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

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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 \(< 1.0 \times 10^9/L\), Troponin T \( > 0.014 \text{ng/mL} \) 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).\textsuperscript{[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.\textsuperscript{[2]} Currently, no effective treatment has been developed for COVID-19, especially for patients developed MODS. Therefore, it is critical to identify patients with...
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; 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 PaO2/ FiO2 <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 × 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 <500mL/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.

2.3. Statistical methods
Variables were expressed as frequency and percentage. χ² 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, leukocytes, 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 Windows. Armonk, NY: IBM Corp). A P value less than.05 was considered statistically 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 × 10^9/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.

| Age, yrs- no. (%) | All patients (N=526) | MODS (n=109) | Non-MODS (n=417) | \( P \) value |
|------------------|----------------------|--------------|------------------|-------------|
| <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%)          | 69 (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.

| Blood tests-no. (%) | All patients (N = 526) | MODS (n = 109) | Non-MODS (n = 417) | P value |
|---------------------|------------------------|----------------|--------------------|---------|
| 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 (63.2%)     | 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 (14.7%)     | 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)
3.5. Risk factors for multiple organ failure

Multivariate Logistic regression analysis showed that lymphocyte counts <1.0 x 10^9/L (OR=3.606, 95% CI 1.131-11.500, \( P < .001 \)), 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, \( P < .001 \)). 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.

### Table 2 (continued)

|                              | All patients (N = 526) | MODS (n = 109) | Non-MODS (n = 417) | \( P \) value |
|------------------------------|------------------------|----------------|--------------------|--------------|
| Sodium (mmol/L)              |                        |                |                    |              |
| <137                         | 69 (14.0%)             | 29 (27.9%)     | 40 (10.3%)         | .002         |
| 137-147                      | 406 (82.7%)            | 68 (65.4%)     | 338 (82.3%)        | .002         |
| >147                         | 16 (3.3%)              | 7 (6.7%)       | 9 (2.3%)           | .002         |
| **Renal function-no. (%)**   |                        |                |                    |              |
| Creatinine (\( \mu \)mol/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 (8.8%)       | 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 (22.6%)     | 41 (17.6%)         | .001         |
| 35-45                        | 180 (55.4%)            | 50 (42.3%)     | 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.

3.7. 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
| Demographics and clinical characteristics | Univariable OR (95% CI) | P value | Multivariable OR (95% CI) | P value |
|------------------------------------------|-------------------------|---------|---------------------------|---------|
| Demographic and clinical characteristics  |                         |         |                           |         |
| Age, yrs                                 |                         |         |                           |         |
| <60                                      | 1 (ref)                 | <.001   | 1.671 (0.490-5.695)       | .412    |
| ≥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)     | <.001   |                         |         |
| 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)     | <.001   |                         |         |
| Diabetes                                 | 1.711 (1.006-2.908)     | <.001   |                         |         |
| 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)                       |                         |         |                           |         |
| >3.5                                     | 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)
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

| 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.

Figure 1. Survival curves of COVID-19 patients with or without multiple organ failure. Data are shown in the form of n (%).
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 4

| Demographics and clinical characteristics                                      | Univariate HR (95% CI) | P value | Multivariate HR (95% CI) | P value |
|---------------------------------------------------------------------------------|------------------------|---------|--------------------------|---------|
| **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**                                                           |                        |         |                          |         |
| Neutrophil percentage (%)                                                        | 1.955 (0.907-4.214)    | .087    |                          |         |
| Lymphocyte percentage (%)                                                        | 0.439 (0.172-1.126)    | .087    |                          |         |
| Lymphocytes (10^9/L)                                                             | 0.823 (0.383-1.771)    | .619    |                          |         |
| **Inflammatory parameters**                                                      |                        |         |                          |         |
| Procalcitonin (ng/mL)                                                           | 2.310 (1.094-4.878)    | .028    | 2.803 (1.268-6.195)      | .011    |
| hsCRP (mg/L)                                                                    | 21.008 (0.000-88785226.09 | .696    |                          |         |
| ESR (mm/h)                                                                      | 0.783 (0.099-6.172)    | .817    |                          |         |
| Myocardial enzyme                                                               |                        |         |                          |         |
| CTnT (ng/mL)                                                                    | 1.866 (0.975-3.570)    | .059    |                          |         |
| Heart failure indicator                                                          | 1.494 (0.605-3.692)    | .384    |                          |         |
| **Liver function**                                                              |                        |         |                          |         |
| Aspartate aminotransferase (IU/L)                                               | 1.330 (0.747-2.368)    | .332    |                          |         |
| GFR <40 vs ≥40                                                                 | 0.870 (0.385-1.965)    | .737    |                          |         |
| Arterial blood gas analysis                                                      |                        |         |                          |         |
| Lac (mmol/L)                                                                    | 2.369 (1.258-4.463)    | .008    | 2.520 (1.283-4.950)      | .007    |
| Oxygenation index                                                               | 2.271 (0.945-5.453)    | .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.
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 x 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 the mortality rate was higher in the MODS group compared to the non-MODS group (P < .001).

Promising results were obtained for the early detection of MODS. An elevated serum level of procalcitonin (PCT) could be used as an early indicator of MODS. Additionally, other studies have suggested that lymphocytes could be used as a reference index for the diagnosis of SARS-CoV-2 infection. 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. 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.

### 4.2. Lymphocyte

SARS-CoV-1, MERS-CoV and SARS-CoV-2 in the coronavirus family all can 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. Some study even suggested that the number of lymphocytes can be used as a reference index for the diagnosis of SARS-CoV-2 infection. Furthermore, some studies 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. 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 that the occurrence of elevated cardiac biomarkers in COVID-19 hospitalized patients.
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-CtNl, and nearly 80% of the patients with myocardial injury needed intensive care.\(^7\)

Beside lung, the involvement of heart is also very common in COVID-19.\(^{12,26}\) Previous pathology reports\(^{115}\) 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%, \(P=0.025\)). 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.\(^{42}\) It has been reported that among all 1099 hospitalized COVID-19 patients, only 18.7% complained difficulty breathing, even though the prevalence of low PaO2/FiO2 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 \(<1.0 \times 10^3/\text{L}\), 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.

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