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ARTICLE

Clinical and Autoimmune Characteristics of Severe and Critical Cases of COVID-19

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In this study we report on the clinical and autoimmune characteristics of severe and critical novel coronavirus pneumonia caused by severe acute respiratory syndrome–associated coronavirus 2 (SARS-CoV-2). The clinical, autoimmune, and laboratory characteristics of 21 patients who had laboratory-confirmed severe and critical cases of coronavirus disease 2019 (COVID-19) from the intensive care unit of the Huangshi Central Hospital, Hubei Province, China, were investigated. A total of 21 patients (13 men and 8 women), including 8 (38.1%) severe cases and 13 (61.9%) critical cases, were enrolled. Cough (90.5%) and fever (81.0%) were the dominant symptoms, and most patients (76.2%) had at least one coexisting disorder on admission. The most common characteristics on chest computed tomography were ground-glass opacity (100%) and bilateral patchy shadowing (76.2%). The most common findings on laboratory measurement were lymphocytopenia (85.7%) and elevated levels of C-reactive protein (94.7%) and interleukin-6 (89.5%). The prevalence of anti–52 kDa SSA/Ro antibody, anti–60 kDa SSA/Ro antibody, and antinuclear antibody was 20%, 25%, and 50%, respectively. We also retrospectively analyzed the clinical and laboratory data from 21 severe and critical cases of COVID-19. Autoimmune phenomena exist in COVID-19 subjects, and the present results provide the rationale for a strategy of preventing immune dysfunction and optimal immunosuppressive therapy.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Viral effects and immune-mediated mechanisms are the two pathogeneses of severe acute respiratory syndrome–associated coronavirus (SARS-CoV) infection, and autoimmune responses have been found in SARS-CoV infection and SARS-CoV antigen can cross-react with autoantibodies in autoimmune diseases. In consideration of the high genetic similarity between SARS-CoV-2 and SARS-CoV, it is necessary to explore the immune-mediated mechanism of SARS-CoV-2 and to seek ways to prevent its spread.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ In this study we present the clinical and autoimmune characteristics of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ In these cases, the prevalence of autoimmune markers, including anti–52 kDa SSA/Ro antibody, anti–60 kDa SSA/Ro antibody, and antinuclear antibody was 20%, 25%, and 50%, respectively, and we also found that autoimmune phenomena were present in COVID-19 subjects.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The results provide the rationale for a strategy of prevention of dysfunction of immune and optimal immunosuppressive therapy for COVID-19 in the future.

Since the end of 2019, we have been witnessing the emergence of the coronavirus disease 2019 (COVID-19) outbreak and pandemic caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of April 16, 2020, 2,079,978 cases have been confirmed worldwide, including 83,797 confirmed cases and 3,352 deaths in China, and 1,996,181 confirmed cases and 133,861 deaths in countries other than China. Within the first 2 months of the COVID-19 outbreak, the new disease has demonstrated varying degrees of severity, with clinical characteristics having been reported in 1,099 laboratory-confirmed subjects from 552 hospitals in 30 provinces, autonomous regions, and municipalities in China.[1] However, it has not been reported on whether autoimmune phenomena exist in COVID-19 patients.

Yaqing Zhou and Tao Han contributed equally to this work.

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Viral effects and immune-mediated mechanisms are the two pathogeneses of severe acute respiratory syndrome–associated coronavirus (SARS-CoV) infection, and autoimmune responses have been found in SARS-CoV infection.[2] One study suggested that the SARS-CoV antigen can cross-react with autoantibodies in autoimmune diseases.[3] Therefore, autoimmune phenomena exist in SARS subjects. In consideration of the high genetic similarity between SARS-CoV-2 and SARS-CoV, it is necessary to explore the immune-mediated mechanism of SARS-CoV-2 and to seek ways to prevent its spread. In this study, we present the clinical and autoimmune characteristics of COVID-19 caused by SARS-CoV-2.

SUBJECTS AND METHODS

The present study was approved by the ethics committee of The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province, China, and the ethics committee of the Huangshi Central Hospital, Hubei Province, China. The investigation conformed to the ethical principles of the Declaration of Helsinki. Written informed consent was waived due to retrospective nature of the study and the urgent need to collect data regarding this disease.

Study participants

From January 28, 2020 to March 2, 2020, we enrolled 21 consecutive adult subjects (13 men and 8 women), aged 42–85 years, who had laboratory-confirmed severe and critical COVID-19. All patients were from the intensive care unit (ICU) of the Huangshi Central Hospital, Hubei Province, China. Of these subjects, 8 (38.1%) and 13 (61.9%) were diagnosed as severe and critical cases, respectively.

According to the sixth edition of *Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management*, issued by China's National Health Commission, the diagnostic criteria for the clinical classification of COVID-19 are as follows: (i) *mild*——clinical symptoms are mild and no pneumonia manifestation can be found on imaging; (ii) *ordinary*——symptoms such as fever and respiratory tract symptoms and pneumonia manifestations can be seen on imaging; (iii) *severe*——any of the following: respiratory distress, respiratory rate (RR) ≥30 breaths/min, oxygen saturation <93% at rest, arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FIO_2) ≤300 mmHg (1 mmHg = 0.133 kPa), or >50% lesion progression within 24–48 hours on pulmonary imaging; and (iv) *critical*——any of the following: respiratory failure in which mechanical ventilation is required, shock occurs, or complications with another organ failure that require monitoring and treatment in the ICU.[4]

Laboratory measurements

The number and proportion of red blood cells, white blood cells, and platelets, and their morphologic distributions were evaluated using a whole blood cell analyzer (XN 2000® (Sysmex®); Sysmex, Kobe, Japan).

The inflammation profiles, including hypersensitive C-reactive protein (mg/L), CRP (mg/L), procalcitonin (PCT, ng/mL), and interleukin-6 (IL-6, pg/mL) were measured using an automatic biochemical analyzer (Cobas 6000 c501; Roche, Mannheim, Germany).

Blood biochemical indicators, such as electrolytes, urea nitrogen (mM), creatinine (Cr, μM), estimated glomerular filtration rate (eGFR, mL/min), total serum bilirubin (μM), direct bilirubin (μM), indirect bilirubin (μM), total protein (g/L), albumin (g/L), globulin (mM), albumin/globulin ratio, aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), AST/ALT ratio, glutamyltransferase (U/L), alkaline phosphatase (U/L), and total bile acid (μM) were measured with a fully-automated analyzer (ADVIA 2400B immunoassay; Siemens Healthineers, Erlangen, Germany).

A coagulometer (BEXRM-A; Amelung, Lemgo, Germany) was used to perform comparative tests of coagulation indexes, consisting of prothrombin time (s), prothrombin activity (%), international normalized ratio (INR), activated partial thromboplastin time (s), fibrinogen (g/L), and D-dimer (μg/mL).

Anti–Scl-70 (RU/mL), anti–Jo-1 antibody (RU/mL), anticentromere B antibody (RU/mL), anti-SmD1 antibody (RU/mL), anti–60 kDa SSA/Ro antibody (RU/mL), anti–52 kDa SSA/Ro antibody (RU/mL), anti–U1-RNP antibody (RU/mL), anti-SSB antibody (RU/mL), antinuclear antibody (AU/mL), and anti–double-stranded DNA antibody (RU/mL) were determined using an automatic immunoassay analyzer (SMART 6500; Chongqing Keysmile Biological Technology Co.,Ltd., Chongqing, China).

Another analyzer (Cobas Fara; Roche Diagnostics, Mijdrecht, The Netherlands) was used to test anti–streptolysin O (IU/mL), rheumatoid factor (IU/mL), immunoglobulin A (IgA, g/L), immunoglobulin G (IgG, g/L), immunoglobulin M (IgM, g/L), complement 3 (C3, g/L), and complement 4 (g/L). COVID-19 antibody IgG and IgM were measured with an immunoanalyzer (iFlash 3000; YHLO Biotech, Shenzhen, China).

Statistical analyses

Data were analyzed using the SPSS version 16.0 (SPSS, Chicago, IL). Subjects were categorized into two groups according to the COVID-19 severity. Normally distributed variables are presented as mean ± standard deviation (SD), and comparisons were analyzed using independent-sample *t*-test. Variables with a skewed distribution are presented as median and quartile range, and comparisons were made using the Mann–Whitney *U*-test. Categorical variables were compared using the χ^2 test. Spearman's two-way test was used to assess the relationship between two quantitative variables. Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Demographics, and the baseline and clinical characteristics of subjects infected with SARS-CoV-2

Demographics and baseline and clinical characteristics of 21 severe and critical subjects infected with SARS-CoV-2 are presented in **Table 1**.

With regard to clinical classification, 8 (38.1%) cases were severe and 13 (61.9%) patients were critical. The mean age of the subjects was 66.10 (standard deviation (SD), 13.94) years, and a total of 38.1% were women. Among these, one patient

Table 1 Clinical characteristics of study subjects according to COVID-19 severity

Characteristic	All cases (*n* = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (*n* = 8)	Critical cases (*n* = 13)	*t* value/χ^2	*P* value
Age, years (mean ± SD)	66.10 ± 13.94	64.00 ± 15.51	67.38 ± 13.36	–0.531	0.602
Gender, M/F	13/8	3/5	10/3	3.264	0.071
Body mass index, kg/m^2	24.10 ± 2.03	23.41 ± 2.18	24.53 ± 1.90	–1.244	0.229
Smoking history					
Never smoked/smoker	15/6	7/1	8/5	1.636	0.201
		Exposure to source of transmission within past 14 days before admission			
Living in Wuhan	1/21 (4.8%)	0/8 (0)	1/13 (7.7%)	0.646	0.421
Contact with wildlife	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Recently visited Wuhan	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Had contact with Wuhan residents	3/21 (14.3%)	1/8 (12.5%)	2/13 (15.4%)	0.034	0.854
Temperature on admission	38.07 ± 0.84	38.17 ± 0.78	37.86 ± 0.98	–1.261	0.222
Fever	17/21 (81.0%)	5/8 (62.5%)	12/13 (92.3%)	2.854	0.091
Symptoms on admission, *n* (%)					
Conjunctival congestion	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Nasal congestion	1/21 (4.8%)	0/8 (0)	1/13 (7.7%)	0.646	0.421
Headache	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Cough	19/21 (90.5%)	7/8 (87.5%)	12/13 (92.3%)	0.133	0.716
Sore throat	4/21 (19.0%)	0/8 (0)	4/13 (30.8%)	3.041	0.081
Sputum production	10/21 (47.6%)	4/8 (50.0%)	6/13 (46.2%)	0.029	0.864
Fatigue	5/21 (23.8%)	3/8 (37.5%)	2/13 (15.4%)	1.335	0.248
Hemoptysis	1/21 (4.8%)	1/8 (12.5%)	0/13 (0)	1.706	0.191
Shortness of breath	13/21 (61.9%)	5/8 (62.5%)	8/13 (61.5%)	0.002	0.965
Nausea or vomiting	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Diarrhea	5/21 (23.8%)	4/8 (50.0%)	1/13 (7.7%)	4.887	**0.027**
Myalgia or arthralgia	2/21 (9.5%)	0/8 (0)	2/13 (15.4%)	1.360	0.243
Chills	2/21 (9.5%)	0/8 (0)	2/13 (15.4%)	1.360	0.243
		Signs of infection on admission, *n* (%)			
Throat congestion	4/21 (19.0%)	0/8 (0)	4/13 (30.8%)	3.041	0.081
Tonsil swelling	2/21 (9.5%)	0/8 (0)	2/13 (15.4%)	1.360	0.243
Enlargement of lymph nodes	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Rash	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
		Coexisting disorder on admission, *n* (%)			
Any	16/21 (76.2%)	8/8 (100.0%)	8/13 (61.5%)	4.038	**0.044**
COPD	2/21 (9.5%)	2/8 (25.0%)	0/13 (0)	3.592	0.058
Diabetes	5/21 (23.8%)	3/8 (37.5%)	2/13 (15.4%)	1.335	0.248
Hypertension	10/21 (47.6%)	5/8 (62.5%)	5/13 (38.5%)	1.147	0.284
CHD	8/21 (38.1%)	4/8 (50.0%)	4/13 (30.8%)	0.777	0.378
CVD	3/21 (14.3%)	1/8 (12.5%)	2/13 (15.4%)	0.034	0.854
Hepatitis B infection	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Cancer	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Chronic renal disease	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA
Immunodeficiency	0/21 (0)	0/8 (0)	0/13 (0)	NA	NA

Bold values indicate statistical significance.The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. The primary composite end point was admission to an intensive care unit, the use of mechanical ventilation, or death. These patients were not residents of Wuhan. The presence of hepatitis B infection was defined as a positive result on testing for hepatitis B surface antigen with or without elevated levels of alanine or aspartate aminotransferase.
CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVD, cerebrovascular disease; NA, not applicable.

Table 2 Radiographic characteristics of study subjects according to COVID-19 severity

Characteristic	All cases (*n* = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (*n* = 8)	Critical cases (*n* = 13)	χ^2	*P* value
Abnormalities on chest CT before admission					
Ground-glass opacity	21/21 (100%)	8/8 (100%)	13/13 (100%)	NA	NA
Local patchy shadowing	5/21 (23.8%)	4/8 (50.0%)	1/13 (7.7%)	4.887	**0.027**
Bilateral patchy shadowing	16/21 (76.2%)	4/8 (50.0%)	12/13 (92.3%)	4.887	**0.027**
Interstitial abnormalities	12/21 (57.1%)	2/8 (25.0%)	10/13 (76.9%)	5.452	**0.020**

Data are expressed as number/total number (%). Bold values indicate statistical significance.
COVID-19, coronavirus disease 2019; CT, computed tomography; NA, not applicable.

Table 3 Laboratory measurements of study subjects according to COVID-19 severity

Characteristic	All cases (*n* = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (*n* = 8)	Critical cases (*n* = 13)	*t* value/χ^2	*P* value
Arterial partial pressure of oxygen/oxygen concentration (400–500)					
Mean ± SD	156.33 ± 50.98	205.25 ± 30.59	126.23 ± 34.77	5.282	**0.000**
<400	21/21 (100.0%)	8/8 (100.0%)	13/13 (100.0%)	NA	NA
>500	0/21 (0)	0/8 (0)	0/13 (0)		
Blood routine test					
Red blood cell count, 10^{12}/L (4.30–5.80)					
Mean ± SD	3.79 ± 0.58	3.99 ± 0.63	3.67 ± 0.54	1.211	0.241
<4.30	15/21 (71.4%)	4/8 (50.0%)	11/13 (84.6%)	2.908	0.088
>5.80	0/21 (0)	0/8 (0)	0/13 (0)		
Hemoglobin, g/L (130–175)					
Mean ± SD	117.10 ± 19.83	122.00 ± 23.11	114.08 ± 17.83	0.884	0.388
<130	17/21 (81.0%)	5/8 (62.5%)	12/13 (92.3%)	2.854	0.091
>175	0/21 (0)	0/8 (0)	0/13 (0)		
Platelet count, 10^9/L (125–350)					
Mean ± SD	209.95 ± 113.85	219.25 ± 107.11	204.23 ± 121.73	0.287	0.777
<125	5/21 (23.8%)	1/8 (12.5%)	4/13 (30.8%)	0.949	0.622
>350	2/21 (9.5%)	1/8 (12.5%)	1/13 (7.7%)		
White blood cell count, 10^9/L (3.50–9.50)					
Mean ± SD	10.16 ± 5.37	9.30 ± 4.78	10.68 ± 5.83	–0.562	0.580
<3.50	0/21 (0)	0/8 (0)	0/13 (0)	0.940	0.322
>9.50	8/21 (13.8%)	2/8 (25.0%)	6/13 (46.2%)		
Neutrophil count, 10^9/L (1.80–6.30)					
Mean ± SD	8.84 ± 5.04	7.83 ± 4.50	9.47 ± 5.42	–0.715	0.483
<1.80	0/21 (0)	0/8 (0)	0/13 (0)	1.615	0.204
>6.30	14/21 (66.7%)	10/13 (76.9%)	4/8 (50.0%)		
Eosinophil count, 10^9/L) (0.02–0.52)					
Mean ± SD	0.00 (0.00–0.10)	0.09 ± 0.14	0.04 ± 0.10	–0.561	0.575
<0.02	14/21 (66.7%)	5/8 (62.5%)	9/13 (69.2%)	0.101	0.751
>0.52	0/21 (0)	0/8 (0)	0/13 (0)		
Basophilic cells count, 10^9/L (0–0.06)					
Mean ± SD	0.01 (0.00–0.02)	0.03 ± 0.04	0.01 ± 0.01	–1.420	0.156
>0.06	3/21 (14.3%)	3/8 (37.5%)	0/13 (0.0%)	5.688	0.017
Lymphocyte count, 10^9/L (1.10–3.20)					
Mean ± SD	0.71 ± 0.44	0.79 ± 0.41	0.66 ± 0.46	0.644	0.528

(Continues)

Table 3 (Continued)

Characteristic	All cases (*n* = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (*n* = 8)	Critical cases (*n* = 13)	*t* value/χ^2	*P* value
<1.10	18/21 (85.7%)	6/8 (75.0%)	12/13 (92.3%)	1.212	0.271
>3.20	0/21 (0)	0/8 (0)	0/13 (0)		
Monocyte count, 10^9/L (0.10–0.60)					
Mean ± SD	0.53 ± 0.34	0.58 ± 0.42	0.50 ± 0.29	0.500	0.623
<0.10	1/21 (14.8%)	1/8 (12.5%)	0/13 (0.0%)	1.726	0.422
>0.60	9/21 (42.9%)	3/8 (37.5%)	6/13 (46.2%)		
Blood biochemical indicators					
K^+, mM (3.50–5.30)					
Mean ± SD	3.88 ± 0.55	4.01 ± 0.64	3.80 ± 0.49	0.858	0.401
<3.50	3/21 (14.3%)	1/8 (12.5%)	2/13 (15.4%)	0.034	0.854
>5.30	0/21 (0)	0/8 (0)	0/13 (0)		
Na^+, mM (137.00–147.00)					
Mean ± SD	138.71 ± 8.70	140.50 ± 6.30	137.62 ± 9.97	0.730	0.475
<137	6/21 (28.6%)	2/8 (25.0%)	4/13 (30.8%)	0.601	0.740
>147	4/21 (19.0%)	1/8 (12.5%)	3/13 (23.1%)		
Cl^-, mM (99.0–110.0)					
Mean ± SD	102.29 ± 7.84	104.25 ± 7.13	101.08 ± 8.29	0.896	0.382
<99.0	3/21 (14.3%)	1/8 (12.5%)	2/13 (15.4%)	0.151	0.927
> 110	2/21 (9.5%)	1/8 (12.5%)	1/13 (7.7%)		
Ca^{2+}, mM (2.11–2.52)					
Mean ± SD	1.96 ± 0.11	1.99 ± 0.13	1.94 ± 0.11	0.977	0.341
<2.11	19/21 (90.5%)	6/8 (75.0%)	13/13 (100.0%)	3.592	0.058
>2.52	0/21 (0)	0/8 (0)	0/13 (0)		
Urea nitrogen, mM (3.10–8.00)					
Mean ± SD	7.95 ± 5.46	9.52 ± 7.90	6.91 ± 2.95	0.896	0.396
<3.10	2/20 (10.0%)	2/8 (25.0%)	0/13 (0)	4.259	0.119
>8.00	9/20 (45.0%)	4/8 (50.0%)	5/12 (41.7%)		
Creatinine, μM (57.0–97.0)					
Mean ± SD	52.00 (42.25–82.25)	70.75 ± 54.93	60.42 ± 24.45	0.500	0.629
<57.0	13/20 (65.0%)	5/8 (62.5%)	8/12 (66.7%)	1.277	0.528
>97.0	3/20 (15.0%)	2/8 (25.0%)	1/12 (8.3%)		
Estimated glomerular filtration rate, mL/min (90.00–120.00)					
Mean ± SD	94.95 ± 2.87	91.65 ± 37.54	97.14 ± 22.73	−0.409	0.687
<90.0	8/20 (40.0%)	3/8 (37.5%)	5/12 (41.7%)	1.076	0.584
>120	3/20 (15.0%)	2/8 (25.0%)	1/12 (8.3%)		
Total serum bilirubin, μM (3.40–20.50)					
Mean ± SD	15.17 ± 9.42	13.43 ± 9.27	16.24 ± 9.73	−0.655	0.520
<3.40	0/21 (0)	0/8 (0)	0/13 (0)	0.359	0.549
>20.5	4/21 (19.0%)	1/8 (12.5%)	3/13 (23.1%)		
Direct bilirubin, μM (0–6.80)					
Mean ± SD	5.78 ± 4.44	5.64 ± 5.37	5.87 ± 3.99	−0.113	0.911
>6.80	6/21 (28.6%)	1/8 (12.5%)	5/13 (38.5%)	1.636	0.201
Indirect bilirubin, μM (2.80–13.20)					
Mean ± SD	9.39 ± 6.05	7.79 ± 4.44	10.37 ± 6.84	−0.947	0.356
<2.80	1/21 (4.8%)	1/8 (12.5%)	0/13 (0)	1.918	0.383
>13.2	4/21 (19.0%)	1/8 (12.5%)	3/13 (23.1%)		
Total protein, g/L (65.0–85.0)					
Mean ± SD	58.12 ± 7.71	59.49 ± 9.91	57.12 ± 5.98	0.650	0.524

(Continues)

Table 3 (Continued)

Characteristic	All cases (*n* = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (*n* = 8)	Critical cases (*n* = 13)	*t* value/χ^2	*P* value
<65.0	17/19 (89.5%)	7/8 (87.5%)	10/11 (90.9%)	0.057	0.811
>85.0	0/21 (0)	0/8 (0)	0/13 (0)		
Albumin, g/L (40.0–55.0)					
Mean ± SD	33.53 ± 4.66	35.43 ± 5.32	32.37 ± 3.98	1.505	0.149
<40.0	19/21 (90.5%)	6/8 (75.0%)	13/13 (100.0%)	3.592	0.058
>55.0	0/21 (0)	0/8 (0)	0/13 (0)		
Globulin, mM (20.0–40.0)					
Mean ± SD	24.26 ± 6.64	24.08 ± 7.64	24.39 ± 6.19	−0.100	0.922
<20.0	6/19 (31.6%)	3/8 (37.5%)	3/11 (27.3%)	0.224	0.636
>40.0	0/21 (0)	0/8 (0)	0/13 (0)		
Albumin/globulin ratio (1.20–2.40)					
Mean ± SD	1.51 ± 0.51	1.60 ± 0.64	1.45 ± 0.42	0.638	0.532
<1.20	4/19 (21.1%)	1/8 (12.5%)	3/11 (27.3%)	1.858	0.395
>2.40	1/19 (5.3%)	1/8 (12.5%)	0/13 (0)		
AST, U/L (15.0–40.0)					
Mean ± SD	53.67 ± 38.95	56.13 ± 51.24	52.15 ± 31.47	0.221	0.827
<15.0	0/21 (0)	0/8 (0)	0/13 (0)	0.777	0.378
>40.0	13/21 (61.9%)	4/8 (50.0%)	9/13 (61.9%)		
ALT, U/L (9.0–50.0)					
Mean ± SD	30.00 (15.00–57.00)	92.75 ± 138.79	38.00 ± 26.72	1.103	0.305
<9.0	1/21 (4.8%)	1/8 (12.5%)	0/13 (0)	1.716	0.424
>50.0	6/21 (28.6%)	2/8 (25.0%)	4/13 (30.8%)		
AST/ALT ratio					
Mean ± SD	1.60 ± 0.86	1.53 ± 1.01	1.65 ± 0.80	−0.325	0.749
Gamma glutamyltransferase, U/L (10.0–60.0)					
Mean ± SD	54.32 ± 39.16	60.38 ± 52.89	49.91 ± 27.41	0.564	0.580
<10.0	0/19 (0)	0/8 (0)	0/11 (0)	0.120	0.729
>60.0	8/19 (42.1%)	3/8 (37.5%)	5/11 (45.5%)		
Alkaline phosphatase, U/L (45.0–125.0)					
Mean ± SD	89.84 ± 42.38	103.75 ± 54.86	79.73 ± 29.30	1.238	0.233
<45.0	2/19 (10.5%)	0/8 (0.0%)	2/11 (18.2%)	4.232	0.121
>125	2/19 (10.5%)	2/8 (25.0%)	0/11 (0.0%)		
Total bile acid, μM (0–10.0)					
Mean ± SD	2.02 ± 1.93	2.50 ± 2.59	1.66 ± 1.28	0.841	0.421
<0	0/19 (0)	0/8 (0)	0/11 (0)	NA	NA
>10.0	0/19 (0)	0/8 (0)	0/11 (0)		
Hemostasis system parameter					
Prothrombin time, s (9.0–14.0)					
Mean ± SD	12.57 ± 1.88	12.74 ± 2.80	12.46 ± 1.13	0.319	0.753
<9.0	0/21 (0)	0/8 (0)	0/13 (0)	0.133	0.716
>14.0	2/21 (9.5%)	1/8 (12.5%)	1/13 (7.7%)		
Prothrombin activity, % (75.0–150.0)					
Mean ± SD	82.99 ± 31.91	79.20 ± 37.74	85.51 ± 2.89	−0.424	0.676
<75.0	3/20 (15.0%)	2/8 (25.0%)	1/12 (8.3%)	1.046	0.306
>150	0/21 (0)	0/8 (0)	0/12 (0)		
International normalized ratio (0.85–1.15)					
Mean ± SD	1.00 ± 0.19	1.03 ± 0.28	0.98 ± 0.10	0.521	0.609

(Continues)

Table 3 (Continued)

Characteristic	All cases (*n* = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (*n* = 8)	Critical cases (*n* = 13)	*t* value/χ^2	*P* value
<0.85	1/20 (5.0%)	1/8 (12.5%)	0/12 (0)	3.333	0.189
>1.15	1/20 (5.0%)	1/8 (12.5%)	0/12 (0)		
Activated partial thromboplastin time, s (20.0–41.0)					
Mean ± SD	34.64 ± 7.61	30.26 ± 6.54	37.34 ± 7.15	–2.273	**0.035**
<20.0	0/21 (0)	0/8 (0)	0/13 (0)	0.911	0.340
>41.0	5/21 (23.8%)	1/8 (12.5%)	4/13 (30.8%)		
Fibrinogen, g/L (2.00–4.00)					
Mean ± SD	4.67 ± 1.72	4.00 ± 0.98	5.09 ± 1.97	–1.446	0.165
<2.00	0/21 (0)	0/8 (0)	0/13 (0)	2.908	0.088
>4.00	15/21 (71.4%)	4/8 (50.0%)	11/13 (84.6%)		
D-dimer, μg/mL (0–0.50)					
Mean ± SD	1.65 ± 1.43	1.48 ± 1.48	1.76 ± 1.45	–0.418	0.681
<0	0/20 (0)	0/8 (0)	0/21 (0)	0.000	1.000
>0.50	15/20 (75.0%)	6/8 (75.0%)	9/12 (75.0%)		

Data are expressed as number/total number (%). Bold values indicate statistical significance.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; NA, not applicable.

was living in Wuhan city before admission, one recently visited Wuhan city before admission, three had been in contact with Wuhan residents before admission, none had contact with the seafood market in South China, and none were medical staff.

Fever was present in 81.0% of patients on admission, and the mean ± SD for body temperature on admission for all subjects was 38.07 ± 0.84°C. The most common symptom was cough (90.5%); none had the symptoms of nausea or vomiting, and 23.8% had diarrhea. Among the the 21 subjects, 16 (76.2%) had at least one coexisting disorder on admission.

Radiologic characteristics of subjects infected with SARS-CoV-2

Table 2 shows the radiologic characteristics of patients on admission. All patients had abnormal chest computed tomography (CT) images. The most common characteristics of chest CT were ground-glass opacity (100%) and bilateral patchy shadowing (76.2%). Interstitial abnormalities and local patchy shadowing were seen in 12 (57.1%) and 5 (23.8%) cases, respectively.

Laboratory measurements of subjects infected with SARS-CoV-2

Table 3 shows the laboratory measurements of patients infected with SARS-CoV-2 on admission. Lymphopenia, eosinopenia, thrombocytopenia, and leukopenia were present in 85.7%, 66.7%, 23.8%, and 0% of the patients, respectively. For liver function, 6 patients (28.6%) showed above-normal ALT and 13 (61.9%) above-normal AST levels. Nineteen patients (90.5%) had an albumin level in the lower-than-normal range (40 g/L). Fifteen patients (71.4%) had higher-than-normal fibrinogen (4.00 g/L). Blood urea nitrogen levels of nine patients (45.0%) exceeded normal (8.00 mM), and Cr level of three patients (15.0%) exceeded normal (97.0 μM). D-dimer levels were increased in 15 patients (75.0%).

Inflammatory and immunologic markers assay of study subjects infected with SARS-CoV-2

Table 4 shows the inflammatory and immunologic markers assay of the SARS-CoV-2 patients. Eighteen (94.7%) patients had high CRP and 17 (89.5%) had high IL-6, but only 1 (5.6%) had elevated PCT. The prevalence of anti–52 kDa SSA/Ro antibody, anti–60 kDa SSA/Ro antibody, and antinuclear antibody was 20%, 25%, and 50%, respectively. The frequency of COVID-19 antibody IgG and COVID-19 antibody IgM was 100% and 89.5%, respectively.

Treatment for subjects infected with SARS-CoV-2

Table 5 shows the treatments for COVID-19. Most patients (81.0%) were treated empirically with intravenous antibiotic therapy, and all received antiviral therapy with ribavirin and arbidol. Five patients (23.8%) received hormone therapy, and three (14.3%) received IVIg therapy. Thirteen (61.9%), seven (33.3%), and six (28.6%) patients were managed with noninvasive ventilation (i.e., face mask), high-flow oxygen, and mechanical ventilation, respectively. In addition, noninvasive ventilation, high-flow oxygen, and mechanical ventilation were initiated in more subjects with critical disease than in those with severe disease (noninvasive ventilation: 0% vs. 100%, $P = 0.000$; high-flow oxygen: 62.5% vs. 15.4%, $P = 0.026$; mechanical ventilation: 0% vs. 46.2%, $P = 0.023$). Furthermore, extracorporeal membrane oxygenation (ECMO) was performed in one subject (4.8%) with critical disease. Five subjects (23.8%) used traditional Chinese medicine.

Prognosis of subjects infected with SARS-CoV-2

Up to March 2, 2020, 13 of 21 patients (61.9%) were discharged from the hospital, five subjects were still in the hospital for treatment, and three patients died.

Table 4 Inflammatory and immunologic markers assay of study subjects according to COVID-19 severity

Characteristic	All cases (n = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (n = 8)	Critical cases (n = 13)	t value/χ^2	P value
Inflammatory markers					
Hypersensitive C-reactive protein, mg/L (0–1.00)					
Mean ± SD	5.00 (5.00–5.00)	5.00 (5.00–5.00)	5.00 (5.00–5.00)	NA	0.264
> 1.00[a]	18/18 (100%)	8/8 (100%)	10/10 (100%)	NA	NA
C-reactive protein, mg/L (0–10.0)					
Mean ± SD	59.66 ± 41.09	36.89 ± 20.64	69.96 ± 43.65	–1.977	0.065
>10.0[a]	18/19 (94.7%)	7/8 (87.5%)	11/11 (100%)	1.451	0.228
Procalcitonin, ng/mL (0–5.00)					
Mean ± SD	0.43 (0.34–0.51)	0.42 (0.35–0.56)	0.40 (0.33–0.48)	NA	0.423
>5.00[a]	1/18 (5.6%)	1/8 (12.5%)	0/10 (0)	1.324	0.250
Interleukin-6, pg/mL (0–7.00)					
Mean ± SD	25.33 ± 2.30	35.28 ± 3.21	17.16 ± 9.77	1.541	0.162
>7.00[a]	17/19 (89.5%)	8/8 (100%)	9/11 (81.8%)	1.626	0.202
Immunologic markers					
Anti–Scl-70, RU/mL (0–20.00)					
Mean ± SD	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–2.03)	NA	0.487
>20.00[a]	1/20 (5%)	0/8 (0)	1/12 (8.3%)	0.702	0.402
Anti–Jo-1 antibody, RU/mL (0–20.00)					
Mean ± SD	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	NA	1.000
>20.00[a]	0/20 (0)	0/8 (0)	0/12 (0)	NA	NA
Anticentromere B antibody, RU/mL (0–20.00)					
Mean ± SD	0.00 (0.00–0.94)	2.06 ± 3.06	0.00 (0.00)	NA	0.221
>20.00[a]	0/20 (0)	0/8 (0)	0/12 (0)	NA	NA
Anti-SmD1 antibody, RU/mL (0–20.00)					
Mean ± SD	2.36 ± 2.15	2.17 ± 2.34	2.72 ± 2.07	–0.547	0.591
>20.00[a]	0/20 (0)	0/8 (0)	0/12 (0)	NA	NA
Anti–60 kDa SSA/Ro antibody, RU/mL (0–20.00)					
Mean ± SD	12.85 ± 20.94	7.15 ± 11.08	18.16 ± 25.96	–1.122	0.278
>20.00[a]	5/20 (25%)	1/8 (12.5%)	4/12 (33.3%)	1.111	0.292
Anti–52 kDa SSA/Ro antibody, RU/mL (0–20.00)					
Mean ± SD	10.63 ± 12.77	9.41 ± 12.67	12.49 ± 13.46	–0.505	0.620
>20.00[a]	4/20 (20%)	2/8 (25%)	2/12 (16.7%)	0.208	0.648
Anti–U1-RNP antibody, RU/mL (0–20.00)					
Mean ± SD	2.29 (0.00–3.37)	2.75 ± 2.96	6.00 ± 1.37	–0.657	0.520
>20.00[a]	1/20 (5%)	0/8 (0)	1/12 (8.3%)	0.702	0.402
Anti-SSB antibody, RU/mL (0–20.00)					
Mean ± SD	0.00 (0.00–2.21)	0.00 (0.00)	1.52 ± 2.10	NA	0.193
>20.00[a]	0/20 (0)	0/8 (0)	0/12 (0)	NA	NA
Antinuclear antibody, AU/mL (0–40.00)					
Mean ± SD	141.20 ± 172.17	98.60 ± 142.77	184.83 ± 191.24	–1.073	0.298
>40.00[a]	10/20 (50.0%)	3/8 (37.5%)	7/12 (58.3%)	0.833	0.361
Anti–double-stranded DNA antibody, RU/mL (0–10.00)					
Mean ± SD	0.00 (0.00–1.14)	0.46 ± 0.79	0.38 ± 0.67	0.186	0.856
>10.00[a]	0/15 (0)	0/7 (0)	0/8 (0)	NA	NA
Anti–streptolysin O, IU/mL (0–170.00)					
Mean ± SD	82.93 ± 48.19	74.33 ± 52.94	98.50 ± 39.28	–0.984	0.345
>170.0[a]	0/14 (0)	0/6 (0)	0/8 (0)	NA	NA
Rheumatoid factor, IU/mL (0–30.00)					
Mean ± SD	6.08 ± 4.67	8.90 ± 6.35	4.05 ± 1.79	1.819	0.122
>30.0[a]	0/14 (0)	0/6 (0)	0/8 (0)	NA	NA

(Continues)

Table 4 (Continued)

Characteristic	All cases (*n* = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (*n* = 8)	Critical cases (*n* = 13)	*t* value/χ^2	*P* value
Immunoglobulin A, g/L (0.72–4.29)					
Mean ± SD	2.42 ± 0.68	2.30 ± 0.83	2.54 ± 0.64	−0.615	0.549
<0.72[a]	0/15 (0)	0/6 (0)	0/9 (0)	NA	NA
>4.29[a]	0/15 (0)	0/6 (0)	0/9 (0)		
Immunoglobulin G, g/L (8.00–17.00)					
Mean ± SD	15.11 ± 5.09	16.26 ± 5.92	14.73 ± 4.91	0.543	0.596
<8.0[a]	0/15 (0)	0/6 (0)	0/9 (0)	1.250	0.264
>17.0[a]	5/15 (33.3%)	3/6 (50.0%)	2/9 (22/2%)		
Mean ± SD	1.39 ± 0.96	1.08 ± 0.46	1.46 ± 1.15	−0.766	0.457
Immunoglobulin M, g/L (0.29–3.44)					
<0.29[a]	0/15 (0)	0/6 (0)	0/9 (0)	0.714	0.398
>3.44[a]	1/15 (6.7%)	0/6 (0%)	1/9 (11.1%)		
Mean ± SD	0.72 ± 0.19	0.76 ± 0.23	0.72 ± 0.14	0.364	0.722
Complement 3, g/L (0.80–1.85)					
<0.80a	6/14 (42.9%)	2/6 (33.3%)	4/8 (50.0%)	0.389	0.533
>1.85[a]	0/14 (0)	0/6 (0)	0/8 (0)		
Mean ± SD	0.22 ± 0.07	0.22 ± 0.08	0.22 ± 0.07	0.137	0.893
Complement 4, g/L (0.17–0.40)					
<0.17[a]	5/14 (35.7%)	2/6 (33.3%)	3/8 (37.5%)	0.026	0.872
>0.40[a]	0/14 (0)	0/6 (0)	0/8 (0)		
COVID-19 antibody IgG (0–10.00)					
Mean ± SD	122.61 ± 46.88	117.19 ± 24.50	127.80 ± 60.69	−0.524	0.608
>10.0[a]	19/19 (100%)	8/8 (100%)	11/11 (100%)	NA	NA
COVID-19 antibody IgM (0–10.00)					
Mean ± SD	151.02 ± 221.26	127.67 ± 158.65	175.90 ± 271.15	−0.448	0.660
>10.0[a]	17/19 (89.5%)	6/8 (75.0%)	11/11 (100%)	3.074	0.080

Data are expressed as number/total number (%).
COVID-19, coronavirus disease 2019; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; NA, not applicable.
[a]Below or above the normal range.

DISCUSSION

In this single-center and retrospective study, we have reported on the clinical and laboratory characteristics of 8 severe and 13 critical cases of SARS-CoV-2 in Huangshi, Hubei Province, China. Our main findings are as follows: cough and fever were the dominant symptoms; most patients had at least one coexisting disorder on admission; the most common characteristic on chest CT was ground-glass opacity; the most common findings on laboratory measurements were lymphocytopenia and elevated levels of CRP and IL-6; and prevalence of anti–52 kDa SSA/Ro antibody, anti–60 kDa SSA/Ro antibody, and antinuclear antibody was 20%, 25%, and 50%, respectively.

Table 5 Treatment of study subjects according to COVID-19 severity

Characteristic	All cases (*n* = 21)	Disease severity of COVID-19		Statistical parameter	
		Severe cases (*n* = 8)	Critical cases (*n* = 13)	χ^2	*P* value
Antibiotic treatment	20/21 (95.2%)	7/8 (87.5%)	13/13 (100%)	1.706	0.191
Antiviral treatment	21/21 (100%)	8/8 (100%)	13/13 (100%)	NA	NA
Hormone therapy	5/21 (23.8%)	0/8 (0)	5/13 (23.1%)	4.038	**0.044**
IVIg	3/21 (14.3%)	0/8 (0)	3/13 (23.1%)	2.154	0.142
Noninvasive (ie, face mask)	13/21 (61.9%)	0/8 (0)	13/13 (100%)	21.000	**0.000**
High flow oxygen	9/21 (42.9%)	8/8 (100%)	1/13 (7.7%)	17.231	**0.000**
Mechanical ventilation	8/21 (38.1%)	0/8 (0)	8/13 (61.5%)	7.953	**0.005**
ECMO	1/21 (4.8%)	0/8 (0)	1/13 (7.7%)	0.646	0.421
Traditional Chinese medicine	5/21 (23.8%)	1/8 (12.5%)	4/13 (30.8%)	0.911	0.340

Data are expressed as number/total number (%). Bold values indicate statistical significance.
COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; IVIg, intravenous immunoglobulin.

One study reported on the clinical characteristics of 52 critically ill subjects with SARS-CoV-2 pneumonia who were admitted to the ICU of Wuhan Jin Yin-tan Hospital (Wuhan, China) between late December 2019 and January 26, 2020.[5] However, the data on critically ill subjects with SARS-CoV-2 infection outside of Wuhan are scarce. Due to the high mortality of critically ill subjects with SARS-CoV-2 pneumonia, one study focused on the clinical and laboratory information necessary for the diagnosis and treatment of COVID-19. In the present work we found that the clinical characteristics of COVID-19 mimicked those of other study populations,[6–8] with cough, fever, lymphocytopenia, elevated levels of CRP, ground-glass opacity, and bilateral patchy shadowing on chest CT being the dominant findings. The case fatality rate from the present study was 9.5%, substantially lower than that recently reported for 32 (61.5%) patients who died at 28 days.[5] There is no clear explanation for this difference, but we believe differences in case inclusion criteria and individual differences may be a reason.

The identification of the potential risk factors of D-dimer >1 μg/L and high IL-6 level for identifying subjects with a poor prognosis has been described in a retrospective, multicenter cohort study conducted at Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China).[9] In agreement with that study, we found that D-dimer and IL-6 levels were higher than the reference range, and that these markers may play diagnostic and therapeutic roles in combating COVID-19.

Another study was conducted to explore the clinical characteristics and allergy status of subjects with SARS-CoV-2. The results suggested eosinopenia and lymphopenia may be indicators for a COVID-19 diagnosis, but that allergic diseases, asthma, and COPD are not risk factors for SARS-CoV-2 infection.[10] To date, however, the relationship between immune status and autoimmune phenomena with SARS-CoV-2 infection has not been reported. Herein we found that prevalence of anti–52 kDa SSA/Ro antibody, anti–60 kDa SSA/Ro antibody, and antinuclear antibody was 20%, 25%, and 50%, respectively. Therefore, we conclude that autoimmune phenomena exist in COVID-19 subjects, which provides a rationale for a strategy of prevention of dysfunction of immune and optimal immunosuppressive therapy in the future. To the best of our knowledge, this is the first report to describe COVID-19 patients with features of autoreactivity.

Our study has several limitations. The clinical and laboratory data were from only 21 severe and critical COVID-19 cases. Thus, larger samples and a multicenter studies will needed to verify our initial observations. Furthermore, because this study was retrospective in nature, prognostic data were unavailable. In addition, several cases had incomplete data on laboratory testing due to the urgent timeline for document extraction.

CONCLUSIONS

In this work we have retrospectively analyzed the clinical and laboratory data from 21 severe and critical cases of COVID-19. Autoimmune phenomena exist in COVID-19 subjects, which provides a rationale for a strategy of prevention of immune dysfunction and optimization of immunosuppressive therapy.

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