# Early Risk Factors for Extrapulmonary Organ Injury in Adult COVID-19 Patients

**Fang Huang**
First Affiliated Hospital of Soochow University
**Wenxia Ma**
First Affiliated Hospital of Soochow University
**Jun Jin**
First Affiliated Hospital of Soochow University
**Hui Zheng**
Soochow University
**Yan Ye**
Tongji Hospital of Tongji Medical College of Huangzhong University of Science and Technology
**Hui Chen**
First Affiliated Hospital of Soochow University
**Nan Su**
First Affiliated Hospital of Soochow University
**Xinyue Li**
First Affiliated Hospital of Soochow University
**Xiaoping Li**
First Affiliated Hospital of Soochow University
**Xiangqiong Lu**
First Affiliated Hospital of Soochow University
**Yang He**
First Affiliated Hospital of Soochow University
**Yuyu Wang**
First Affiliated Hospital of Soochow University
**Yongsheng Li**
First Affiliated Hospital of Soochow University
**Jun Wang** ( dr_wangjun@suda.edu.cn )
The first affiliated hospital of Soochow University https://orcid.org/0000-0001-8708-3096

**Research**

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# Abstract

**Objective** COVID-19 is becoming a global pandemic and often develops extrapulmonary organ injury. However, the risk factors for extrapulmonary organ injury are still unclear. We aim to explore the risk factors for extrapulmonary organ injury for COVID-19 and the association between extrapulmonary organ injury and the prognosis of COVID-19 patients.

**Methods** This is a single-center, retrospective, observational study and total 349 confirmed COVID-19 patients admitted to Tongji Hospital from January 25 to February 25, 2020 were enrolled. We collected demographic, clinical, laboratory and treatment data from electronic medical records. Potential risk factors for extrapulmonary organ injury of COVID-19 patients were analyzed by a multivariable binary logistic model, and multivariable COX proportional hazard regression model was used for survival analysis in the patients with extrapulmonary organ injury.

**Results** Average age of the included patients was 61.73±14.64 years. In the final logistic model, variables including aged 60 or older (OR 1.826, 95% CI 1.060-3.142), ARDS (OR 2.748, 95% CI 1.051-7.185), lymphocytes count lower than 1.1 $\times 10^9$/L (OR 0.478, 95% CI 0.240-0.949), level of IL-6 greater than 7 pg/ml (OR 1.664, 95% CI 1.005-2.751) and D-Dimer greater than 0.5 μg/ml (OR 2.190, 95% CI 1.176-4.084) were significantly associated with the extrapulmonary organ injury. Kaplan-Meier curve and log-rank test showed that the probabilities of survival for patients with extrapulmonary organ injury were significantly lower than those without extrapulmonary organ injury.between Multivariate COX proportional hazards model showed that only myocardial injury (P=0.000, HR: 5.068, 95% CI: 2.728-9.417) and circulatory system injury (P=0.000, HR: 4.076, 95% CI: 2.216-7.498) were the independent factors associated with COVID-19 patients' poor prognosis.

**Conclusion** Older age, lymphocytopenia, high level of D-Dimer and IL-6 and the severity of lung injury were the high-risk factors of extrapulmonary organ injury in COVID-19 patients. Myocardial and circulatory system injury were the most important risk factors related to poor outcomes of COVID-19 patients. It may help clinicians to identify extrapulmonary organ injury early and provide relevant management strategy.


# Background

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection is becoming a global pandemic, and it has spread quickly in more than 210 countries, areas or territories. There have been over 2 300 000 confirmed cases, with 10–20% developing severe COVID-19, more than 157 000 patients died[1], furthermore the number of daily confirmed cases is continuing to increase. Although, until 21th April, the mortality (6.8%, 157 970 confirmed deaths of 2 319 066 confirmed cases) of COVID-19 is lower than Severe Acute Respiratory Syndrome (SARS) in 2003 (9.6%, 774 died of 8096 infected) and Middle East Respiratory Syndrome (MERS) in 2012 (34·4%, 858 died of 2494 infected)[1, 2], the deaths toll will be a huge number because of the large and increasing number of infections.

COVID-19 is a respiratory infection disease, which may cause pneumonia even severe acute respiratory distress syndrome(ARDS) in severe cases[3]. In addition to lung lesion, some critically ill patients often develop dysfunction of extra-pulmonary organs, including acute kidney injury, cardiac injury, liver dysfunction and gastrointestinal hemorrhage. Recent study showed AKI occurred in 5.1% patients and kidney disease was associated with in-hospital death of patients with COVID-19[4]. Respiratory failure and organ dysfunction are common causes of death in patients with COVID-19[5, 6]. Nevertheless, previous studies about extrapulmonary organ injury is limited and most of them focused on a single organ injury for COVID. It is crucial to explore the risk factors for extrapulmonary organ injury and the association with prognosis.

In our study, we investigated severe and critically ill patients with confirmed SARS-CoV-2 pneumonia who were admitted to Wuhan Tongji hospital. Through observing and comparing the demographic, clinical and laboratory characteristics as well as complications, treatments and outcomes of all these patients, we aim to indicated the potential early risk factors for the injury of extra-pulmonary organs when infected with SARS-CoV-2, furthermore we try to explore the relationship between the extrapulmonary organ injury and prognosis in severe and critically ill confirmed patients.

# Methods

### Study Design and Participants

This single-center, retrospective, observational study was performed at Wuhan Tongji hospital, Huazhong University of Science and Technology, which was a designated treatment center for confirmed patients with COVID-19 in Wuhan. All the patients enrolled in the study were severe and critical ill patients who were diagnosed with SARS-CoV-2 pneumonia according to WHO interim guidance by positive result of a RT-PCR assay of nasal and (or) throat-swab specimens and were admitted to the hospital from January 25 to February 25, 2020[7]. Only patients who had died or were discharged from hospital were included in this study. 5 patients died within 24 hours after admission and the records were not completed, were excluded. Patients who were younger than 18 years old were also excluded. This was a retrospective case series study, and no patients were involved in the study design or in setting the research questions or the outcome measures directly. No patients were asked to advise on interpretation or writing up of results.

### Data collection

We obtained clinical data, including chronic comorbidities, demographic information, clinical symptoms, laboratory tests, as well as treatment, complication and outcome data, from electronic medical records system by using data collection forms. We also recorded the time from symptoms onset to hospital admission of all the patients, not every patient received arterial blood gas analysis Because of too many patients in the early stage of COVID-19 outbreak, and peripheral capillary oxygen saturation (SpO2) and fraction of inspired oxygen (FiO2) were recorded. The SpO2/FiO2 (S/F) ratio was used to evaluate the status of respiration, which had been reported could be a useful replaceable index of ARDS evaluation when arterial oxygen partial pressure (PaO2) could not be obtained[8]. All the data were entered and cross checked independently by three physicians in a computerized database.

### Organ injury

All the patients were confirmed COVID-19 pneumonia, some of them developed acute respiratory distress syndrome (ARDS). ARDS was diagnosed according to the Berlin Definition[9]. In addition to the pneumonia, we focused on the damage to extrapulmonary organs, including myocardial injury, liver injury, acute kidney injury as well as injury of blood and circulatory system. Myocardial injury was diagnosed according to the serum level of cardiac biomarkers or new abnormalities in electrocardiography and echocardiography. Liver injury was diagnosed as the elevated serum levels of bilirubin and aminotransferase. AKI was defined according to KIDGO clinical practice guidelines[10]. According to the MODS score, blood system injury was defined as platelet count lower than $120\times10^9$/L[11]. Circulation system injury was defined as mean arterial blood pressure (MAP) lower than 70mmHg or the need of vasopressor to maintain MAP of 70mmHg according to SOFA score.

### Laboratory tests

Clinical laboratory investigation included complete blood cell count, serum biochemical tests (including level of creatinine, ALT, AST, lactate dehydrogenase, albumin, immunoglobulin and electrolytes), coagulation index(including level of D-Dimer), cardiac biomarkers (including high-sensitivity cardiac troponin I, myoglobin and CK-MB), inflammatory cytokines (including interleukin-2R, interleukin-6, interleukin-8, interleukin-10 and TNF-α), procalcitonin (PCT) and high sensitivity C reactive protein (hs-CRP)

### Management of patients

All the patients received intensive care after admission to the hospital, vital signs and SpO2 were monitored consecutively. We gave all the patients enough supportive treatments, which included sufficient calories and stabilities of internal environment such as water, electrolyte, and acid-base balance. Oxygen therapy should be given immediately to patients with

hypoxemia, if hypoxemia could not be improved by oxygen aspiration, advanced respiratory supports were performed, such as high-flow nasal catheter oxygen therapy (HFNC), non-invasive ventilation and invasive mechanical ventilation. When all these treatments failed, extracorporeal membrane pulmonary oxygenation (ECMO) could be recommended by the experts according to evaluation of the patient's condition. Empirical antimicrobial therapy, including anti-virus and antibiotics, were considered according to clinical practice and physicians' experience.

### Statistical analysis

Continuous variables were reported in mean ± standard deviation (±s) and tested using Kruskal-Wallis H. Categorical variables were expressed in frequency (%) and compared using the $c^2$ test or Fisher's exact test. An orderly logistic regression model was used to explore the risk factors associated with the extrapulmonary injury. The odds ratio (OR) along with the 95% confidence interval (95% CI) were reported. The Kaplan-Meier method and the log-rank test were used for survival analysis of extrapulmonary injury and the Cox proportional-hazards regression model was used to investigate risk factors. A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were done using IBM SPSS23.0.

## Results

### Baseline Characteristics

A total of 361 confirmed COVID-19 patients were enrolled, but only 349 patients who had complete data were included in the study. Average age of the including patients was 61.73 ± 14.64 years. Among them 197(56.4%) patients were aged 60 years or older and 167(47.9%) patients were female. Among these patients, the most common original comorbidity was hypertension, 143(41.1%) patients had hypertension and 63(18.2%) patients took ACE inhibitors, while the other comorbidities were diabetes 66(19%), cardiovascular disease 41(11.7%), chronic obstructive pulmonary disease (COPD) 16(4.6%). The most common symptoms of early stage of onset was fever (87.1%), dry cough (67.3%), dyspnea (60.7%), fatigue (49.3%), expectoration (39.3%), anorexia (26.9%) and diarrhea (26.4%) successively (Table 1).

Table 1
Baseline characteristics of COVID-19 patients

| | All patients(n = 349) | No extrapulmonary injury(n = 184) | Extrapulmonary injury (n = 165) | | | | | P value |
|---|---|---|---|---|---|---|---|---|
| | | | one injury(n = 43) | two injuries(n = 26) | three injuries(n = 36) | four injuries (n = 35) | five injuries (n = 25) | |
| **Base line information** | | | | | | | | |
| Age range, year | | | | | | | | 0.000 |
| ≤ 60 | 152(43.6) | 103(56.0) | 17(39.5) | 8(30.8) | 16(44.4) | 4(11.4) | 4(16.0) | |
| > 60 | 197(56.4) | 81(44.0) | 26(60.5) | 18(69.2) | 20(55.6) | 31(88.6) | 21(84.0) | |
| Gender | | | | | | | | 0.311 |
| Male | 182(52.1) | 92(50.0) | 21(48.8) | 18(69.2) | 21(58.3) | 15(42.9) | 15(60.0) | |
| Female | 167(47.9) | 92(50.0) | 21(51.2) | 8(30.8) | 15(41.7) | 20(57.1) | 10(40.0) | |
| Original comorbidities | | | | | | | | |
| Hypertension | 143(41.1) | 65(35.3) | 14(32.6) | 15(57.7) | 14(38.9) | 19(55.9) | 16(64.0) | 0.011 |
| ACE inhibitors | 63(18.2) | 31(16.8) | 3(7.0) | 5(19.2) | 5(13.9) | 10(29.4) | 9(37.5) | 0.031 |
| Diabetes | 66(19.0) | 28(15.2) | 10(23.3) | 8(32.0) | 5(13.9) | 9(25.7) | 6(24.0) | 0.220 |
| Cardiovascular disease | 41(11.7) | 16(8.7) | 4(9.3) | 7(26.9) | 5(13.9) | 3(8.6) | 6(24.0) | 0.038 |
| COPD | 16(4.6) | 4(2.2) | 3(7.0) | 1(3.8) | 4(11.1) | 3(8.6) | 1(4.0) | 0.165 |
| **Signs and symptoms** | | | | | | | | |
| Fever | 304(87.1) | 160(87.0) | 40(93.0) | 22(84.6) | 30(83.3) | 30(85.7) | 22(88.0) | 0.846 |
| Dry cough | 235(67.3) | 119(64.7) | 30(69.8) | 18(69.2) | 26(72.2) | 24(68.6) | 18(72.0) | 0.923 |
| Fatigue | 172(49.3) | 88(47.8) | 22(51.2) | 13(50.0) | 17(47.2) | 17(48.6) | 15(60.0) | 0.920 |
| Expectoration | 137(39.3) | 73(39.7) | 18(41.9) | 10(38.5) | 11(30.6) | 18(51.4) | 7(28.0) | 0.442 |
| Diarrhea | 92(26.4) | 53(28.8) | 16(37.2) | 3(11.5) | 9(25.0) | 4(11.4) | 7(28.0) | 0.070 |
| Anorexia | 94(26.9) | 47(25.5) | 14(32.6) | 9(34.6) | 5(13.9) | 10(28.6) | 9(36.0) | 0.320 |
| Dyspnea | 212(60.7) | 98(53.3) | 25(58.1) | 14(53.8) | 27(75.0) | 28(80.0) | 20(80.0) | 0.004 |
| **Vital signs** | | | | | | | | |
| Heart rate, bpm | 92.93 ± 16.83 | 91.17 ± 14.92 | 90.53 ± 15.37 | 93.58 ± 15.81 | 96.63 ± 23.21 | 96.80 ± 18.86 | 98.64 ± 0.55 | 0.360 |
| Respiratory rate, rpm | 23.68 ± 6.98 | 22.45 ± 6.83 | 23.44 ± 6.30 | 23.54 ± 5.79 | 26.75 ± 8.05 | 25.31 ± 7.13 | 26.52 ± 6.51 | 0.000 |
| Systolic pressure, mmHg | 132.2 ± 19.77 | 132.10 ± 18.20 | 132.49 ± 19.29 | 133.04 ± 18.75 | 133.0 ± 21.16 | 129.43 ± 23.18 | 134.36 ± 26.33 | 0.873 |

Abbreviations: COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; WBC: White blood count cell; N/L: neutrophil-to-lymphocyte ratio; RDW: RBC Distribution Width; HS-CRP: high-sensitivity C-reactive protein; PCT: procalcitonin; e-GFR: glomerular filtration rate; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; IV: invasive ventilation.

| | All patients(n = 349) | No extrapulmonary injury(n = 184) | Extrapulmonary injury (n = 165) | | | | | P value |
|---|---|---|---|---|---|---|---|---|
| | | | one injury(n = 43) | two injuries(n = 26) | three injuries(n = 36) | four injuries (n = 35) | five injuries (n = 25) | |
| $SpO_2/FiO_2$ | 353.78 ± 128.65 | 316.53 ± 100.47 | 270.74 ± 134.40 | 170.47 ± 103.89 | 167.17 ± 101.84 | 151.13 ± 98.75 | 121.19 ± 74.29 | 0.000 |
| ARDS | 148(42.4) | 20(10.9) | 15(34.9) | 19(73.1) | 34(94.4) | 35(100) | 25(100) | 0.000 |
| **Laboratory findings at admission** | | | | | | | | |
| WBC, $\times10^9$/L | 7.65 ± 4.94 | 4.87 ± 2.56 | 7.35 ± 6.38 | 8.10 ± 6.17 | 10.50 ± 6.04 | 10.51 ± 5.22 | 12.92 ± 5.07 | 0.000 |
| Neutrophils, $\times10^9$/L | 6.44 ± 6.52 | 4.25 ± 2.46 | 5.86 ± 5.82 | 10.43 ± 17.14 | 9.09 ± 5.64 | 9.37 ± 5.09 | 11.86 ± 4.95 | 0.000 |
| lymphocytes, $\times10^9$/L | 1.55 ± 10.48 | 2.28 ± 14.38 | 0.94 ± 0.54 | 0.5 ± 0.23 | 0.81 ± 0.67 | 0.65 ± 0.35 | 0.56 ± 0.31 | 0.000 |
| N/L | 11.08 ± 17.03 | 4.77 ± 4.47 | 7.32 ± 6.43 | 26.45 ± 41.75 | 15.62 ± 11.82 | 21.54 ± 20.11 | 27.89 ± 19.87 | 0.000 |
| Platelets, $\times10^9$/L | 207.0 ± 95.9 | 240.8 ± 86.4 | 188.4 ± 99.51 | 185.56 ± 93.06 | 193.43 ± 98.24 | 142.06 ± 70.03 | 114.04 ± 61.77 | 0.000 |
| RDW | 13.14 ± 5.88 | 12.56 ± 1.16 | 15.26 ± 16.11 | 13.30 ± 1.50 | 12.95 ± 1.35 | 12.95 ± 1.28 | 14.25 ± 3.86 | 0.001 |
| HS-CRP, mg/L | 71.11 ± 69.56 | 42.35 ± 48.46 | 63.94 ± 56.51 | 93.77 ± 67.45 | 129.33 ± 77.28 | 90.74 ± 60.84 | 163.45 ± 81.25 | 0.000 |
| PCT, ng/ml | 0.76 ± 4.75 | 0.32 ± 2.41 | 0.22 ± 0.47 | 0.67 ± 1.62 | 0.66 ± 1.03 | 0.61 ± 1.01 | 4.85 ± 15.34 | 0.000 |
| IL-2R, U/ml | 952.04 ± 686.50 | 734.0 ± 387.31 | 839.14 ± 448.27 | 1443.14 ± 1357.08 | 1197.68 ± 677.09 | 1116.76 ± 439.55 | 1640.76 ± 1142.94 | 0.000 |
| IL-6, pg/ml | 62.68 ± 141.44 | 19.54 ± 23.87 | 38.73 ± 48.97 | 76.78 ± 135.77 | 189.15 ± 346.97 | 98.21 ± 85.17 | 179.33 ± 203.38 | 0.000 |
| IL-8, pg/ml | 42.42 ± 101.57 | 22.32 ± 39.85 | 57.46 ± 149.33 | 89.28 ± 275.33 | 37.11 ± 31.95 | 63.12 ± 58.83 | 87.17 ± 98.71 | 0.000 |
| IL-10, pg/ml | 20.26 ± 19.57 | 6.51 ± 5.65 | 7.94 ± 7.11 | 10.56 ± 9.79 | 11.48 ± 6.88 | 14.43 ± 8.54 | 20.3 ± 19.57 | 0.000 |
| TNF-α, pg/ml | 10.77 ± 7.96 | 8.34 ± 3.63 | 8.74 ± 2.52 | 11.24 ± 5.91 | 12.97 ± 7.13 | 16.05 ± 13.67 | 20.77 ± 14.71 | 0.000 |
| PT, s | 15.32 ± 7.62 | 14.72 ± 10.02 | 14.53 ± 1.10 | 15.10 ± 1.87 | 15.16 ± 1.79 | 17.01 ± 3.94 | 18.78 ± 5.20 | 0.000 |
| APTT, s | 43.24 ± 13.79 | 41.6 ± 11.17 | 43.66 ± 13.43 | 45.56 ± 16.68 | 40.58 ± 14.64 | 45.73 ± 18.21 | 52.03 ± 16.75 | 0.175 |
| D-Dimer, μg/ml | 5.37 ± 8.48 | 1.96 ± 3.95 | 4.61 ± 10.95 | 7.02 ± 10.32 | 10.61 ± 9.01 | 11.01 ± 9.74 | 14.46 ± 9.31 | 0.000 |

Abbreviations: COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; WBC: White blood count cell; N/L: neutrophil-to-lymphocyte ratio; RDW: RBC Distribution Width; HS-CRP: high-sensitivity C-reactive protein; PCT: procalcitonin; e-GFR: glomerular filtration rate; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; IV: invasive ventilation.

| | All patients(n = 349) | No extrapulmonary injury(n = 184) | Extrapulmonary injury (n = 165) | | | | | P value |
|---|---|---|---|---|---|---|---|---|
| | | | one injury(n = 43) | two injuries(n = 26) | three injuries(n = 36) | four injuries (n = 35) | five injuries (n = 25) | |
| Fibrinogen, g/L | 4.85 ± 1.70 | 5.00 ± 1.29 | 4.64 ± 1.31 | 5.19 ± 1.70 | 5.67 ± 1.83 | 3.98 ± 2.35 | 3.98 ± 2.48 | 0.000 |
| High-sensitivity cardiac troponin I, pg/ml | 739.22 ± 3470.45 | 43.50 ± 234.79 | 12.50 ± 14.70 | 83.87 ± 175.67 | 637.00 ± 1973.86 | 2581.52 ± 8213.76 | 3861.09 ± 5633.70 | 0.000 |
| CK-MB, ng/ml | 6.38 ± 23.815 | 5.46 ± 23.41 | 1.73 ± 2.29 | 2.49 ± 2.35 | 6.38 ± 10.29 | 16.01 ± 48.75 | 9.60 ± 9.89 | 0.000 |
| ALT, U/L | 46.57 ± 157.70 | 29.92 ± 29.31 | 35.15 ± 43.84 | 35.40 ± 29.29 | 37.03 ± 23.34 | 29.06 ± 17.51 | 235.92 ± 550.67 | 0.000 |
| AST, U/L | 57.33 ± 199.81 | 32.29 ± 21.97 | 40.74 ± 34.90 | 46.76 ± 35.05 | 48.79 ± 28.41 | 46.74 ± 26.18 | 306.76 ± 703.085 | 0.000 |
| TBIL, μmol/L | 13.67 ± 28.29 | 9.27 ± 4.30 | 10.57 ± 4.60 | 13.36 ± 5.36 | 12.69 ± 8.02 | 17.11 ± 16.38 | 48.34 ± 96.96 | 0.000 |
| Albumin, g/L | 33.78 ± 6.30 | 35.81 ± 5.13 | 34.63 ± 7.01 | 33.06 ± 7.78 | 29.72 ± 6.45 | 29.5 ± 4.89 | 29.7 ± 5.51 | 0.000 |
| Creatinine, μmol/L | 92.70 ± 95.60 | 80.08 ± 84.84 | 73.24 ± 27.97 | 108.72 ± 107.63 | 115.94 ± 175.19 | 104.32 ± 58.97 | 152.96 ± 84.20 | 0.000 |
| e-GFR, ml/min/1.73 $m^2$ | 82.95 ± 27.34 | 91.01 ± 22.95 | 89.66 ± 20.88 | 75.00 ± 31.37 | 75.61 ± 29.37 | 68.43 ± 24.93 | 50.90 ± 27.98 | 0.000 |
| LDH, U/L | 420.40 ± 295.79 | 295.80 ± 135.91 | 351.79 ± 150.49 | 428.88 ± 168.20 | 559.94 ± 250.14 | 613.06 ± 334.78 | 981.92 ± 514.34 | 0.000 |
| Glu, mmol/L | 8.36 ± 4.49 | 7.08 ± 3.20 | 8.42 ± 3.12 | 10.51 ± 5.95 | 8.49 ± 3.20 | 11.66 ± 7.22 | 11.01 ± 5.80 | 0.000 |
| **Treatments** | | | | | | | | |
| Antiviral | 287(82.2) | 163(88.6) | 39(90.7) | 19(73.1) | 30(83.3) | 25(71.4) | 11(44.0) | 0.000 |
| Antibiotic | 270(77.4) | 122(66.3) | 33(76.7) | 23(88.5) | 34(94.4) | 33(94.3) | 25(100) | 0.000 |
| Corticosteroid | 226(64.8) | 90(48.9) | 29(67.4) | 22(84.6) | 32(88.9) | 32(91.4) | 21(84.0) | 0.000 |
| Immunoglobulin | 159(45.6) | 56(30.4) | 20(46.5) | 15(57.7) | 24(66.7) | 27(77.1) | 17(68.0) | 0.000 |
| Oxygen support | | | | | | | | |
| HFNC | 40(11.5) | 3(1.6) | 7(16.3) | 6(23.1) | 10(27.8) | 10(28.6) | 4(16.0) | 0.000 |
| NIV | 86(24.6) | 12(6.5) | 11(25.6) | 14(53.8) | 21(58.3) | 15(42.9) | 13(52.0) | 0.000 |
| IV | 101(28.9) | 1(0.5) | 8(18.6) | 12(46.2) | 30(83.3) | 31(88.6) | 19(76.0) | 0.000 |
| **Prognosis** | | | | | | | | |
| death | 140(40.1) | 17(9.2) | 11(25.6) | 20(76.9) | 34(94.4) | 33(94.3) | 25(100) | 0.000 |

Abbreviations: COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; WBC: White blood count cell; N/L: neutrophil-to-lymphocyte ratio; RDW: RBC Distribution Width; HS-CRP: high-sensitivity C-reactive protein; PCT: procalcitonin; e-GFR: glomerular filtration rate; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; IV: invasive ventilation.

### Associated risk factors in patients with different number of extrapulmonary organ function impairment

In the study, we compared the clinical features and laboratory findings according to whether patients had extrapulmonary injury and stratified by the number of injured organs. All the patients were separated to six groups (no extrapulmonary injury, one to five extrapulmonary organ injury).

Overall, 165 patients developed extrapulmonary organ injury. We found that aged patients, especially aged over 60 years old, were more likely to suffer from extrapulmonary injury ($P < 0.001$). The proportion of male patients was higher in patients with extrapulmonary injury than that of female patients but no significant difference was observed. ($P = 0.311$). Patients with hypertension ($P = 0.011$) (including taken ACE inhibitors, $P = 0.031$) and cardiovascular disease ($P = 0.038$) were prone to extrapulmonary organ damage. We also found that with the increasing number of injured extrapulmonary organs, the respiratory rate increased significantly ($P < 0.001$) and the S/F ratio decreased notably ($P < 0.001$). Of 148 patients with ARDS, 128 cases developed extrapulmonary injury. The proportion of ARDS was much higher in patients with extrapulmonary injury than in those without extrapulmonary injury($P < 0.001$), and more than 90% patients with three and more extrapulmonary organs dysfunction developed ARDS.

By comparing the results of laboratory tests on admission, we discovered that the count of neutrophils, lymphocytes, platelets, and neutrophils/lymphocytes ratio (N/L) were different in different groups ($P < 0.001$). Furthermore, the more extrapulmonary organs were injured, the higher neutrophils count, N/L ratio, and the lower lymphocytes count were observed. There were also significant differences in inflammation indicators (including hs-CRP, PCT, IL-2R, IL-6, IL-8, IL-10 and TNF-α) in different groups ($P < 0.001$). The level of serum IL-2R and IL-6 rose with the increasing number of injured extrapulmonary organs. The similar phenomenon was found in the D-dimer, fibrinogen, high-sensitivity cardiac troponin I, CK-MB, LDH and liver and kidney function indicators. However, there was no significant difference in APTT among different groups ($P = 0.175$) (Table 1).

Because there was some certain collinearity between laboratory findings, partial collinear indicators were filtered out after correlation testing. Only 7 indicators screened out and other significant factors tested by single-factor analysis were included in the ordered logistic regression model. Indicator assignments were shown in Table 2. Using likelihood ratio test to determine the parallelism of the 5 regression equations, the results showed that the ordered logistic regression model could be used to analysis (2 = 77.280, P = 0.955). Likelihood ratio test showed that the model was statistically significant (2 = 328.009, P = 0.000). In the final logistic model, variables such as age 60 or older (OR 1.826, 95% CI 1.060–3.142), ARDS (OR 2.748, 95% CI 1.051–7.185), lymphocytes count lower than $1.1 \times 10^9$/L (OR 0.478, 95% CI 0.240–0.949), IL-6 greater than 7 pg/ml (OR 1.664, 95% CI 1.005–2.751) and D-Dimer greater than 0.5 μg/ml (OR 2.190, 95% CI 1.176–4.084) were significantly associated with the extrapulmonary injury (Table 3).

Table 2
Value assignment of ordinal logistic regression model variables

| Variable | Value assignment |
|---|---|
| Age range, year | ≤ 60 = 0, > 60 = 1 |
| Hypertension | No = 0, Yes = 1 |
| ACE inhibitors | No = 0, Yes = 1 |
| Cardiovascular disease | No = 0, Yes = 1 |
| Respiratory rate, rpm | < 24 = 0, ≥ 24 = 1 |
| $SpO_2/FiO_2$ | ≤ 150 = 1, 150–235 = 2, 235–315 = 3, > 315 = 4 |
| ARDS | No = 0, Yes = 1 |
| Neutrophils, $\times 10^9$/L | ≤ 1.8 = 1, 18 – 6.3 = 2, > 6.3 = 3 |
| lymphocytes, $\times 10^9$/L | < 1.1 = 0, ≥ 1.1 = 1 |
| RDW | < 14.9 = 0, ≥ 14.9 = 1 |
| HS-CRP, mg/L | ≤ 1 = 0, > 1 = 1 |
| PCT, ng/ml | < 0.5 = 0, ≥ 0.5 = 1 |
| IL-6, pg/ml | < 7 = 0, > 7 = 1 |
| D-Dimer, μg/ml | < 0.5 = 0, ≥ 0.5 = 1 |
| LDH, U/L | ≤ 225 = 0, > 225 = 1 |
| Dependent Variable: Extrapulmonary injury | No extrapulmonary injury = 0, One extrapulmonary injury = 1, Two extrapulmonary injuries = 2, Three extrapulmonary injuries = 3, Four extrapulmonary injuries = 4, Five extrapulmonary injuries = 5 |

Abbreviations: ARDS: acute respiratory distress syndrome; RDW: RBC Distribution Width; HS-CRP: high-sensitivity C-reactive protein; PCT: procalcitonin.

Table 3
Ordinal logistic regression model of extrapulmonary injury

| Variable | Estimate | Std. Error | Wald value | P | OR | 95% Confidence Interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| Age range | 0.602 | 0.277 | 4.711 | 0.030 | 1.826 | 1.060 | 3.142 |
| Hypertension | 0.136 | 0.299 | 0.206 | 0.650 | 1.146 | 0.637 | 2.059 |
| ACE inhibitors | 0.202 | 0.383 | 0.279 | 0.598 | 1.224 | 0.578 | 2.591 |
| Cardiovascular disease | -0.390 | 0.392 | 0.989 | 0.320 | 0.677 | 0.314 | 1.459 |
| Respiratory rate | 0.042 | 0.271 | 0.024 | 0.878 | 1.043 | 0.613 | 1.774 |
| ARDS | 1.011 | 0.490 | 4.250 | 0.039 | 2.748 | 1.051 | 7.185 |
| lymphocytes | -0.739 | 0.351 | 4.444 | 0.035 | 0.478 | 0.240 | 0.949 |
| RDW | -0.181 | 0.380 | 0.226 | 0.634 | 0.834 | 0.396 | 1.758 |
| HS-CRP | 0.194 | 0.562 | 0.119 | 0.730 | 1.214 | 0.403 | 3.655 |
| PCT | 0.628 | 0.357 | 3.087 | 0.079 | 1.874 | 0.930 | 3.773 |
| IL6 | 0.509 | 0.257 | 3.916 | 0.048 | 1.664 | 1.005 | 2.751 |
| D-Dimer | 0.784 | 0.318 | 6.099 | 0.014 | 2.190 | 1.176 | 4.084 |
| LDH | 0.232 | 0.400 | 0.337 | 0.562 | 1.261 | 0.576 | 2.765 |
| [SpO2/FiO2 = 1] | 0.238 | 0.479 | 0.246 | 0.620 | 1.269 | 0.496 | 3.245 |
| [SpO2/FiO2 = 2] | 0.079 | 0.452 | 0.031 | 0.861 | 1.082 | 0.446 | 2.627 |
| [SpO2/FiO2 = 3] | -0.360 | 0.378 | 0.906 | 0.341 | 0.698 | 0.332 | 1.465 |
| [SpO2/FiO2 = 4] | - | - | - | - | - | - | - |
| [Neutrophils = 1] | 0.000 | 0.553 | 0.000 | 1.000 | 1.000 | 0.338 | 2.959 |
| [Neutrophils = 2] | -0.142 | 0.318 | 0.198 | 0.656 | 0.868 | 0.466 | 1.618 |
| [Neutrophils = 3] | - | - | - | - | - | - | - |

Abbreviations: ARDS: acute respiratory distress syndrome; RDW: RBC Distribution Width; HS-CRP: high-sensitivity C-reactive protein; PCT: procalcitonin.

**Effect of extrapulmonary organ injury on COVID-19 patients' prognosis.**

Of 140 patients in death, 123 patients had extrapulmonary organ injury. With the increasing number of injured extrapulmonary organs, higher fatality rate was observed ($P < 0.001$). Moreover, of 25 cases with 5 extrapulmonary organs injury, all the patients died.

To identify the impact of extrapulmonary organs injury on the patients' prognosis, we used Kaplan-Meier curve and log-rank test to analysis the relationship between the extrapulmonary organs injury and surviving. We found that there were significant differences in survival rate when the five extrapulmonary organs injury we focused on occurred. The survival rate of patients with myocardial damage was lower than the patients without (2 = 268.884, P = 0.000). The similar trends were found in liver injury, kidney injury, blood system injury and circulatory system injury patients separately (2 = 51.684, 2 = 141.527, 2 = 85.940, 2 = 242.322; P = 0.000). The results were showed in the Fig. 1–5. However, when all the extrapulmonary organs injury were included in the multivariate COX proportional hazards model, the result showed that only myocardial

injury (P = 0.000, HR: 5.068, 95% CI: 2.728–9.417) and circulatory system injury (P = 0.000, HR: 4.076, 95% CI: 2.216–7.498) were the independent factors associated with COVID-19 patients' prognosis (Table 4).

Table 4
COX proportional hazards model

| Variable | Estimate | Std. Error | Wald value | P | HR | 95% Confidence Interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| myocardial injury | 1.623 | 0.316 | 26.370 | 0.000 | 5.068 | 2.728 | 9.417 |
| liver injury | 0.175 | 0.197 | 0.797 | 0.372 | 1.192 | 0.811 | 1.752 |
| kidney injury | -0.297 | 0.220 | 1.824 | 0.177 | 0.743 | 0.483 | 1.143 |
| blood system injury | 0.255 | 0.188 | 1.838 | 0.175 | 1.291 | 0.893 | 1.866 |
| circulatory system injury | 1.405 | 0.311 | 20.418 | 0.000 | 4.076 | 2.216 | 7.498 |

# Discussion

It is well known that COVID-19 has been a global pandemic. Although the overall hospitalization fatality rate of COVID-19 is lower than ARDS (9.6%) and MERS (34.4%)[1, 2], it has ultimately caused a huge number of death just as its faster spread speeds than the other two diseases[5, 12] and enormous infected cases. Moreover, it was reported the fatal rate of severe and critically ill patients of COVID was much higher than general patients, even the highest fatal rate was reported as 61.5% [13, 14]. Severe and critically ill patients usually developed extrapulmonary organ injury, including acute cardiac injury, acute kidney injury, acute liver injury, disseminated intravascular coagulation and gastrointestinal bleeding rather than ARDS[3, 15]. In our study, we found that extrapulmonary injury occurred in nearly half of severe and critically ill patients with COVID, which occurred more commonly in patients with ARDS. Aged 60 or older, ARDS, lymphocytes count lower than $1.1 \times 10^9$/L, IL-6 greater than 7 pg/ml and D-Dimer level greater than 0.5 μg/ml were significantly associated with the extrapulmonary injury. Of five extrapulmonary organs injury, myocardial and circulatory system injury were associated with poor prognosis in COVID patients.

Extrapulmonary injury was common in severe and critically ill patients, which occurred in 165 patients in our study. The findings were in accordance with other studies, suggesting more attention should be paid on extrapulmonary injury as well as lung injury. however, the underlying mechanism was not exactly clear. Recent researches have demonstrated that the novel coronavirus SARS-CoV-2 spike protein directly binds with the host cell surface ACE2 receptor facilitating virus entry and replication[16]. ACE2 receptor densely distributed in human alveolar epithelial cells (AEC), and 83% of ACE2-expressing cells were alveolar epithelial type II cells (AECII) served as a reservoir for viral invasion. ACE2-expressing AECII had high levels of multiple viral process-related genes, including regulatory genes for viral processes, viral life cycle, viral assembly, and viral genome replication, which facilitate coronaviral replication in the lung[16, 17]. ACE2 receptor also expressed in many extrapulmonary tissues, such as heart, liver, kidney, endothelium and intestine[18–20], even in some hematopoietic cells, including monocytes and macrophages[21], which may explain the extrapulmonary organ injury observed in critical patients.

Another possible reason for the occurrence of extrapulmonary damage was reported as the cytokine release syndrome (CRS), which occurred in a large number of COVID-19 patients, and IL-6 was the key molecule of CRS, which was an important cause of death[21, 22]. CRS was characterized by elevated proinflammatory cytokines and chemokines which could lead to multiorgan failure. As we founded in our study, the levels of serum IL-6, IL-2R, IL-10 and TNF-α were higher in the severe and critically ill patients with extrapulmonary injury than in those without extrapulmonary injury and the level of IL-6 was independent risk factor of extrapulmonary injury. SARS-CoV-2 infection of monocytes, macrophages, and dendritic cells accounts for their activation and secretion of IL-6 and other inflammatory cytokines. IL-6 can bind to the soluble form of IL-6R (sIL-6R), which activate IL-6–sIL-6R–JAK-STAT3 signaling, resulting in a systemic "cytokine storm"[23]. This

involves secreting vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), IL-8, additional IL-6, and reduced E-cadherin expression on endothelial cells, leading to vascular permeability and leakage, which may contribute to extrapulmonary injury and ARDS. Our findings suggested patients with ARDS were more likely to develop extrapulmonary injury, which may be explained by CRS due to activation of IL-6. IL-6 also can bind to membrane-bound IL-6 receptor (mIL-6R), activating cis signaling involving the acquired immune system (B and T cells), which contributes to lymphocytopenia[24]. In our study, we found that lymphocytopenia was more common in COVID patients with extrapulmonary injury, which may result from activation of IL-6 through cis signaling. Moreover, comparing to the patients with one extrapulmonary organ injury, much higher level of IL-6 and much lower lymphocytes count were observed in patients with more than one extrapulmonary organs injury in present study. Hence, detecting and monitoring level of inflammatory cytokines such as IL-6 in especial and lymphocytes count may help clinicians to focus on extrapulmonary organ function except for ARDS so as to identify severe COVID patients and give better treatment.

A few studies have demonstrated D-Dimer was a biomarker of severity and predicting the mortality of COVID[25]. In our study, elevated D-Dimer was associated with the extrapulmonary organ injury, suggesting D-Dimer played an important role in multiorgan injury. A pathological report of COVID cases by autopsies showed that hematopoietic function decreased, swelling of endothelial cells in glomerulus of kidney and thrombosis in capillaries[26]. It was also reported that venous thromboembolism was founded in COVID-19 patients in autopsy findings[25, 27]. It is possible that D-Dimer involves the pathological process of thrombosis, which may contribute to extrapulmonary injury.

Previous studies showed older age was associated with death in COVID patients. Current study indicated older age was correlated with extrapulmonary injury. Elderly patients had more prolonged proinflammatory responses and due to the decreased T-cell and B-cell function than young patients[28].

In the study, we found that in case of extrapulmonary organs injury occurrence, the survival rate decreased significantly. Some researches reported the similar result in the association between the single organ injury and survival rate separately[29–32]. However, some organs injury often co-exist in severe COVID patients. In our study, the multivariate COX proportional hazards analysis indicated that myocardial injury and circulatory system injury correlated with the poor prognosis of COVID-19 patients independently. The potential mechanism was that myocardial and circulatory system injury could cause arrhythmia, heart failure and even acute myocardial infarction, furthermore circulatory system damage leaded to tissue hypoperfusion[33].

# Conclusion

COVID-19 was identified a wildly spread infectious disease. SARS-CoV-2 infection can not only cause lung injury but also lead to the damage of extrapulmonary organs. Older age, lymphocytopenia, high level of IL-6 and D-Dimer and the severity of lung injury were the high-risk factors of the damage of extrapulmonary organs injury. Myocardial and circulatory system injury maybe were the most important risk factors related to poor outcomes of COVID-19 patients.

# Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; MERS: Middle East Respiratory Syndrome; ARDS: Acute respiratory distress syndrome; AKI: Acute kidney injury; S/F: $SpO_2/FiO_2$, the oxygen saturation to fraction of inspired oxygen ratio; HFNC: High-flow nasal catheter oxygen therapy; ECMO: Extracorporeal membrane pulmonary oxygenation; MAP: Mean arterial blood pressure; SOFA: Sequential organ failure assessment; CRS: Cytokine release syndrome; SPSS: Statistical product and service solutions.

# Declarations

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### Authors' contributions

Conceptualization: Jun Wang. Acquisition, analysis, or interpretation of the data: Jun Wang, Nan Su, Hui Chen, Xinyue Li, Xiaoping Li, Xiangqiong Lu, Yang He. Statistical analysis: Wenxia Ma. Investigation: Fang Huang, Wenxia Ma, Jun Jin. Drafting of the manuscript and editing: Fang Huang, Jun Jin, Hui Zheng, Yan Ye. Funding acquisition: Jun Wang, Yongsheng Li, Yuyu Wang.

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### Availability of data and materials

Dr. J. Wang had full access to all of the data in the study. After publication, the data will be made available to others on reasonable requests after approval from the corresponding author (J.W, dr_wangjun@suda.edu.cn) and Wuhan Tongji Hospital.

### Ethics approval and consent to participate

Ethical approval was waived by the Ethics Committee of Tongji Hospital (Wuhan, China) in view of the retrospective and observational nature of the study and all the procedures being performed were part of the routine care.

### Consent for publication

The informed consents of patients were waived by the Ethics Commission of Tongji Hospital (Wuhan, China) for the rapid emergence of this epidemic.

### Conflict of Interest Disclosures

The authors declare no competing interests.

### Author details

[1]Department of Intensive Care Medicine, The First Affiliated Hospital of Soochow University, Suzhou, China. [2]Department of Quality Management, The First Affiliated Hospital of Soochow University, Suzhou, China. [3]Institutes of Biology and Medical Sciences, Soochow University, Suzhou, China. [4]Department of Intensive Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. [5]Department of Respiratory Medicine, The First Affiliated Hospital of Soochow University, Suzhou, China

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# Figures

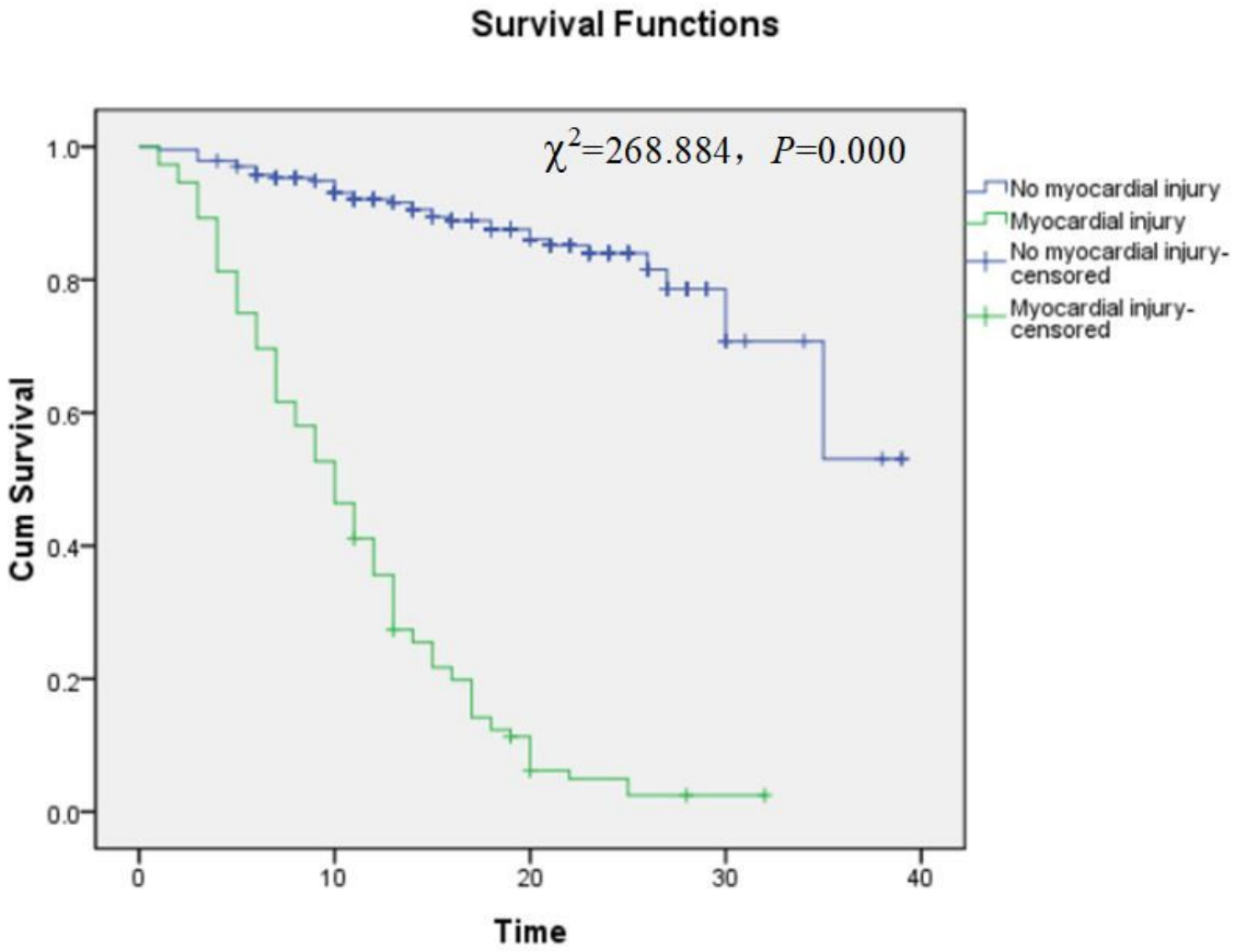


**Figure 1**

Kaplan–Meier curves of myocardial injury for survival of COVID-19.

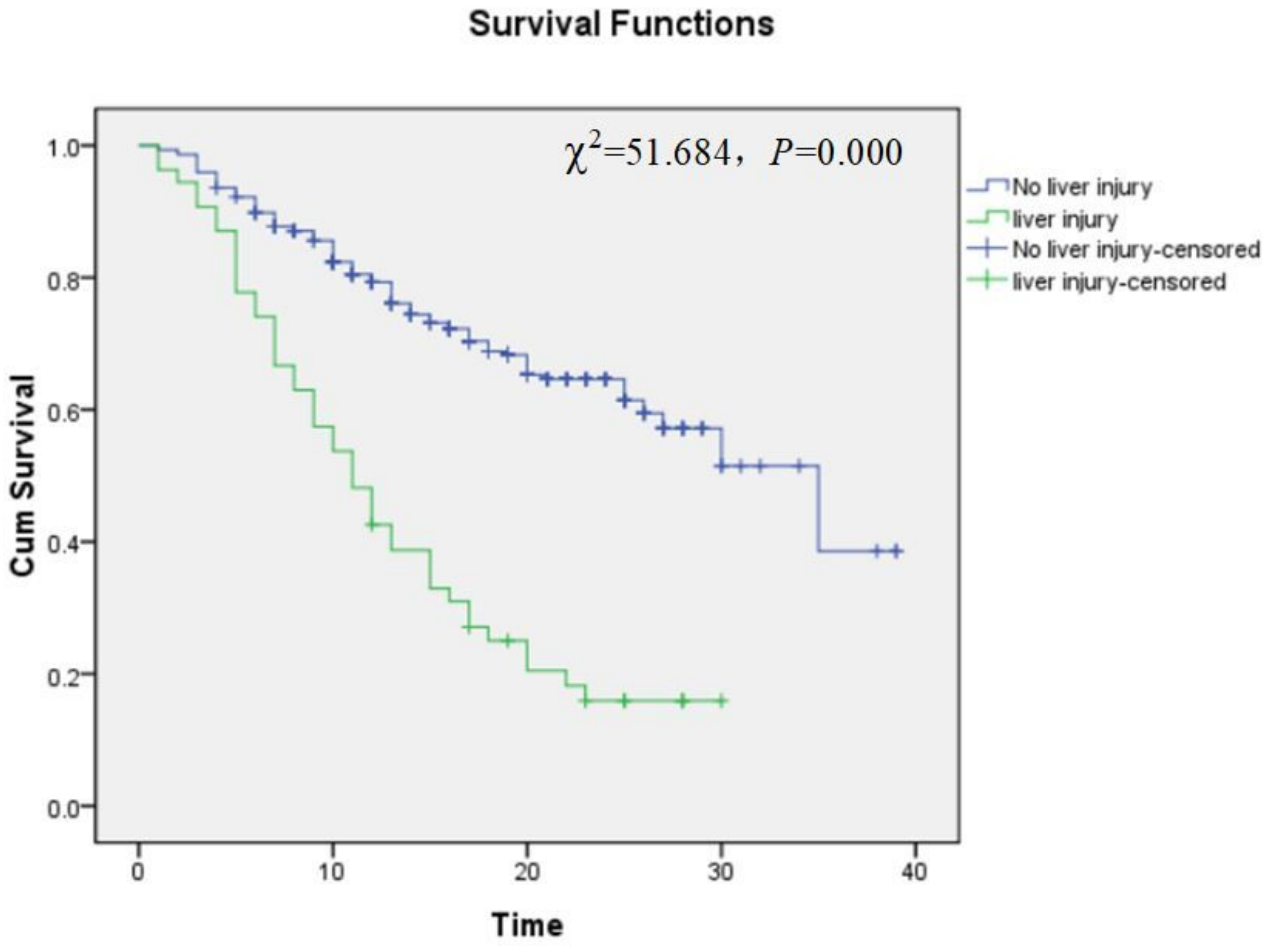


**Figure 2**

Kaplan–Meier curves of liver injury for survival of COVID-19

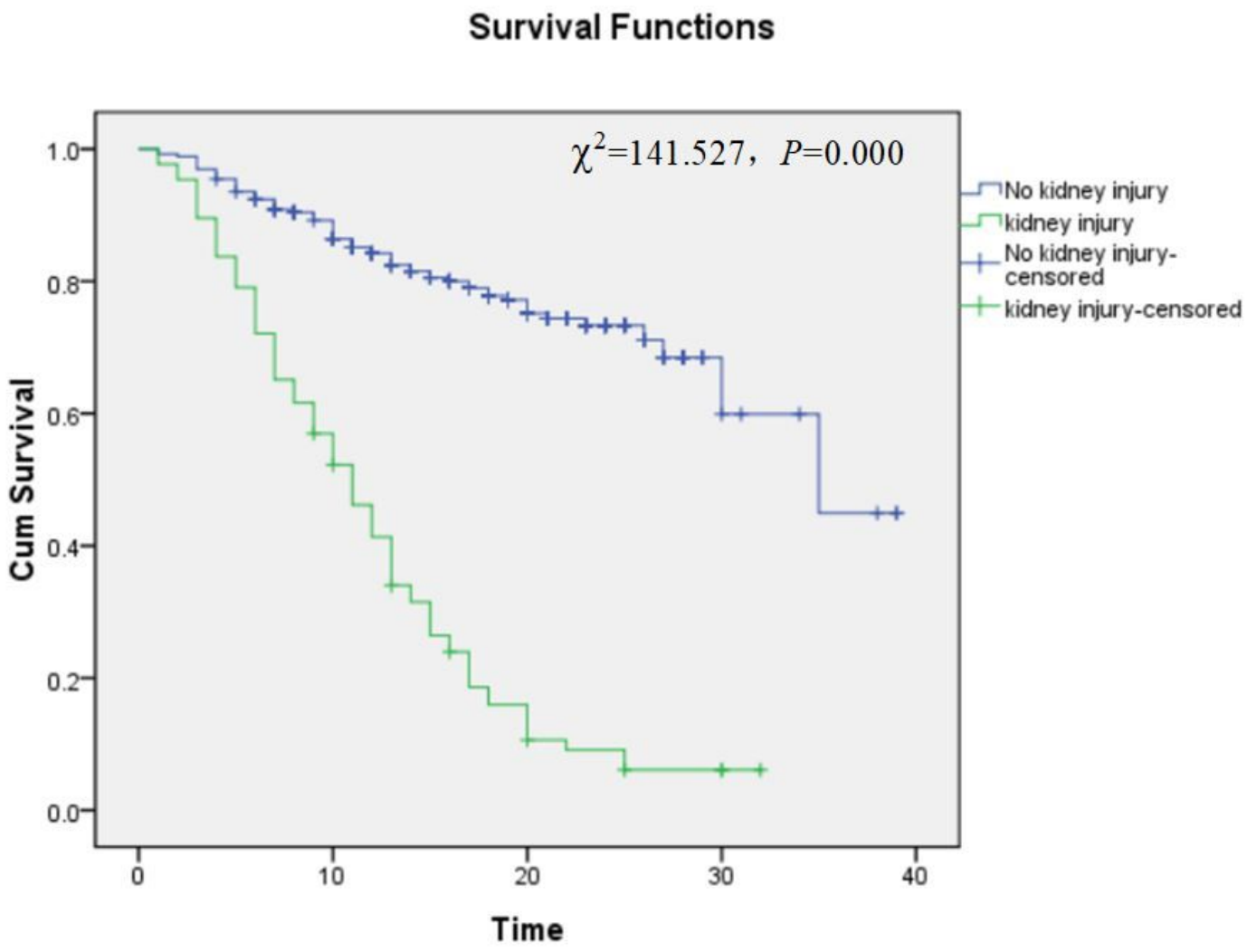


**Figure 3**

Kaplan–Meier curves of kidney injury for survival of COVID-19

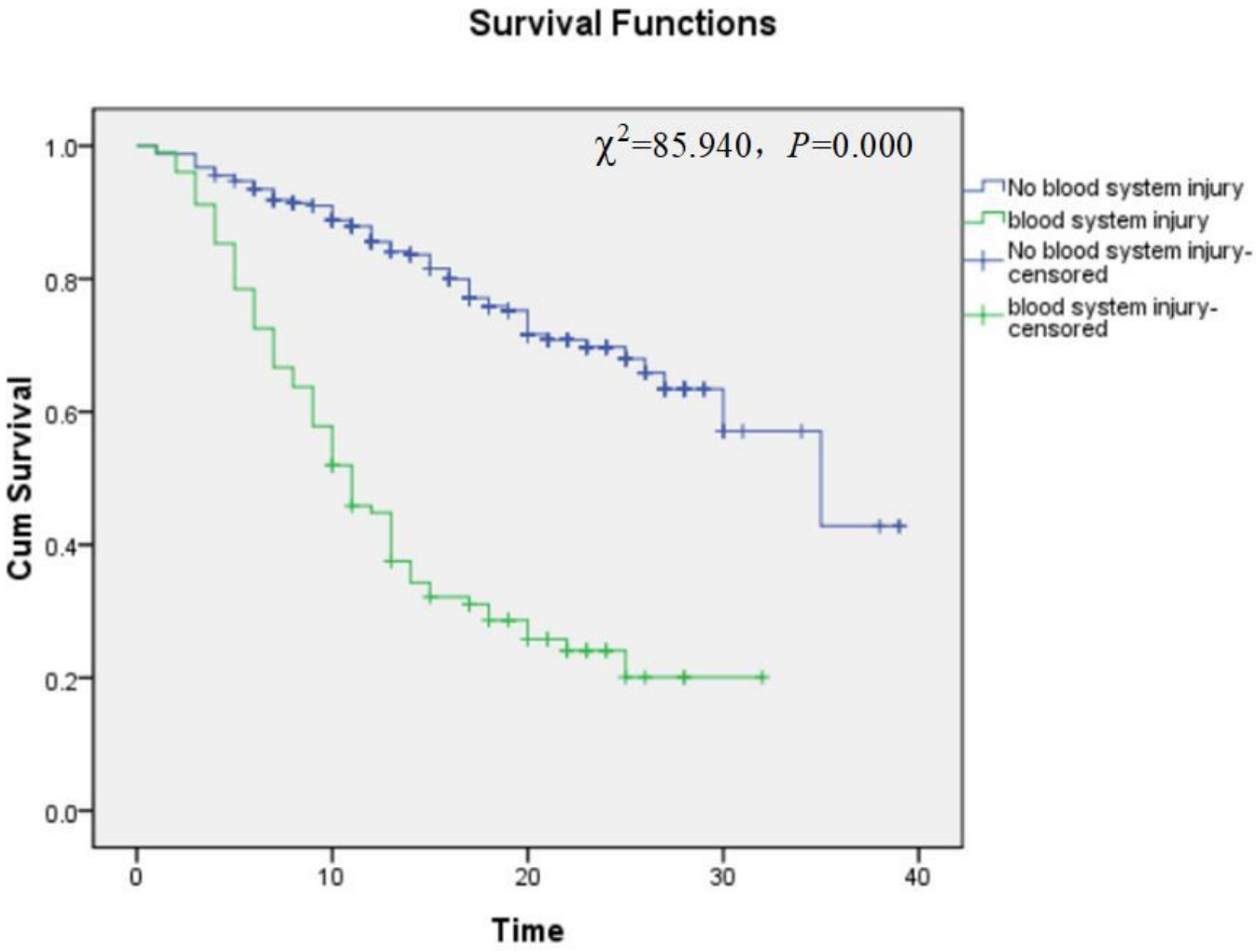


**Figure 4**

Kaplan–Meier curves of blood system injury for survival of COVID-19

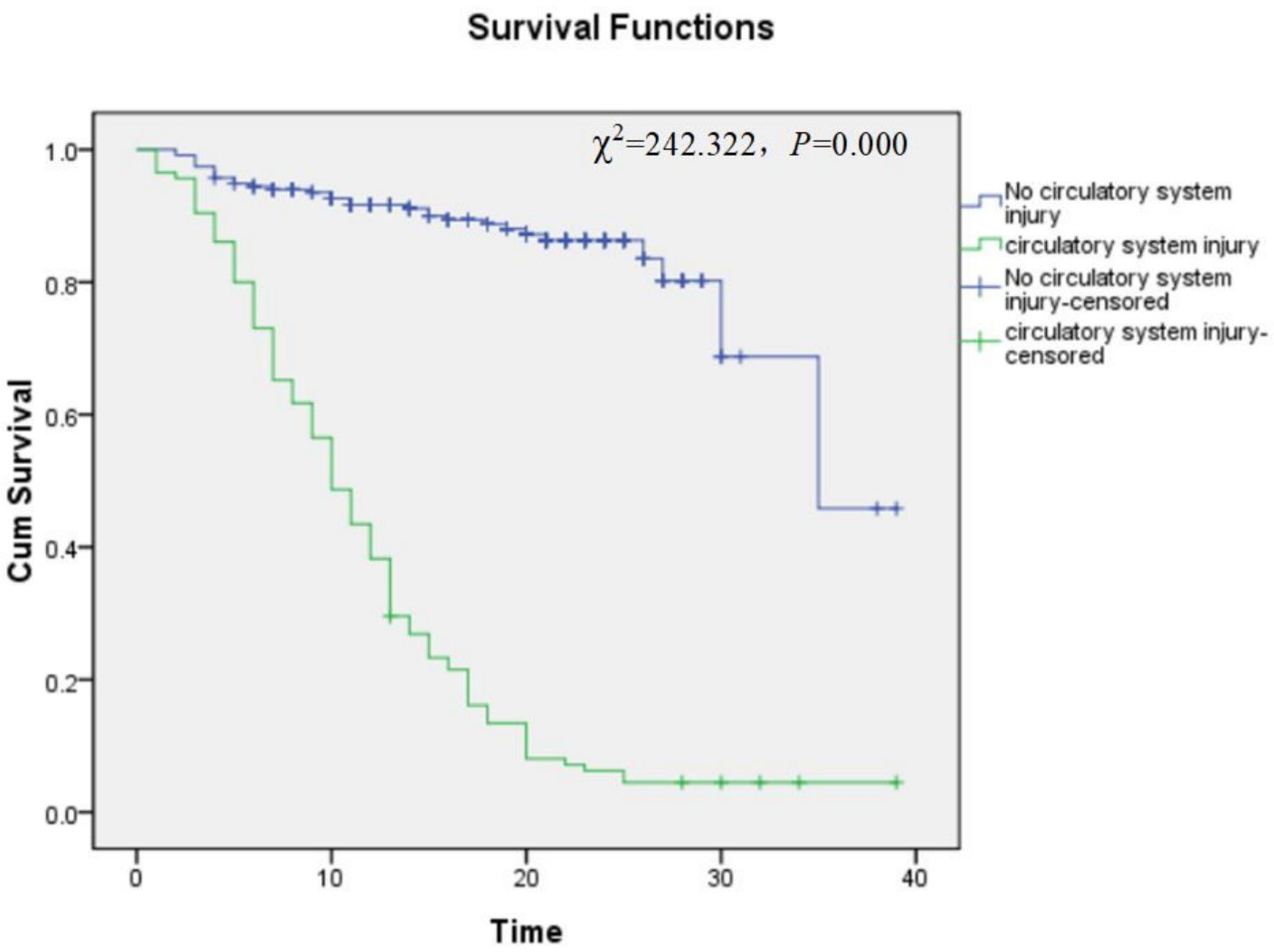


**Figure 5**

Kaplan–Meier curves of circulatory system injury for survival of COVID-19