = 85)	
Age, median (IQR), y	54 (42–66)	46 (35–56)	61 (51–70)	<.001
Male sex	86 (55.5)	31 (44.3)	55 (64.7)	.01
Current smoker	6 (3.9)	2 (2.9)	4 (4.7)	.86
Exposure to source transmission	37 (23.9)	16 (22.9)	21 (24.7)	.79
Comorbid conditions, median (IQR), no.	0 (0–1)	0 (0–1)	1 (0–1)	<.001
Comorbid condition				
Hypertension	37 (23.9)	15 (21.4)	22 (25.9)	.52
Diabetes	15 (9.7)	3 (4.3)	12 (14.1)	.04
Cardiovascular disease	15 (9.7)	0 (0)	14 (16.5)	.002
Cerebrovascular disease	7 (4.5)	0 (0)	7 (8.2)	.04
Cancer	7 (4.5)	2 (2.9)	5 (5.9)	.61
Chronic liver disease	7 (4.5)	2 (2.9)	5 (5.9)	.61
Chronic renal disease	6 (3.9)	2 (2.9)	4 (4.7)	.86
COPD	5 (3.2)	0 (0)	4 (4.7)	.49
Tuberculosis	3 (1.9)	0 (0)	3 (3.5)	.32
HIV	2 (1.3)	0 (0)	2 (2.4)	.56
Symptoms and signs	3 (2–4)	3 (2–4)	3 (2–4)	.82
Fever	126 (81.3)	63 (90.0)	63 (74.1)	.01
Maximum temperature, median (IQR), °C	38.5 (38.0–39.0)	38.3 (38.0–39.0)	38.8 (38.1–39.2)	.005
Cough	97 (62.6)	43 (61.4)	54 (63.5)	.79
Chest distress	61 (39.4)	22 (31.4)	39 (45.9)	.07
Fatigue	60 (73.2)	33 (75.0)	27 (71.1)	.69
Shortness of breath	50 (32.3)	15 (21.4)	35 (41.2)	.009
Myalgia or arthralgia	50 (61.0)	28 (63.6)	22 (57.9)	.60
Anorexia	26 (31.7)	8 (18.2)	18 (47.4)	.005
Headache	8 (9.8)	3 (6.8)	5 (13.2)	.55
Diarrhea	7 (4.5)	2 (2.9)	5 (5.9)	.61
Abdominal pain	3 (1.9)	0 (0)	2 (2.4)	>.99
Nausea	3 (3.7)	2 (4.5)	0 (0)	>.99
Vomiting	3 (3.7)	0 (0)	2 (5.3)	.90
Chest pain	3 (3.7)	2 (4.5)	0 (0)	>.99
Dizziness	2 (2.4)	0 (0)	1 (2.6)	>.99
Dyspnea	2 (2.4)	0 (0)	2 (5.3)	.41
Severity assessment at admission				
Stable	63 (40.6)	43 (61.4)	20 (23.5)	<.001
Serious	55 (35.5)	24 (34.3)	31 (36.5)	
Critical	37 (23.9)	3 (4.3)	34 (40.0)	

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Data represent no. (%) of patients unless otherwise specified.

Compared with patients with general COVID-19, those with refractory disease had higher levels of neutrophils (P = .02), aspartate aminotransferse (P = .004), LDH (P = .02) and C-reactive protein (CRP) (P = .001), and lower platelet counts (P = .049) and albumin levels (P = .001). Moreover, patients with refractory COVID-19 had a higher incidence of bilateral pneumonia (P = .03) and pleural effusion (P = .006).

Treatment

Of the 155 patients, 102 patients (65.8%) received oxygen, and 36 (23.2%) mechanical ventilation (Table 3). Eighty-seven patients (56.1%) received expectorant, 79 (51%) received intravenous corticosteroid, 45 (29%) received special antiviral treatment (arbidol, 20.0%, lopinavir and ritonavir, 17.4%, interferon inhalation, 19.4%), 14 (9%) received immune enhancing treatment (thymalfasin, 7.1%; immunoglobulin, 5.8%). The frequency of combined administration of adjunctive agents was 18.7% for corticosteroid plus antiviral drug, 8.4% for corticosteroid plus immune enhancer, 6.5% for antiviral drug plus immune enhancer, and 5.8% for the all. Patients with refractory COVID-19 were more likely than those with general COVID-19 to receive oxygen (P < .001), mechanical ventilation (P < .001), expectorant (P < .001), corticosteroid (P < .001), lopinavir and ritonavir (P = .008), and immune enhancers (P = .01), especially thymalfasin (P = .005).

Table 2. Laboratory and Radiological Findings in Patients with Refractory Coronavirus Disease 2019

Finding	Normal Range	Median Value (IQR)			*P* Value
		Total (n = 155)	General (n = 70)	Refractory (n = 85)	
Blood cells counts, $\times 10^9$/L					
White blood cells	3.5–9.5	4.36 (3.30–6.03)	4.16 (3.33–5.18)	4.65 (3.14–6.84)	.06
Neutrophils	1.8–6.3	2.89 (1.97–4.41)	2.72 (1.88–3.53)	3.28 (1.99–5.08)	.02
Lymphocytes	1.1–3.2	0.90 (0.66–1.11)	0.97 (0.79–1.28)	0.80 (0.56–1.04)	.10
Platelets	125–350	170 (127–208)	179 (146–219)	159 (119–202)	.049
Blood biochemistry					
ALT, U/L	9–50	23 (16–38)	20 (15–33)	28 (17–42)	.54
AST, U/L	15–40	32 (24–48)	32 (23–38)	37 (25–65)	.004
Albumin, g/L	40–55	38 (34–41)	39 (36–42)	36 (32–40)	.001
Globulin, g/L	20–30	28 (26–31)	29 (26–32)	28 (26–31)	.77
Creatinine, μmol/L	64–104	71 (60–87)	65 (58–78)	79 (65–96)	.16
LDH, U/L	125–243	277 (195–404)	241 (198–338)	293 (193–434)	.02
Creatine kinase, U/L	<171	93 (60–139)	100 (60–146)	89 (60–140)	.56
Coagulation function					
D-dimer, ng/mL	0–500	191 (123–358)	178 (100–289)	213 (126–447)	.29
Infection-related biomarkers					
ESR, mm/h	0–15	25 (14–47)	23 (13–41)	28 (16–51)	.09
CRP, mg/L	0–10	33 (16–74)	23 (10–47)	46 (22–106)	.001
Interleukin 6, pg/mL	0–7	45 (17–96)	23 (9–57)	64 (31–165)	.26
Procalcitonin, ng/mL	<0.05	0.05 (0.05–0.09)	0.05 (0.05–0.05)	0.05 (0.05–0.19)	.30
Coinfected respiratory pathogens, No. (%)	NA	12 (7.7)	3 (4.3)	9 (10.6)	.14
Parainfluenza virus	NA	3 (1.9)	0 (0)	2 (2.4)	>.99
Syncytial virus	NA	3 (1.9)	0 (0)	2 (2.4)	>.99
Adenovirus	NA	3 (1.9)	0 (0)	3 (3.5)	.32
Mycoplasma	NA	2 (1.3)	1 (1.4)	1 (1.2)	>.99
Influenza virus A	NA	2 (1.3)	0 (0)	2 (2.4)	.56
Influenza virus B	NA	2 (1.3)	0 (0)	2 (2.4)	.56
Chest CT or radiographic finding, No. (%)					
Bilateral distribution	NA	143 (92.3)	61 (87.1)	82 (96.5)	.03
Pleural effusion	NA	16 (10.3)	2 (2.9)	14 (16.5)	.006

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CT, computed tomographic; ESR, erythrocyte sedimentation rate; IQR, interquartile range; LDH, lactate dehydrogenase; NA, not available.

[a]Data represent median (IQR) unless otherwise specified.

Multivariate Analysis of Factors Associated With COVID-19 Refractoriness

Twenty-four significant factors in univariate analysis were put into the multivariate analysis to identify reliable predictive factor for COVID-19 refractoriness (Table 4). The results indicated male sex (odds ratio, 2.206; 95% confidence interval, 1.012–4.809; $P = .047$) and anorexia at admission (3.921; 1.144–13.443;

Table 3. Treatment of Patients With Refractory Coronavirus Disease 2019 Disease

Treatment	Patients, No. (%)			*P* Value
	Total (n = 155)	General COVID-19 (n = 70)	Refractory COVID-19 (n = 85)	
Oxygen	102 (65.8)	30 (42.9)	72 (84.7)	<.001
Mechanical ventilation	36 (23.2)	0 (0)	35 (41.2)	<.001
Expectorant	87 (56.1)	24 (34.3)	63 (74.1)	<.001
Corticosteroid	79 (51.0)	24 (34.3)	55 (64.7)	<.001
Antiviral treatment	45 (29.0)	18 (25.7)	27 (31.8)	.41
Arbidol	31 (20.0)	14 (20.0)	17 (20.0)	>.99
Lopinavir and ritonavir	27 (17.4)	6 (8.6)	21 (24.7)	.008
Interferon inhalation	30 (19.4)	9 (12.9)	21 (24.7)	.06
Immune enhancer	14 (9.0)	2 (2.9)	12 (14.1)	.01
Thymalfasin	11 (7.1)	0 (0)	11 (12.9)	.005
Immunoglobulin	9 (5.8)	2 (2.9)	7 (8.2)	.28

Abbreviation: COVID-19, coronavirus disease 2019.

Table 4. Multivariate Analysis of Factors Associated with Refractory Coronavirus Disease 2019

Factor	B	SE	Wald	*P* Value	OR (95% CI)
Age	0.02	0.01	2.73	.10	1.023 (.996–1.052)
Male	0.79	0.40	3.96	.047	2.206 (1.012–4.809)
Comorbid conditions	0.41	0.26	2.41	.12	1.501 (.899–2.505)
Diabetes	0.76	0.76	1.00	.32	2.138 (.483–9.471)
Cardiovascular disease	2.13	1.10	3.74	.053	8.377 (.973–72.15)
Cerebrovascular disease	20.21	13 501.26	0.00	>.99	NA
Fever	−1.10	0.53	4.26	.04	0.331 (.116–.945)
Maximum temperature	0.33	0.27	1.49	.22	1.393 (.818–2.371)
Shortness of breath	−0.42	0.52	0.66	.42	0.655 (.236–1.822)
Anorexia	1.37	0.63	4.72	.03	3.921 (1.144–13.443)
Blood test					
Neutrophils	0.05	0.09	0.28	.60	1.051 (.876–1.261)
Platelets	0.00	0.00	1.15	.28	0.997 (.992–1.002)
Aspartate aminotransferase	0.00	0.01	0.00	.97	1.000 (.984–1.0150)
Albumin	−0.02	0.04	0.33	.56	0.980 (.914–1.050)
Lactate dehydrogenase	0.00	0.00	0.95	.33	0.998 (.994–1.002)
CRP	0.01	0.01	2.05	.15	1.009 (.997–1.021)
Chest CT or radiographic findings					
Bilateral distribution	0.07	0.77	0.01	.92	1.074 (.240–4.817)
Pleural effusion	1.17	0.85	1.89	.17	3.217 (.607–17.036)
Treatment					
Oxygen	1.12	0.48	5.38	.02	3.065 (1.189–7.897)
Expectorant	0.99	0.41	5.82	.02	2.688 (1.204–6.003)
Corticosteroid	0.80	0.39	4.14	.04	2.232 (1.030–4.838)
Lopinavir and ritonavir	2.64	0.74	12.68	<.001	13.975 (3.274–59.655)
Immune enhancer	2.19	0.84	6.80	.009	8.959 (1.724–46.564)
Thymalfasin	21.27	10 401.18	0.00	>.99	NA

Abbreviations: B, partial regression coefficient; CI, confidence interval; CRP, C-reactive protein; CT, computed tomographic; NA, not available; OR, odds ratio; SE, standard error; Wald, Wald test.

$P = .03$) as the risk factors for disease refractoriness, and fever at admission as the protective factor (0.331; .116–.945; $P = .03$). Moreover, patients with refractory COVID-19 were more likely to receive oxygen (odds ratio, 3.065; 95% confidence interval, 1.189–7.897; $P = .02$), expectorant (2.688; 1.204–6.003; $P = .02$), corticosteroids (2.232; 1.030–4.838; $P = .04$), lopinavir and ritonavir (13.975; 3.274–59.655; $P < .001$), and immune enhancers (8.959; 1.724–46.564; $P = .009$).

DISCUSSION

Since the outbreak of COVID-19, the number of patients had increased dramatically, and some patients had died of the disease. It had been reported that the median hospital stay of patients with COVID-19 pneumonia was 10 days [11]. In the study, the median (IQR) hospital stay was 10.5 (8–16) days for patients who died (n = 22) and 10 (7–15) days for those who recovered. After 10 days or longer treatment, some patients had an exacerbation in clinical symptoms or radiological findings. Therefore, clinicians should identify refractory and critical illness quickly and provide early interventions, which was conducive to shortening the course of disease, preventing disease progression, and reducing the mortality rate. Up to now, large-scale analyses of clinical characteristics of refractory COVID-19 had been scarce. In the current study, 155 patients with COVID-19 were divided into general and refractory groups. We compared clinical features, imaging manifestations, serological examination results, and treatment between 2 groups.

We found that despite a similar proportion of male and female patients in COVID-19, male patients had a higher incidence of refractory disease. The mean age of patients with refractory COVID-19 was significantly older than that of patients with general COVID-19. In addition, 49% of patients with COVID-19 had other chronic diseases, which was consistent with recent reports [11, 12]. Thus, it could be seen that elderly male patients with certain chronic diseases were more difficult to treat, resulting in long hospital stays and slow recoveries.

COVID-19 was similar to SARS and MERS in some clinical manifestations. In patients with COVID-19, fever, cough, and myalgia were the most common symptoms, followed by shortness of breath and respiratory distress. However, upper respiratory tract symptoms (eg, nasal congestion, nasal discharge, and sore throat) and gastrointestinal symptoms (eg, abdominal pain and diarrhea) were relatively rare. Fever occurred in 98%–100% of patients with SARS or MERS, compared with 81.3% of patients with COVID-19 in this study [13, 14], and 18.7% of patients presented no fever at admission, suggesting that the

absence of fever could not rule out the possibility of COVID-19. If fever was used to trigger screening/testing for COVID-19, a substantial number of patients without fever might be missed. It was worth noting that only 74.1% of patients with refractory disease presented with fever, a significantly lower proportion than in those with general COVID-19. These findings suggested that patients with a slow or muted response to the virus were more likely to have severe disease.

With regard to radiological findings, all patients in the current study had abnormal chest CT results. The lung lesions manifested mainly as ground glass–like and patchy shadows on CT scans. Patients with refractory COVID-19 had a higher incidence of pleural effusion than those with general COVID-19, suggesting a more obviously inflammatory response in the lung. These findings also indicated that SARS–CoV-2 mainly targets the cells in the lower respiratory tract.

For laboratory findings, 73.5% of patients with COVID-19 had lymphopenia, but no significant difference was detected between the groups. In patients with refractory COVID-19, blood LDH and CRP levels increased significantly. LDH is an inflammatory predictor in many pulmonary diseases, such as obstructive disease and microbial and interstitial pulmonary disease [15, 16]. CRP has been widely used as a biochemical indicator for inflammation, reflecting the acute severe systemic inflammatory response caused by viral infection. In a recent study, patients with COVID-19 treated in the ICU had higher levels of LDH and CRP than those not treated in the ICU [11]. These findings indicate that SARS–CoV-2 might act mainly on lymphocytes, involving cell-mediated immunity and cytokine storms. The immunological mechanism needs further study.

Currently, there are no published data indicating that any of the antiviral agents used in this outbreak have had a significant impact on outcome. Most patients recovered despite receiving antiviral and anti-inflammatory treatments, but recovery was due more to supportive care with oxygen, fluid management, mechanical ventilation as needed, pressor support, and ICU management. In the current study, patients with refractory COVID-19 were more likely than those with general COVID-19 to receive oxygen therapy, ventilator support, and a variety of adjunctive agents, indicating treatment insensitivity for these patients and resulting in a delay in the clinical course.

The current study had some limitations. First, selection bias might occur for this retrospective study, and further prospective studies are needed. Second, this study was based on a single center, and a large-scale nationwide study is needed

In conclusion, in nearly 50% of patients with COVID-19, clinical and radiological remission could not be reached within 10 days after hospitalization. The presence of anorexia and no fever at admission was predictive of poor treatment efficacy.

Notes

Acknowledgments. The authors thank the patients, the nurses, and the physicians who provided care for the patients, and the investigators at Zhongnan Hospital of Wuhan University.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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