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The clinical characters and prognosis of COVID-19 patients with multiple organ dysfunction

Jianghua Cui, MS[a], Boyun Yuan, MS[b], Yan Li, BS[b], Zhu Li, MS[c], Yadong Yuan, PhD[b,*]

Abstract

To depict the clinical characters and prognosis of coronavirus disease 2019 patients who developed multiple organ dysfunction syndrome (MODS).

A cohort consisted of 526 patients, which including 109 patients complicated MODS, was retrospectively analyzed to examine the clinical characteristics and risk factors of MODS.

Among the 526 novel coronavirus-infected pneumonia patients, 109 patients developed multiple organ failure, the incidence rate was 20.7%. Among all 109 patients with MODS, 81.7% were over 60 years old, and 63.3% were male. The most common symptoms were fever (79.8%), dyspnea (73.4%), and fatigue (55.0%). Compared with patients non-MODS patients, there were 70 cases of MODS patients with one or more underlying diseases (64.2% vs 41.0%, $P < .001$). Respiratory failure (92.7%), circulatory failure (52.0%), and liver function injury (30.9%) were the most common symptoms within the spectrum of MODS. Invasive ventilator, noninvasive ventilator, and high-flow respiratory support treatment for patients in MODS patients were higher than those in the non-MODS group ($P < .001$). The antiviral therapy and 2 or more antibacterial drug treatments in MODS patients were higher than those in the non-MODS group ($P < .001$). The median hospital stay of all patients was 16 days (interquartile range [IQR], 9-26), of which 20 days (IQR, 11.5-30.5) in the MODS patients, which was approximately 4 days longer than that of non-MODS patients. In addition, our data suggested that lymphocyte counts <1.0 * 109/L, Troponin T > 0.014 ng/mL and lower oxygenation index were risk factors for MODS. In the early stage of hospital admission, higher inflammatory indexes and lactic acid concentration were associated with increased risk of death.

MODS often leads to poor prognosis in coronavirus disease 2019. Our data suggested the importance of early identification of MODS. We recommend close monitoring and timely supportive therapy for patients with high risks, stopping the disease progression before it was too late.

Abbreviations: COVID-19 = coronavirus disease 2019, IQR = interquartile range, MODS = multiple organ dysfunction syndrome, PCT = procalcitonin.

Keywords: coronavirus disease 2019, COVID-19, multiple organ dysfunction, prognosis, retrospectively analyzed

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has already evolved into a relentless global pandemic crisis. Most patients with COVID-19 have mild symptoms, but the disease can rapidly progress in about 5% and develop systemic inflammatory response syndrome, septic shock, and even multiple organ dysfunction syndrome (MODS).[1] A previous study included 99 patients suggested that 17% of patients developed acute respiratory distress syndrome and 11% died of MODS within a short time.[2] Currently, no effective treatment has been developed for COVID-19, especially for patients developed MODS. Therefore, it is critical to identify patients with

Editor: Ali Amanati.

Funding support received from Hebei Province Science and Technology Support Program (20277706D).

This study approved by the ethics commmittee of Second Hospital of Hebei Medical University. All patients signed a surgical consent form. Informed consent was obtained from all individual participants included in the study.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Intensive Care Medicine, Peking University Shougang Hospital, Beijing, China., [b] Department of Respiratory and Critical Care Medicine, Second Hospital of Hebei Medical University, Shijiazhuang Hebei, China, [c] Department of Respiratory and Critical Care Medicine, First Hospital of Hebei Medical University, Shijiazhuang Hebei, China.

[*] Correspondence: Yadong Yuan, Department of Respiratory and Critical Care Medicine, Second Hospital of Hebei Medical University, Shijiazhuang Hebei 050051, China (e-mail: yuanyd1108@163.com).

How to cite this article: Cui J, Yuan B, Li Y, Li Z, Yuan Y. The clinical characters and prognosis of COVID-19 patients with multiple organ dysfunction. Medicine 2021;100:41(e27400).

Received: 19 January 2021 / Received in final form: 17 May 2021 / Accepted: 19 May 2021

http://dx.doi.org/10.1097/MD.0000000000027400

increasing risks so timely treatment adjustment and precautions can be made. However, the characteristic and risk factors for MODS in COVID-19 had not been well examined. In this study, a total of 526 patients (341 confirmed cases, and 125 clinically diagnosed cases) were retrospectively analyzed and we identified 109 patients who developed MODS. Those patients were further examined to depict the clinical characteristic, risk factors and the cause of death of MODS.

2. Methods

2.1. Object of study

A total of 550 patients that had been diagnosed as COVID-19 according to the diagnosis and treatment of pneumonia infected by the Chinese COVID-19 management guideline (3rd-7th Edition) at Wuhan Seventh Hospital from January 11 to March 13, 2020 were retrospectively screened for the study. After screening process, a total of 526 patients were included and 109 patients (20.7%) developed MODS. The inclusion criteria was made as follow: age ≥18 years old; epidemiological contact history and classic clinical manifestations (① fever and/or respiratory symptoms; ② classic imaging features of COVID-19: early multiple plaques and interstitial changes, especially in the extrapulmonary zone that can develop into ground glass shadow and infiltration shadow of both lungs and lung consolidation may occur in severe cases. ③ The total leukocyte count is normal or decreased and lymphocyte count decreased in the early stage of the disease. The diagnosis can be made if patients had any 2 signs, or 3 signs without clear contact history); confirmed cases: those with one of the following etiological or serological evidence: ① novel coronavirus nucleic acid positive detected by real-time fluorescent RT-PCR; ② Positive gene sequence analysis. ③ Positive COVID-19 IgM antibody and IgG antibody, and the serum IgG antibody changed from negative to positive or increased by at least 4 times in the convalescent stage. Exclusion criteria: patients transferred to other hospital or voluntarily discharged; patients with incomplete clinical data. This study was approved by the second Hospital of Hebei Medical University (2020-R016). The informed consent was waived due to the retrospective nature of the study.

2.2. Data collection

A standardized case record form was generated to collect information including patient information such as baseline background diseases, clinical manifestations, imaging manifestations, laboratory examination results, medication, and outcome. The data extraction was approved by the director of Wuhan Seventh Hospital. All the data was collected by 2 trained researchers through double-blind access to medical records. The third researcher made a final ruling upon differences in interpretation between 2 main reviewers. Patients with N terminal B type natriuretic peptide >222 pg/mL were diagnosed with heart failure; the level of serum troponin T above the upper limit of the 99th percentile was defined as myocardial injury[2]; abnormalities in the heart rate including rhythm, origin, conduction velocity, or activation order of cardiac impulses were defined as arrhythmias. Patients with above situation were defined as cardiovascular dysfunction. Oxygenation index $PaO_2/FiO_2 < 300$ mm Hg was defined as respiratory dysfunction. Apathy or restlessness of consciousness, lethargy, shallow coma, deep coma or Glasgow coma score ≤14 were defined as central nervous system dysfunction; platelet count $< 100 \times 109$/L or abnormal clotting time, activated partial thromboplastin time, prothrombin time and positive 3P test (plasma protamine paracoagulation test) were recognized as coagulation system dysfunction. Serum creatinine > 123.76 μmol/L, or urine volume <500 mL/24 hour was regarded as renal dysfunction. Total bilirubin > 20.5 μmol/L, or serum albumin <28 g/L were considered as liver system dysfunction. Patients with above 2 or more system dysfunction were diagnosed as MODS.[3]

2.3. Statistical methods

Variables were expressed as frequency and percentage. χ^2 test was used to compare the differences between groups and Fisher exact test was used when the amount of data in the group was small. The continuous variables were expressed as Mean/Median, and interquartile range (IQR). When the data distribution followed the normal distribution, the Student *t* test was used, otherwise, the Mann-Whitney *U* test was used to compare the difference between groups. The Kaplan-Meier curve was conducted to compare the survival curve. Univariate Logistic regression analysis was used to screen variables followed by multivariate Logistic regression test that to identify risk factors for MODS. We chose a total of 26 variables that had been commonly observed in MODS or non-MODS patients for the initial logistic regression model. Variables were excluded if their *P* values >.05, if their accuracy could not be confirmed (symptom, which was self-reported), if the difference between the 2 groups is close (gender, Potassium, Sodium), if they were unavailable under emergency circumstances (erythrocyte sedimentation rate, NT-pro BNP), if the sample size was relatively small (diabetes, heart disease, Malignancy), if they might be related to other variables (age, hypertension, leucocytes, neutrophil percentage, lymphocyte percentage, procalcitonin [PCT], hypersensitive C-reactive protein, troponin T). To evaluate the patient's condition, we applied a 10-score index where 10 referred to the most severe condition and used in univariate and multivariate logistic regression analysis. COX risk regression model was used to analyze the factors affecting the short-term prognosis of COVID-19 with MODS. All statistical analyses were analyzed by SPSS software (22.0 version) (IBM Corp. IBM SPSS Statistics for Window. Armonk, NY: IBM Corp). A *P* value less than.05 was considered statically significant.

3. Results

3.1. Epidemiological and demographic characteristics

After excluding 24 patients with an unknown prognosis, a total of 526 patients were included for the study. 109 (20.7%) patients were complicated with 2 or more organ injuries, including 69 males (63.3%) and 40 females (36.7%). Among all 109 patients, 99 patients were over 60 years old (81.7%) and only 17 patients (15.6%) had an obvious contact history. The average time from symptoms onset to hospitalization was 9 (7-11) days.

3.2. Clinical features

More than half (64.3%) of the 526 patients with COVID-19 had fever and the proportion was further increased in patients with MODS (79.8%). Other common symptoms were dyspnea (73.4%), fatigue (55.0%), dry cough (51.4%), expectoration (34.9%), and chills (33.9%). 19 patients complained of abdominal pain/diarrhea (17.4%).

3.3. Background diseases

Among patients with MODS, 55 (50.5%) had a history of hypertension, 20 (18.3%) had heart disease, 22 (20.2%) had diabetes, 11 (10.1%) had malignant tumor and 5 (4.6%) had chronic lung disease. Among patients without MODS, the prevalences of above background diseases were 29.0%, 8.2%, 12.7%, 2.4% and 2.9%, respectively. Compared to patients without MODS, patients with MODS were more likely to have at least one underlying disease (64.2% vs 41.0% $P < .001$). As shown in Table 1.

3.4. Laboratory examination

Routine blood tests and other inflammatory indicators: patients with MODS were more likely to have increased neutrophil count (74.3%, $P < .001$) and decreased lymphocyte count ($<1.0 \times 109$/l) (85.7%, $P < .001$). The levels of PCT, hypersensitive C-reactive protein, and erythrocyte sedimentation rate were more frequently increased in MODS patients than those in non-MODS patients ($P < .001$).

Cardiac function: Troponin T was more commonly increased in MODS patients (57.4%, $P < .001$). Furthermore, in 48 MODS patients who were tested positive for N terminal pro B type natriuretic peptide, their troponin T levels were also significantly increased (75.0% $P < .001$), indicating a severe damage to myocardium and cardiac function.

Liver function: The elevation of glutamic oxaloacetic transaminase was more frequent among MODS patients ($P < .001$), whereas the increase of glutamic-pyruvic transaminase was more common in non-MODS patients ($P < .001$). Among MODS patients who underwent liver function examination, 19 patients had albumin < 28 g/L(16.4%, $P = .776$).

Renal function: The renal system was seemed spared in COVID-19 associated MODS. Our data suggested that decreased glomerular filtration and increased creatine was less likely to be seen in patients with MODS (19 cases, 17.0%, $P < .001$).

Coagulation function: 57 cases (82.6%) of MODS patients showed an increase of D-dimer ($P < .001$).

Blood gas analysis: The oxygenation index (OI) of 68 (73.9%) MODS patients were less than or equal to 300, including 18 (19.6%) less than 100. 33 (30.3%) patients' condition worsened during hospitalization, and OI gradually decreased to less than 300. The lactic acid level was more frequently elevated in patients with MODS (35.9%) compared to non-MODS patients (23.6%). There was no significant difference in terms of lung involvement (unilateral or bilateral) between 2 groups ($P = .779$). As shown in Table 2.

Table 1

Demographics and clinical characteristics of patients with COVID-19.

	All patients (N = 526)	MODS (n = 109)	Non-MODS (n = 417)	*P* value
Age, yrs- no. (%)				
<60	262 (49.8%)	20 (18.3%)	242 (58.0%)	<.001
≥60	264 (50.2%)	89 (81.7%)	175 (42.0%)	<.001
Sex- no. (%)				
Male	247 (47.0%)	69 (63.3%)	178 (42.7%)	<.001
Female	279 (53.0%)	40 (36.7%)	239 (57.3%)	<.001
Signs and symptoms -no. (%)				
Fever	338 (64.3%)	87 (79.8%)	251 (60.2%)	<.001
Dyspnea	230 (43.7%)	80 (73.4%)	150 (36.0%)	<.001
Dry cough	246 (46.8%)	56 (51.4%)	190 (45.6%)	.279
Fatigue	215 (40.9%)	60 (55.0%)	155 (37.2%)	.001
Sputum production	151 (28.7%)	38 (34.9%)	113 (27.1%)	.111
Stomachache	60 (11.4%)	15 (13.8%)	45 (10.8%)	.385
Diarrhea	41 (7.8%)	9 (8.3%)	32 (7.7%)	.840
Chill	120 (22.8%)	37 (33.9%)	83 (19.9%)	.002
Nausea/vomit	69 (13.1%)	14 (12.8%)	55 (13.2%)	.924
Myalgia	57 (10.8%)	12 (11.0%)	45 (10.8%)	.948
Tachycardia	33 (6.3%)	7 (6.4%)	26 (6.2%)	.943
Sore throat	45 (8.6%)	4 (3.7%)	41 (9.8%)	.041
Dizziness	17 (3.2%)	4 (3.7%)	13 (3.1%)	>.999
Sneeze	1 (0.2%)	0 (0.0%)	1 (0.2%)	>.999
Rash	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Arthralgia	1 (0.2%)	0 (0.0%)	1 (0.2%)	>.999
Comorbidity -no. (%)				
Hypertension	176 (33.5%)	55 (50.5%)	121 (29.0%)	<.001
Cardiovascular disease	54 (10.3%)	20 (18.3%)	34 (8.2%)	.003
Diabetes	75 (14.3%)	22 (20.2%)	53 (12.7%)	.047
Malignancy	21 (4.0%)	11 (10.1%)	10 (2.4%)	.001
Cerebrovascular disease	19 (3.6%)	6 (5.5%)	13 (3.1%)	.368
Chronic liver disease	14 (2.7%)	5 (4.6%)	9 (2.2%)	.285
Chronic pulmonary disease	17 (3.2%)	5 (4.6%)	12 (2.9%)	.552
Underlying diseases	241 (45.8%)	70 (64.2%)	171 (41.0%)	<.001

Data are shown in the form of n (%).

MODS = multiple organ dysfunction syndrome.

Table 2

Laboratory results of patients with COVID-19 on hospital admission.

	All patients (N = 526)	MODS (n = 109)	Non-MODS (n = 417)	*P* value
Blood tests-no. (%)				
Leucocytes (10^9/L)				
<4	117 (23.9%)	10 (9.5%)	107 (27.9%)	<.001
4-10	330 (67.5%)	74 (70.5%)	256 (66.7%)	<.001
>10	42 (8.6%)	21 (20.0%)	21 (5.5%)	<.001
Neutrophil percentage (%)				
40-75	318 (65.0%)	27 (25.7%)	291 (75.8%)	<.001
>75	171 (35.0%)	78 (74.3%)	93 (24.2%)	<.001
Lymphocyte percentage (%)				
<20	228 (46.6%)	90 (85.7%)	138 (35.9%)	<.001
20-50	261 (53.4%)	15 (14.3%)	246 (64.1%)	<.001
Lymphocytes (10^9/L)				
<1.0	245 (50.1%)	85 (81.0%)	160 (41.7%)	<.001
≥1.0	244 (49.9%)	20 (19.0%)	224 (58.3%)	<.001
Hemoglobin (g/L)				
Normal	314 (64.2%)	83 (79.0%)	231 (60.2%)	<.001
Decreased	175 (35.8%)	22 (21.0%)	153 (39.8%)	<.001
Platelets (10^9/L)				
<100	27 (5.5%)	13 (12.4%)	14 (3.6%)	.001
≥100	462 (94.5%)	92 (87.6%)	370 (96.4%)	.001
Inflammatory parameters-no. (%)				
Procalcitonin (ng/mL)				
≤0.1	276 (71.9%)	29 (33.3%)	247 (83.2%)	<.001
>0.1	108 (28.1%)	58 (66.7%)	50 (16.8%)	<.001
hsCRP (mg/L)				
≤3	119 (29.7%)	2 (2.6%)	117 (36.1%)	<.001
>3	282 (70.3%)	75 (97.4%)	207 (63.9%)	<.001
ESR (mm/h)				
≤15	71 (39.7%)	2 (5.7%)	69 (47.9%)	<.001
>15	108 (60.3%)	33 (94.3%)	75 (52.1%)	<.001
Myocardial enzyme-no. (%)				
CK-MB (ng/mL)				
≤6.22	390 (94.9%)	80 (87.0%)	310 (97.2%)	<.001
>6.22	21 (5.1%)	12 (13.0%)	9 (2.8%)	<.001
Troponin T (ng/mL)				
≤0.014	328 (76.3%)	43 (42.6%)	285 (86.6%)	<.001
>0.014	102 (23.7%)	58 (57.4%)	44 (13.4%)	<.001
Heart failure indicator-no. (%)				
NT-pro BNP (pg/mL)				
≤222	160 (57.1%)	16 (25.0%)	144 (66.7%)	<.001
>222	120 (42.9%)	48 (75.0%)	72 (33.3%)	<.001
Liver function-no. (%)				
Alanine transaminase (IU/L)				
≤50	439 (87.6%)	84 (75.0%)	355 (91.3%)	<.001
>50	62 (12.4%)	28 (25.0%)	34 (8.7%)	<.001
Aspartate aminotransferase (IU/L)				
≤40	385 (77.3%)	52 (46.8%)	333 (86.0%)	<.001
>40	113 (22.7%)	59 (53.2%)	54 (14.0%)	<.001
Albumin (g/L)				
<28	86 (17.3%)	18 (16.4%)	68 (17.5%)	.776
≥28	421 (82.7%)	92 (83.6%)	320 (82.5%)	.776
Coagulation function-no. (%)				
APTT (S)				
24.6-35.4	353 (85.1%)	73 (79.3%)	280 (86.7%)	.081
>35.4	62 (14.9%)	19 (20.7%)	43 (13.3%)	.081
D-dimer (μg/mL)				
≤0.243	172 (49.3%)	12 (17.4%)	160 (57.1%)	<.001
>0.243	177 (50.7%)	57 (82.6%)	120 (42.9%)	<.001
Electrolyte-no. (%)				
Potassium (mmol/L)				
>5.3	36 (7.3%)	8 (7.7%)	28 (7.2%)	<.001
3.5-5.3	382 (77.8%)	60 (57.7%)	322 (83.2%)	<.001

(*continued*)

Table 2
(continued).

	All patients (N = 526)	MODS (n = 109)	Non-MODS (n = 417)	*P* value
<3.5	73 (14.9%)	36 (34.6%)	37 (9.6%)	<.001
Sodium (mmol/L)				
<137	69 (14.0%)	29 (27.9%)	40 (10.3%)	.002
137-147	406 (82.7%)	68 (65.4%)	338 (87.3%)	.002
>147	16 (3.3%)	7 (6.7%)	9 (2.3%)	.002
Renal function-no. (%)				
Creatinine (μmol/L)				
≤123.76	100 (19.9%)	100 (89.3%)	0 (0.0%)	<.001
>123.76	402 (80.1%)	12 (10.7%)	390 (100.0%)	<.001
GFR				
<66	33 (6.6%)	19 (17.0%)	14 (3.6%)	<.001
≥66	469 (93.4%)	93 (83.0%)	376 (96.4%)	<.001
Arterial blood gas analysis-no. (%)				
PH				
<7.35	20 (6.2%)	9 (9.8%)	11 (4.7%)	.105
7.35-7.45	228 (70.2%)	52 (56.5%)	176 (75.5%)	.105
>7.45	77 (23.7%)	31 (33.7%)	46 (19.7%)	.105
OI				
<100	25 (7.7%)	18 (19.6%)	7 (3.0%)	<.001
100-300	93 (28.6%)	50 (54.3%)	43 (18.5%)	<.001
>300	207 (63.7%)	24 (26.1%)	183 (78.5%)	<.001
PCO_2 (mm Hg)				
<35	71 (21.8%)	30 (32.6%)	41 (17.6%)	.001
35-45	180 (55.4%)	50 (54.3%)	130 (55.8%)	.001
>45	74 (22.8%)	13 (13.1%)	62 (26.6%)	.001
Lactic acid (mmol/L)				
≤2.2	237 (72.9%)	59 (64.1%)	178 (76.4%)	.025
>2.2	88 (27.1%)	33 (35.9%)	55 (23.6%)	.025
Radiographic findings -no. (%)*				
Bilateral pneumonia	371 (88.5%)	68 (89.5%)	303 (88.3%)	.779
Unilateral pneumonia	48 (11.5%)	8 (10.5%)	40 (11.7%)	.779

The data was expressed in the form of n (%) where N represented the total number of patients with available data.
APTT = activated partial thromboplastin time, BNP = B-type natriuretic peptide, CKMB = creatine kinase isoenzyme, ESR = erythrocyte sedimentation rate, GFR = glomerular filtration rate, hsCRP = hypersensitive C-reactive protein, MODS = multiple organ dysfunction syndrome, PCO_2 = partial pressure of carbon dioxide.
* Radiographic findings include the findings of both chest X-ray and lung CT scan.

3.5. Risk factors for multiple organ failure

Multivariate Logistic regression analysis showed that lymphocyte counts $<1.0 \times 109$/L (OR = 3.606, 95% CI 1.131-11.500, $P = .030$/L), troponin T > 0.014 ng/mL (OR = 7.576, 95% CI 2.555-22.465, $P < .001$), and low oxygenation index were independent risk factors for MODS. In addition, our data suggested that the risk of MODS was negatively correlated with the oxygenation index (OR = 0.996, 95% CI 0.993-0.999, $P = .015$). As shown in Table 3.

3.6. Prognostic indicators for patients with MODS

Unsurprisingly, multiple organ failure increased the risk of death (log-rank $P < .001$, Fig. 1). Next, we used Cox proportional hazard regression model to identify risk factors that were associated with death in patients with MODS. The results showed that PCT > 0.1 ng/mL (HR = 2.803, 95% CI 1.268-6.195, $P = .011$), lactic acid > 2.2 mmol/L (HR = 2.520, 95% CI 1.283-4.950, $P = .007$) and admission within 24 hours after symptom onsets were the risk factors for death in patients with MODS. As shown in Table 4.

3.7. Treatment

All patients (100%) received intermittent or continuous oxygen inhalation. In the MODS group, 32 patients (29.4%) required invasive ventilation, 26 patients (23.9%) received noninvasive ventilation, 3 patients (2.8%) received high-flow nasal cannula oxygenation and no ECMO was applied in this study. Our study suggested that the proportions of patients who received invasive ventilator, noninvasive ventilator, and high flow respiratory support were higher in the MODS group ($P < .001$). Among MODS patients, 105 (96.3%) were treated with antiviral therapy and 86 (78.9%) were treated with 2 or more antimicrobial agents, both of which were higher compared to those in the non-MODS group ($P < .001$). In addition, 83 patients in the MODS group (76.1%) were treated with glucocorticoid, 29 patients (26.6%) with vasoactive drugs and 18 patients (16.5%) with IV immunoglobulin, which were all more common compared to those in the non-MODS group ($P < .001$; $P < .001$; $P = .003$). As shown in Table 5.

Among all patients, the median time from symptom onset to hospital admission was 9 days (IQR, 6-14). The median time from symptom onset to dyspnea was 0 days (IQR, 0-7), the time

Table 3

Logistic regression analysis of risk factors for MODS in patients with COVID-19.

	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Demographics and clinical characteristics				
Age, yrs				
<60	1 (ref)			
≥60	5.770 (3.550-9.378)	<.001	1.671 (0.490-5.695)	.412
Sex				
Male	2.379 (1.572-3.599)	<.001		
Female	1 (ref)			
Symptom				
Fever	2.429 (1.500-3.933)	<.001		
Dyspnea	3.582 (2.344-5.472)	<.001		
Fatigue	1.735 (1.158-2.599)	.008		
Sputum production	1.546 (1.016-2.353)	.042		
Comorbidity				
Hypertension	2.132 (1.414-3.214)	<.001	0.859 (0.301-2.450)	.859
Cardiovascular disease	2.306 (1.287-4.132)	.005		
Diabetes	1.711 (1.006-2.908)	.047		
Malignancy	3.397 (1.460-7.902)	.005		
Laboratory results				
Blood tests				
Leucocytes (10^9/L)				
<4	0.300 (0.153-0.588)	<.001		
4-10	1 (ref)			
>10	4.373 (2.241-8.535)	<.001		
NE (%)				
40-75	1 (ref)			
>75	9.145 (5.623-14.872)	<.001	1.714 (0.506-5.806)	1.714
LN (%)				
<20	1.153 (0.673-1.978)	.604		
20-50	1 (ref)			
Lymphocyte count (10^9/L)				
<1.0	5.450 (3.307-8.982)	<.001	3.606 (1.131-11.500)	.030
≥1.0	1 (ref)			
Inflammatory parameters				
Procalcitonin (ng/mL)				
≤0.1	1 (ref)			
>0.1	10.825 (6.266-18.702)	<.001	2.786 (0.931–8.333)	.067
hsCRP (mg/L)				
≤3	1 (ref)			
>3	21.562 (5.185-89.659)	<.001	1.453 (0.135–15.680)	.758
ESR (mm/h)				
≤15	1 (ref)			
>15	11.000 (3.217-37.613)	<.001		
Myocardial enzyme				
Troponin T (ng/mL)				
≤0.014	1 (ref)			
>0.014	8.216 (4.986-13.539)	<.001	7.576 (2.555–22.465)	<.001
Heart failure indicator				
NT-pro BNP (pg/mL)				
≤222	1 (ref)			
>222	6.299 (3.387-11.711)	<.001		
Liver function				
Aspartate aminotransferase (IU/L)				
≤40	1 (ref)			
>40	6.569 (4.113-10.491)	<.001	1.216 (0.395–3.746)	.733
Electrolyte				
Potassium (mmol/L)				
>5.3	10.471 (1.990–55.110)	.006		
3.5-5.3	1 (ref)			
<3.5	2.279 (1.412-3.679)	.001		
Sodium (mmol/L)				
<137	2.976 (1.736-5.102)	<.001		
137-147	1 (ref)			

(*continued*)

Table 3
(continued).

	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
>147	3.592 (1.493-8.642)	.004		
Renal function				
GFR				
<66	4.936 (2.434-10.012)	<.001	0.838 (0.146-4.819)	.843
≥66	1 (ref)			
Arterial blood gas analysis				
PH				
<7.35	2.265 (0.939-5.462)	.069		
7.35-7.45	1 (ref)			
>7.45	2.491 (1.427-4.348)	.001		
Lac (mmol/L)				
≤2.2	1 (ref)			
>2.2	1.773 (1.048-2.999)	.033		
Oxygenation index	0.993 (0.991-0.995)	<.001	0.996 (0.993-0.999)	.015

Univariate logistic regression analysis was performed and ten variables were selected for further multivariate analysis.
BNP = B-type natriuretic peptide, ESR = erythrocyte sedimentation rate, GFR = glomerular filtration rate, hsCRP = hypersensitive C-reactive protein, LN = lymphocyte, NE = neutrophil, OR = odds ratio, MODS = multiple organ dysfunction syndrome, PH = potential of hydrogen.

to acute respiratory distress syndrome was 10 days (IQR, 6-15), the time to mechanical ventilation was 10 days (IQR, 6-15) and the time to death was 21 days (IQR, 15.75-27.7). The median hospital stay for all screened patients was 16 days (IQR, 9-26) and it was 20 days in the MODS group (IQR, 11.5-30.5) that was significantly longer than that among non-MODS patients ($P < .001$).

4. Discussion

COVID-19 was a new acute respiratory infectious disease caused by SARS-CoV-2 that belongs to β-coronavirus. Research had shown that it had a homology of more than 85% with bat SARS-like coronavirus.[4–6] It has been well accepted in clinic that the patients will generally have poor prognosis once progressed into MODS. Therefore, comprehensive depiction and examination of

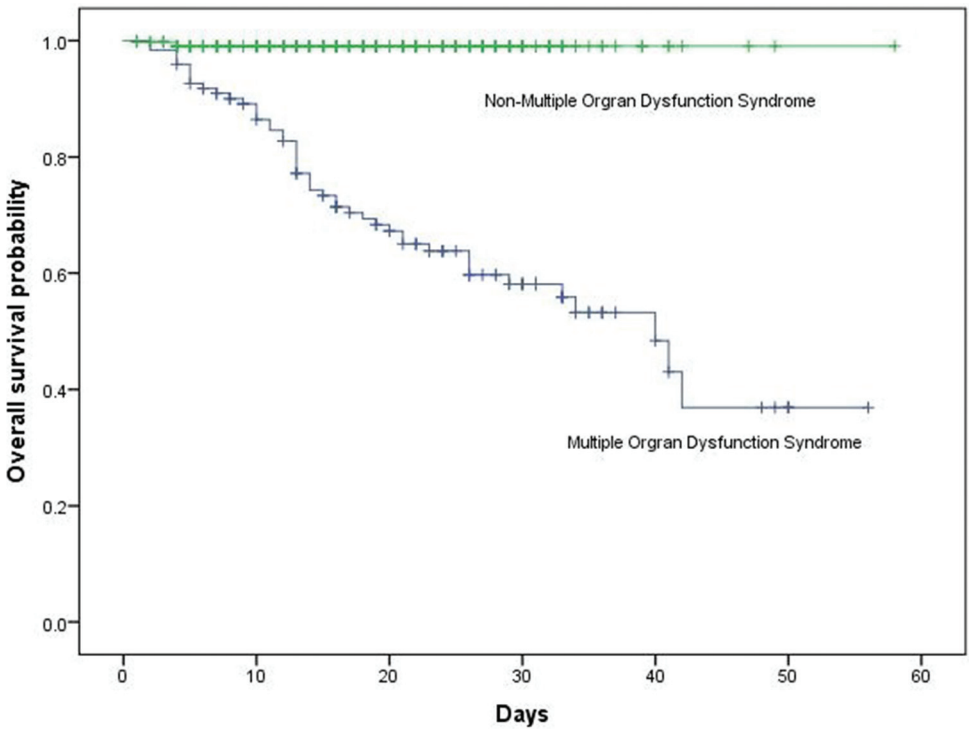

Figure 1. Survival curves of COVID-19 patients with or without multiple organ failure. Data are shown in the form of n (%).

Table 4

Cox proportional hazards model of risk factors for death in patients with COVID-19 complicated with MODS.

	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Demographics and clinical characteristics				
Age, yrs				
<60 vs ≥60	1.969 (0.835-4.644)	.122		
Sex				
Male vs female	1.252 (0.700-2.239)	.449		
Symptom				
Fever (have vs not)	1.353 (0.625-2.929)	.443		
Dyspnea (have vs not)	0.859 (0.452-1.631)	.642		
Fatigue (have vs not)	0.884 (0.500-1.565)	.673		
Sputum production (have vs not)	0.827 (0.464-1.477)	.521		
Comorbidity				
Hypertension (have vs not)	0.905 (0.508-1.612)	.735		
Cardiovascular disease (have vs not)	0.729 (0.349-1.522)	.400		
Diabetes (have vs not)	0.540 (0.285-1.022)	.058		
Malignancy (have vs not)	0.674 (0.285-1.593)	.369		
Laboratory results				
Blood tests				
Neutrophil percentage (%)				
40-75 vs >70	1.955 (0.907-4.214)	.087		
Lymphocyte percentage (%)				
<20 vs 20-50	0.439 (0.172-1.126)	.087		
Lymphocytes (10^9/L)				
<1.0 vs ≥1.0	0.823 (0.383-1.771)	.619		
Inflammatory parameters				
Procalcitonin (ng/mL)				
≤0.1 vs >0.1	2.310 (1.094-4.878)	.028	2.803 (1.268-6.195)	.011
hsCRP (mg/L)				
≤3 vs >3	21.008 (0.000-88785226.09	.696		
ESR (mm/h)				
≤15 vs >15	0.783 (0.099-6.172)	.817		
Myocardial enzyme				
CTnT (ng/mL)				
≤0.014 vs >0.014	1.866 (0.975-3.570)	.059		
Heart failure indicator				
NT-pro BNP (pg/mL)				
≤222 vs >222	1.494 (0.605-3.692)	.384		
Liver function				
Aspartate aminotransferase (IU/L)				
≤40 vs >40	1.330 (0.747-2.368)	.332		
Renal function				
GFR				
<66 vs ≥66	0.870 (0.385-1.965)	.737		
Arterial blood gas analysis				
Lac (mmol/L)				
≤2.2 vs >2.2	2.369 (1.258-4.463)	.008	2.520 (1.283-4.950)	.007
Oxygenation index				
≤300 vs >300	2.271 (0.945-5.453)	0.067		

Univariate and multivariate COX regression analysis were carried out, and 2 variables were selected for further multivariate analysis.

BNP = B-type natriuretic peptide, COVID-19 = coronavirus disease 2019, CTnT = Troponin T, ESR = erythrocyte sedimentation rate, GFR = glomerular filtration rate, hsCRP = hypersensitive C-reactive protein, HR = hazard ration, MODS = multiple organ dysfunction syndrome.

COVID-19 patients with MODS are needed so timely adjustment and proper prevention could be made.

In our research, it was found that after COVID-19 patients were admitted to the hospital, some patients developed into MODS, mainly elderly men, often associated with underlying diseases, such as high blood pressure, heart disease, etc at the same time, in laboratory examinations, patients showed abnormalities of inflammatory indicators, electrolytes and D-Dimer, low absolute value of lymphocytes counts, elevated troponin T, and low oxygenation index were the risk factors of the multiple organ failure.

In this study, our data suggested that among all 109 patients with MODS, most (79.8%) had fever upon admission, followed by dyspnea (73.4%), fatigue (55.0%), dry cough (51.4%), sputum (34.9%) and stomachache (13.8%), diarrhea (8.3%). This discovery was similar to previous studies including smaller cohorts.[6,7]

In terms of demographic characteristics, several epidemiological surveys about COVID-19 showed the median age was 47 to 53 years old.[4,8–11] Unsurprisingly, we showed that the proportion of elderly (over 60 years old) patients in the MODS group was significantly higher compared to those without MODS,

Table 5

Treatment and prognosis of patients with COVID-19.

	All patients (N = 526)	MODS (n = 109)	Non-MODS (n = 417)	*P* value
Antiviral therapy no. %	429 (81.6%)	105 (96.3%)	324 (77.7%)	<.001
Antibacterial therapy no. %				
1 kind	200 (38.0%)	25 (22.9%)	175 (42.0%)	<.001
≥2 kinds	221 (42.0%)	86 (78.9%)	135 (32.4%)	<.001
Antifungal therapy	9 (1.7%)	6 (5.5%)	3 (0.7%)	.003
Glucocorticoids therapy	181 (34.4%)	83 (76.1%)	98 (23.5%)	<.001
Immunotherapy				
Human immunoglobulin	48 (9.1%)	18 (16.5%)	30 (7.2%)	.003
Thymosin	8 (1.8%)	3 (3.3%)	5 (1.4%)	.273
Vasoactive drug	31 (5.9%)	29 (26.6%)	2 (0.5%)	<.001
CRRT	2 (0.4%)	2 (1.8%)	0 (0.0%)	.043
Respiratory support-no. %				
Nasal catheter/mask	459 (87.3%)	48 (44.0%)	411 (98.6%)	<.001
High-flow nasal cannula	5 (1.0%)	3 (2.8%)	2 (0.5%)	<.001
Noninvasive ventilation	29 (5.5%)	26 (23.9%)	3 (0.7%)	<.001
Invasive ventilation	32 (6.3%)	32 (29.4%)	1 (0.2%)	<.001
ECMO	0 (0.0%)	0 (0.0%)	0 (0.0%)	<.001
Prognosis-no. %				
Improved	474 (90.1%)	61 (56.0%)	413 (99.0%)	<.001
Death	52 (9.9%)	48 (44.0%)	4 (1.0%)	<.001
Days from disease onset to, Median (IQR)-d				
Admission	9 (6-14)	9 (7-11)	9 (6-14.5)	.628
Dyspnea	0 (0-7)	3 (0-8)	0 (0-7)	.017
Mechanical ventilation	10 (6-15)	10 (7-13)	7 (5-15)	.004
ARDS	10 (6-15)	10 (7-13)	7 (5-15)	.004
Length of hospital stay	16 (9-26)	20 (11.5-30.5)	16 (9-23.5)	.002
Death	21 (15.75-27.75)	21.5 (18-30.25)	10 (8.75-11.5)	<.001
SOFA score	1 (1-3)	4 (3-5)	1 (1-2)	<.001

The data was shown in the form of median (IQR) and n (%).

ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, CRRT = continuous blood purification treatment, ECMO = extracorporeal membrane oxygenation, IQR = interquartile, MODS = multiple organ dysfunction syndrome, SOFA = sequential organ failure asses.

which further confirmed the idea that aging might be a risk factor for poor prognosis.

In this study, our data suggested that the mortality rate was 44% in the MODS group and 1% in the non-MODS group after hospitalization for as long as 58 days. There was a significant difference in overall survival time between the 2 groups ($P < .001$) which further emphasize the importance of early identification of MODS.

It has been speculated that novel coronavirus suppresses immune response, destroys body's defense system and eventually leads to an uncontrollable inflammatory storm and multiple organ failure. In this study, multivariate Logistic regression analysis revealed that the lymphocyte counts $<1.0 \times 109$/L, troponin T > 0.014 ng/mL and lower oxygenation index were associated with the occurrence of MODS in COVID-19 patients. Meanwhile, our data suggested that PCT > 0.1 ng/mL and lactic acid > 2.2 mmol/L were risk factors of poor prognosis for COVID-19 patients with MODS. Each of these indicators was further reviewed and discussed below:

4.1. Procalcitonin

This study showed that there were significantly more patients with increased PCT in MODS group compared to non-MODS group ($P < .001$). The endotoxin produced by bacteria and the cytokines secreted during inflammatory reactions are the main reasons for the elevation of PCT.[12,13] Generally, the level of PCT does no elevate, or only slightly increases during virus infection.[14,15] The increase of PCT in the MODS group indicated a possible secondary bacterial infection that could be neglected due to similar respiratory symptom that eventually increased the mortality rate.

4.2. Lymphocyte

SARS-CoV,[16] MERS-CoV[17] and SARS-CoV-2 in the coronavirus family can all cause lymphocytopenia in infected patients.

We found that the number of lymphocytes decreased in patients infected with SARS-CoV-2, especially in patients with worse prognosis. This observation was consistent with other studies.[2,5,18,19] Some study even suggested that the number of lymphocytes could be used as a reference index for the diagnosis of SARS-Cov-2 infection.[5] Furthermore, some studies[20] demonstrated that the number of $CD4^+$ and $CD8^+$ T cells were negatively associated with the severity of the disease. It has been proposed that the significant decrease in the total number of lymphocytes indicates an exhaustion of immune cells and suppression of cellular immune function which often lead to the aggravation of the disease.[21,22] Therefore, the early decrease of lymphocytes can reflect patients' overall impaired reserve of immune function and provide an idea for early identification of critically ill patients.

4.3. Troponin

Epidemiological studies have reported[2,6,7,23,24] that the occurrence of elevated cardiac biomarkers in COVID-19 hospitalized

patients ranged from 12% to 23%, which further increased up to 46% in critically ill and dead patients. Among the very first hospitalized COVID-19 patients, 7.2% to 12% of the patients had elevated hs-cTnI, and nearly 80% of the patients with myocardial injury needed intensive care.[2,7]

Beside lung, the involvement of heart is also very common in COVID-19.[25,26] Previous pathology reports[15] identified degeneration and necrosis of cardiomyocytes and infiltration of monocytes, lymphocytes, and/or neutrophils in the interstitium in addition to vascular endothelium exfoliated, intimal inflammation, and thrombosis. However, contradictory findings from autopsy reports showed that there was limited interstitial monocyte infiltration in myocardial tissue accompanied by no substantial myocardial injury. Therefore, it has been proposed that the myocardial injury in patients with COVID-19 was mainly due to the joint action of hypoxemia, respiratory failure, virus,[27] and aberrant immune inflammation. However, further studies are needed to clarify the pathogenesis of myocardial injury induced by SARS-CoV-2.

4.4. Lactic acid

This study showed that the lactic acid level was more frequently elevated in patients with MODS compared to non-MODS patients (35.9% vs 23.6%, $P = .025$). The mortality rate of MODS patients with early lactic acid > 2.0 mmol/L increased by 2.520 times. A retrospective study concluded[28] that patients with septic shock could benefit from early administration of norepinephrine. The increased lactic acid in MODS patients reflected a lack of tissue oxygenation, poor tissue perfusion, and liver injury in later states. Several studies have shown that the time to start vasopressin had an intermediary effect on lactic acid levels.[29] Our results confirmed the benefits of early lactic acid determination and suggested that MODS patients with increased lactic acid levels often associated with poor prognosis.

4.5. Oxygenation index

It has been known that hypercapnia rather than hypoxia can cause dyspnea.[30,31] Many patients with dyspnea were not hypoxemia, whereas those with hypoxemia usually had only a slight improvement in symptoms after the hypoxemia was corrected.[30] Studies have shown the disconnect between the severity of hypoxemia and respiratory symptoms in COVID-19 patients.[32] It has been reported that among all 1099 hospitalized COVID-19 patients, only 18.7% complained difficulty breathing, even though the prevalence of low PaO_2/FiO_2 ratios was much higher.[2] On the other hand, our data suggested that lower oxygenation index were associated with the occurrence of MODS in COVID-19 patients. This discrepancy contrasted sharply with clinic experience in treating critically ill patients with respiratory failure therefore more studies are needed to better understand the pathogenesis.

This study examined and summarized the clinical characteristics and COVID-19 patients with MODS and identified several risk factors. However, it had some limitations: This study was a retrospective study, and some epidemiological data might be incomplete. This study only enrolled patients from a single center that might not fully represent the general population. Some patients were excluded from the study after they were transferred to the superior hospital which might bias the results.

To sum up, COVID-19 patients that eventually developed into MODS were mainly elderly men, often complicated with underlying diseases. The lymphocyte counts $<1.0 * 10^9$/L, troponin T > 0.014 ng/mL and low oxygenation index were the risk factors of multiple organ failure. Meanwhile, in the early stage of admission, increased inflammatory indexes and lactic acid concentration were the risk factors of death in patients with MODS.

Acknowledgments

We acknowledge all the staff from the Wuhan Seventh hospitals for their remarkable efforts to provide care for patients with COVID-19. We are very grateful to all Medical teams to assist Hubei for its great efforts. The authors thank Dr. Xiaowei Gong for the suggestions about this paper. The authors thank the patients and their families for cooperation during the treatment.

Author contributions

Conceptualization: Boyun Yuan.
Data curation: Yan Li.
Visualization: Zhu Li.
Writing – original draft: Jianghua Cui.
Writing – review & editing: Yadong Yuan.

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