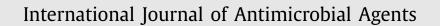


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# Ribavirin therapy for severe COVID-19: a retrospective cohort study

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# ABSTRACT

The aim of this study was to compare ribavirin therapy versus supportive therapy only for patients with severe coronavirus disease 2019 (COVID-19). A total of 115 patients with laboratory-confirmed COVID-19 were retrospectively analysed. All patients received supportive care as well as regular laboratory and clinical monitoring. The 115 patients comprised 44 patients who received intravenous ribavirin (treatment group) and 71 who did not (control group). Baseline laboratory and clinical characteristics were similar between the two groups. The negative conversion time for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR in the ribavirin group was 12.8  $\pm$  4.1 days compared with 14.1  $\pm$  3.5 days in the control group (P = 0.314). Moreover, 7/41 patients (17.1%) in the ribavirin group died compared with 17/69 (24.6%) in the control group (P = 0.475). Adverse effects were similar between the two groups. In conclusion, in patients with severe COVID-19, ribavirin therapy is not associated with improved negative conversion time for SARS-CoV-2 test and is not associated with an improved mortality rate. Further assessment in designed randomised controlled trials is recommended.

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# 1. Introduction

The 2019 novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease that is causes, named coronavirus disease 2019 (COVID-19), which was first discovered in Wuhan, China, in December 2019, is a serious concern worldwide. Patients with COVID-19 show respiratory diseases and severe pneumonia. Since the detection of the outbreak, the number of cases has been increasing worldwide; as of early April 2020, more than 9000 cases and more than 3000 deaths have been reported in China alone, and more than 950 000 cases in other countries. Treatment of patients with COVID-19 consists of supplemental oxygen, admit to an isolation ward, supportive care, antimicrobial therapy and respiratory support [1,2]. To date, no antiviral therapy has been approved for the treatment of COVID-19.

Several therapeutic interventions for coronavirus infection were studied during the severe acute respiratory syndrome coronavirus

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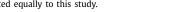
(SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks in 2003 and 2012, respectively [3,4]. Reviews of the literature suggest that ribavirin might be of benefit in patients with coronavirus infection [4]. However, other studies have shown that ribavirin may not improve outcomes [5,6]. In addition, ribavirin has potential adverse effects [7], therefore its clinical use should be carefully assessed.

The aim of this study was to evaluate and compare the efficacy of ribavirin in the treatment of patients with severe COVID-19 pneumonia.

# 2. Study population and methods

# 2.1. Setting

This single-centre, retrospective cohort study included patients diagnosed with laboratory-confirmed SARS-CoV-2 infection in Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) from January-February 2020.





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# 2.2. Informed consent

This study was approved by the Ethics Commission of Union Hospital. Owing to the rapid emergence of this infectious disease, the need for written informed consent was waived.

#### 2.3. PCR assay

SARS-CoV-2 infection was confirmed by positive reverse transcription PCR (RT-PCR) of respiratory tract samples. Two RT-PCR tests were used for SARS-CoV-2 diagnostic confirmation. Nucleocapsid protein (N) and open reading frame 1ab (ORF1ab) were amplified during RT-PCR [8].

#### 2.4. Patients

Patients were excluded if they met the following exclusion criteria: (i) age <18 years or >80 years; and (ii) transferred to another hospital (after the first consultation, some patients with special medical insurance types were transferred to the corresponding hospitals for treatment). Patients were considered severe COVID-19 patients if they met any of the following condition: (i) oxygen saturation  $\leq$ 93% at resting state; (ii) respiratory rate  $\geq$ 30 breaths/min; and (iii) arterial oxygen tension (PaO<sub>2</sub>)/inspiratory oxygen fraction (FiO<sub>2</sub>)  $\leq$ 300 mmHg [9].

### 2.5. Procedure

The experimental group comprised patients who received intravenous ribavirin 500 mg every 12 h (Zhengzhou Cheuk-fung pharmaceutical Co., Ltd., Xinzheng City, Zhengzhou, China), whereas those who did not receive ribavirin therapy formed the control group. The control group received no other potential antiviral treatments. All patients received appropriate antimicrobial therapy and supportive care. In addition to routine clinical monitoring, liver enzymes, renal function, electrolytes and blood cell counts were assessed regularly throughout the course of treatment.

# 2.6. Outcomes

The outcomes for the study were (i) the negative conversion time for SARS-CoV-2 RT-PCR test and (ii) mortality rate in the two groups.

#### 2.7. Statistical analysis

Continuous variables were expressed as the mean  $\pm$  standard deviation (S.D.) and categorical variables were expressed as number (%). The  $\chi^2$  test and *t*-test were used to determine any statistical difference between the proportions and means of the two groups. Single-factor analysis was used for comparison of clinical and laboratory features in the different groups. Univariate and multiple logistic regression models were used to evaluate the associations between patients receiving ribavirin or not and the risk of death. All analyses were performed with EmpowerStats (http://www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and the statistical software package R (http://www.R-project.org; The R Foundation). A *P*-value of <0.05 (two-sided) was considered statistically significant.

# 3. Results

A total of 134 individuals were diagnosed with severe COVID-19 between January–February 2020. Baseline characteristics were similar between patients who received ribavirin and those who did not. After excluding ineligible patients, 115 patients were included in the current study, comprising 71 in the control group and 44 in the treatment group (Fig. 1). The mean  $\pm$  S.D. age of all 115 patients was 54.9  $\pm$  15.1 years and 62 (53.9%) were male (Table 1). Mean  $\pm$  S.D. laboratory values on the day of SARS-CoV-2 diagnosis were haemoglobin 125.5  $\pm$  18.2 g/L, peripheral white blood cell count 9.55  $\times$   $10^9/L$   $\pm$  6.03  $\times$   $10^9/L$ , absolute neutrophil count 5.7  $\times$  10<sup>9</sup>/L  $\pm$  3.5  $\times$  10<sup>9</sup>/L, lymphocyte count 0.9  $\times$  10<sup>9</sup>/L  $\pm$  0.5  $\times$   $10^9/\text{L},$  platelet count 194.1  $\times$   $10^9/\text{L}$   $\pm$  83.8  $\times$   $10^9/\text{L},$  alanine aminotransferase (ALT) 38.3  $\pm$  32.6 U/L, aspartate aminotransferase (AST) 40.1  $\pm$  20.3 IU/L, blood urea nitrogen (BUN) 4.8  $\pm$  3 mmol/L and serum creatinine 73.1  $\pm$  25.1  $\mu$ mol/L. Of the 115 patients overall, 28 (24.3%) required non-invasive ventilation support and 9 patients (7.8%) required invasive ventilation support. All patients received broad-spectrum antibiotic therapy. In the treatment group, ribavirin was initiated within a median of 4 days (range 1-12 days) of the SARS-CoV-2 diagnosis and within a median of 8 days (range 1-18 days) from symptom onset. There were no statistically significant differences in clinical characteristics (Table 1) or support measures (Table 2) between the two groups. The negative conversion time for SARS-CoV-2 test in patients who received ribavirin was 12.8  $\pm$  4.1 days compared with 14.1  $\pm$  3.5 days in the control group (P = 0.314). The overall mortality rate was 20.9% (24/115). The mortality rate was 17.1% (7/41) in the ribavirin group and 24.6% (17/69) in the control group; there was no significant difference in mortality between the two groups (P = 0.475).

Ribavirin treatment was well tolerated and there were no early discontinuations due to adverse effects. There were no significant differences in laboratory parameters (haemoglobin, leukocyte count, lymphocyte count, C-reactive protein, platelet count, serum creatinine, BUN, ALT and AST) between the two groups after the treatment course (Table 3).

#### 4. Discussion

With the global pandemic of COVID-19, there is an urgent need for effective therapeutic interventions in patients with severe SARS-CoV-2 infection. This study shows that ribavirin is not associated with reduced time to negative conversion time for SARS-CoV-2 test and does not provide a survival benefit compared with control treatment (supportive therapy only).

In this study, treatment with ribavirin was well tolerated. Anaemia is a common complication of ribavirin therapy and has been observed in previous studies investigating the treatment of MERS-CoV and SARS-CoV infection [4,10]. In the current study, the degree of change in haemoglobin values during admission was 5.3 g/L in the treatment group and 10.4 g/L in the control group. There was no statistical difference between the two groups (P = 0.051). In addition, there were no interruptions in treatment due to anaemia.

Whether to use ribavirin treatment was based on the doctor's clinical experience. Moreover, during a particular period at the peak of the outbreak, ribavirin was sometimes out of stock, which may also have led to treatment without ribavirin. Although use of ribavirin or not was not completely random, there were no statistically significant differences in clinical characteristics (included medical history, demographic data, physical examination, and haematological, biochemical and radiological results) or support measures (immunoglobulin therapy, ventilation support and corticosteroid therapy) between the ribavirin and control groups, making the two groups comparable.

It was thought that ribavirin might be useful for treating coronavirus infection because of its broad-spectrum inhibition of RNA viruses. Several studies have shown that ribavirin has useful activity against SARS-CoV in vitro [11,12]. However, other studies have found that ribavirin did not inhibit the virus in vivo and did not

#### Table 1

Baseline characteristics on the day of diagnosis of SARS-CoV-2 infection and outcome of severe COVID-19 patients <sup>a</sup>

| Age (pars) $5.1 \pm 16.2$ $54.6 \pm 13.3$ $0.882$ Sex         0.069         0.069           Male         43 (00.6)         19 (43.2)         0.069           Female         28 (39.4)         25 (56.8)         0.533           Temperature (*C)         37.7 ±0.6         38.8 ±0.6         0.302           Cough         0.533         0.533         0.533           No         44 (62.0)         25 (56.8)         0.951           No         68 (55.8)         42 (95.5)         0.951           Yes         3 (42.1)         2 (45.5)         0.961           No         60 (85.7)         37 (85.0)         0.961           No         50 (96.7)         43 (100.0)         1.975           Yes         59 (96.7)         43 (100.0)         1.975           Leukopte count (× 10 <sup>0</sup> /L)         0.94 ±0.5         1.04 ±0.2         0.113           Paterodition (xgl)         1.127.6 + 18.7         122.0 + 17.2         0.113           Prothenomin (me (s)         1.13 ± 1.13         39.8 ± 5.5         0.531           Prothenomin (xgl)         0.2 ± 0.3         0.2 ± 0.3         0.32 ± 0.53         0.324           Creative protein (mgl,1)         7.7 ± 3.  | Characteristic                       | Control group $(n = 71)$ | Ribavirin group $(n = 44)$ | <i>P</i> -value |
|---|--------------------------------------|--------------------------|----------------------------|-----------------|
| Male         43 (60.6)         19 (43.2)           Femperature (°C)         38.7 ± 0.6         38.8 ± 0.6         30.20           Cough         25 (56.8)   |                                      | 55.1 ± 16.2              | 54.6 ± 13.3                |                 |
| remark28 (39.4)25 (56.8)Temperature (°C)38.7 ± 0.638.8 ± 0.60.302No44 (62.0)25 (56.8)   |                                      |                          |                            | 0.069           |
| Temperature (°C)         38.8 ± 0.6         0.302           Cough         25         0.583           No         44 (62.0)         25 (56.8)           Pharyngalgia         0.935           No         68 (9.5.8)         42 (95.5)           No         66 (85.7)         37 (86.0)         0.931           Synon         60 (85.7)         37 (86.0)         0.231           No         000.0         0.231         0.935           No         000.0         0.231         0.931           Yes         000.0         0.231         0.931           No         0.930         0.931         0.931           Yes         000.0         0.231         0.931           Wes         0.330         0.945.1         0.140           Protection (y 10%)         0.94 0.95         1.04 0.6         0.532           Harmoglobin (glu)         127.6 ± 18.7         122.0 ± 17.2         0.113           Harmoglobin (glu)         127.5 ± 18.7         132.0 ± 17.2         0.133           Protections (ngl.1)         0.74 ± 40.1         0.54 ± 16.6         0.833           Escenter (ngl.1)         0.74 ± 40.1         0.54 ± 16.1         0.333           Protoctions   |                                      | . ,                      |                            |                 |
| Cough         0.53           No         44 (6.20)         25 (56.8)           Yes         27 (38.0)         19 (43.2)           Pharyngalga         0.935           No         68 (95.8)         42 (95.5)           Yes         3 (4.2)         2 (4.5)           Dyspneata         0.091         0.991           No         60 (85.7)         37 (86.0)           Yes         10 (14.3)         6 (14.0)           Yes         59 (96.7)         43 (100.0)           Yes         59 (96.7)         43 (100.0)           Leukocyte count (× 10 <sup>9</sup> /L)         0.9 ± 0.5         1.0 ± 0.6         0.592           Leukocyte count (× 10 <sup>9</sup> /L)         197.3 ± 8.8         18.8 ± 7.5         0.611           Patelet count (× 10 <sup>9</sup> /L)         197.4 ± 18.7         120.4 ± 1.2         0.314           Patelet count (× 10 <sup>9</sup> /L)         13.5 ± 1.3         140 ± 2.1         0.110           Patelet count (× 10 <sup>9</sup> /L)         17.5 ± 7.57         63.3 ± 1.3         0.233           Scunt (ratin (µm)/L)         5.2 ± 3.1         43.4 ± 2.8         0.233           Scunt (µmol/L)         5.2 ± 3.1         43.2 ± 2.6         0.934           Scunt (µmol/L)         5.2 ± 3.1         3.4 ± 6.1  |                                      |                          |                            | 0.000           |
| No         25 (56.8)           Yes         27 (30.0)         19 (43.2)           Pharyngdgia         0.80         28 (20.5)           No         66 (95.8)         2 (45.5)           Yes         37 (42.1)         2 (45.5)           Parynos         60 (85.7)         37 (86.0)           No         0.60 (85.7)         37 (86.0)           Yes         10 (14.3)         6 (14.0)           Fever *         0.00.0         221           No         2 (3.3)         0 (0.0)           Yes         59 (96.7)         43 (100.0)           Hemoglobin (gl.0)         127.6 ±18.7         122.0 ±17.2         0.119           Hearenglobin (gl.0)         127.6 ±18.7         122.0 ±17.2         0.161           Profixrobin time (s)         31.5 ±1.3         14.0 ±2.1         0.160           aPT1 (s)         47.8 ±2.7         63.8 ±15.6         0.534           Creactive protein (ngl.1)         67.4 ±49.1         65.4 ±61.6         0.835           ESR (mm/h)         47.8 ±2.7         63.8 ±19.4         0.213           Proteintomin (gl.1)         57.8 ±7.79         63.8 ±19.4         0.213           Proteintomin (gl.1)         57.4 ±49.1         67.4 ±49.1 <td< td=""><td></td><td>38.7 ± 0.6</td><td><math>38.8 \pm 0.6</math></td><td></td></td<>   |                                      | 38.7 ± 0.6               | $38.8 \pm 0.6$             |                 |
| Yes         27 (38.0)         19 (43.2)   |                                      | 44 (62.0)                | 25(568)                    | 0.583           |
| Pharyngalgia         0.935         0.935         0.935           No         68 (95.8)         2 (4.5)         0.961           Dyppnoca <sup>b</sup> 0.041         6 (14.0)         0.961           No         2 (3.3)         0 (0.0)         0.231           No         2 (3.3)         0 (0.0)         0.231           No         2 (3.3)         0 (0.0)         0.231           Ves         59 (96.7)         43 (100.0)         1.0           Lymphocyte count (× 10 <sup>9</sup> /L)         0.94 ± 3.8         3.8 ± 2.6         0.113           Haemoglobin (g/L)         1127.6 ± 1.8.7         122.0 ± 17.2         0.113           Haemoglobin (g/L)         197.3 ± 88.8         188.9 ± 75.9         0.611           Porthombin time (s)         13.5 ± 1.3         14.0 ± 2.1         0.130           Protein (mg/L)         67.4 ± 49.1         16.5 4 ± 5.6         0.503           Protein (mg/L)         67.4 ± 49.1         16.5 4 ± 3.5         0.56         0.324           Creactive protein (mg/L)         75.5 ± 27.9         68.3 ± 1.9.4         0.213           BUN (mmo/L)         75.5 ± 27.9         69.3 ± 1.9.4         0.213           BUA (mmo/L)         77.4 ± 15.9         0.284         1.10.732  |                                      |                          |                            |                 |
| No         68 (95.8)         42 (95.5)         Ves           Dyspnocab         0.42)         2 (4.5)         0.961           No         60 (85.7)         37 (86.0)         7           Yes         10 (14.3)         6 (14.0)         0.231           No         2 (3.3)         0 (0.0)         0.231           No         2 (3.3)         0 (0.0)         0.231           Ves         59 (96.7)         43 (100.0)         0.132           Landput count (x 10 <sup>9</sup> /L)         49 ± 38.         38 ± 6.6         0.132           Haemoglobin (g/L)         127.6 ± 18.7         122.0 ± 17.2         0.119           Prothermbin time (s)         13.5 ± 1.3         14.0 ± 2.1         0.140           aPTT (s)         41.1 ± 11.5         39.8 ± 0.5         0.324           C-reactive protein (mg/L)         0.7 ± 4.9.1         65.4 ± 61.6         0.833           Serum creatinine (xm0/L)         15.5 ± 27.9         69.3 ± 19.4         0.132           Grancular filtration rate ()         93.1 ± 25.9         94.6 ± 18.1         0.132           Grancular filtration rate ()         93.1 ± 25.9         94.6 ± 18.1         0.132           Grand-glass opacity         53 (77.9)         30 (73.2)         0.79   |                                      | 27 (38.0)                | 19 (43.2)                  | 0.935           |
| Yes         3 (4.2)         2 (4.5)   |                                      | 68 (95.8)                | 42 (95 5)                  | 0.555           |
| psymbols         0.8         0         0.8         0.961           No         60         657)         37         0.00           Yes         0         0.431         0         0.00           No         2 (3.3)         0         0.00         0.231           No         2 (3.3)         0         0.00         0.231           Wes         59 (96.7)         43 (100.0)         1.0         4.0         0.592           Leukocyte count (× 10 <sup>9</sup> /L)         0.9 ± 0.5         1.0 ± 0.6         0.592           Leukocyte count (× 10 <sup>9</sup> /L)         1.9 ± 3.8         3.8 ± 2.6         0.113           Haemoglobin (g/L)         1.27.6 ± 18.7         122.0 ± 17.2         0.119           Protectionin (g/L)         1.35 ± 1.3         1.4.0 ± 2.1         0.140           aPTT (s)         9.4 ± 1.4         1.15         3.9 ± 5.5         0.533           Procation (g/L)         0.27 ± 0.3         3.2 ± 0.5         0.533           Serum creatinine (xmoll.)         75.5 ± 27.9         69.3 ± 19.4         0.213           Serum creatinine (xmoll.)         52.4 ± 3.1         3.4 ± 2.6         0.132           Consonidative pulmonary opacities         13         1.5 ± 3.1         0.732 <t< td=""><td></td><td>. ,</td><td></td><td></td></t<>  |                                      | . ,                      |                            |                 |
| No         60 (8.7.)         37 (8.0)           Yes         10 (14.3)         6 (14.0)           No         2 (3.3)         0 (0.0)           Yes         59 (96.7)         43 (100.0)           Lymphocyte count (× 10 <sup>9</sup> /L)         0.9 ± 0.5         1.0 ± 0.6         0.592           Leukcyte count (× 10 <sup>9</sup> /L)         4.9 ± 3.8         3.8 ± 2.6         0.113           Hamedogibin (g/L)         197.3 ± 8.8.8         18.8.9 ± 7.5.9         0.611           Poterotic (x 10 <sup>9</sup> /L)         197.3 ± 8.8.8         18.8.9 ± 7.5.9         0.611           Poterotic (x 10 <sup>9</sup> /L)         13.5 ± 1.3         14.0 ± 2.1         0.140           Poterotic (x 10 <sup>9</sup> /L)         13.5 ± 1.3         14.0 ± 2.1         0.160           Poterotic (x 10 <sup>9</sup> /L)         62 ± 0.3         0.3 ± 0.5         0.324           Poterotic (x 10 <sup>9</sup> /L)         62 ± 0.3         0.5         0.324           Semum creatinine (µmol/L)         67 ± 4.9.1         65 ± 61.6         0.833           Lit (U/L)         47.4 ± 9.1         64 ± 1.8.1         0.132           Giomenilar filtration rate ()         93.1 ± 25.9         9.66 ± 1.8.3         0.159           ALT (U/L)         41.7 ± 21.1         37.4 ± 1.8.9         0.281           Ot (U/L) <td></td> <td>3 (112)</td> <td>2 (10)</td> <td>0.961</td>   |                                      | 3 (112)                  | 2 (10)                     | 0.961           |
| Yes         10 (14.3)         6 (14.0)           No         2 (3.3)         0 (0.0)           Yes         59 (96.7)         43 (100.0)           Lymphocyte count (× 10 <sup>9</sup> /L)         0.9 ± 0.5         1.0 ± 0.6         0.592           Lawnogobio (gL)         127.6 ± 18.7         122.0 ± 17.2         0.113           Harmogobio (gL)         127.6 ± 18.7         122.0 ± 17.2         0.119           Proteincinn (gL)         197.3 ± 88.8         188.9 ± 75.9         0.611           Proteincinn (gL)         0.2 ± 0.3         0.3 ± 0.5         0.324           Creactive protein (mgL)         67.4 ± 49.1         65.4 ± 61.6         0.853           Serum creatinine (mgL)         75.5 ± 27.9         69.3 ± 12.6         0.394           Serum creatinine (mgL)         37.4 ± 32.7         43.3 ± 2.8         0.132           Concurdan filtration rate ()         93.1 ± 25.9         94.6 ± 18.1         0.733           Strum creatinine (mgL)         41.7 ± 21.1         37.4 ± 18.9         0.284           ATT (U/L)         41.7 ± 21.1         37.4 ± 18.9         0.284           Consolidative pulmonary opacities         13 (19.1)         10 (24.4)         0.599           Or infected lung lobes <sup>10</sup> 2 (3.3)         1 (3.2)  |                                      | 60 (85.7)                | 37 (86.0)                  |                 |
| No         2 (3.3)         0 (0.0)           Yes         59 (96.7)         41 (100.0)           Lymphocyte count (× 10 <sup>9</sup> /L)         0.9 ± 0.5         1.0 ± 0.6         0.592           Leukocyte count (× 10 <sup>9</sup> /L)         4.9 ± 3.8         3.8 ± 2.6         0.113           Haemoglobin (gL)         127.6 ± 18.7         12.0 ± 17.2         0.119           Protenomin time (s)         13.5 ± 1.3         14.0 ± 2.1         0.140           aPTT (s)         41.1 ± 11.5         39.8 ± 6.5         0.503           Procalcionin (xgL)         0.2 ± 0.3         0.3 ± 0.5         0.324           Creactive protein (mg/L)         67.4 ± 49.1         65.4 ± 61.6         0.853           Serum creatinine (µmol/L)         75.5 ± 27.9         69.3 ± 19.4         0.213           BUN (mmol/L)         75.5 ± 27.9         69.3 ± 19.4         0.213           BUN (mmol/L)         41.6 ± 38.5         32.6 ± 18.1         0.733           ALT (U/L)         41.6 ± 38.5         32.6 ± 18.1         0.733           ALT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.59           Io (Timaging findings *         0.90         10         0.732           Croad-glass opacity         53 (77.9)         30 (73.2)         0.50  | Yes                                  |                          |                            |                 |
| Yes59 (96.7)43 (100.0)Lymphotyc rount (x 10 <sup>9</sup> /L)49 ± 3.83.8 ± 2.60.113Haemoglobin (g/L)127.6 ± 18.7122.0 ± 17.20.119Platelt court (x 10 <sup>9</sup> /L)197.3 ± 8.8.818.8 ± 7.5.90.611Prothrombin time (s)13.5 ± 1.314.0 ± 2.10.140aPTT (s)41.1 ± 11.538.8 ± 6.50.503Procalcionin ( $\mu$ g/L)0.2 ± 0.30.3 ± 0.50.324Creactive protein (mg/L)67.4 ± 49.15.4 ± 61.60.853ESR (mm/h)47.8 ± 32.748.3 ± 25.60.934Serum creatinine ( $\mu$ m0/L)5.2 ± 3.14.3 ± 2.80.123BUN (mm0/L)5.2 ± 3.14.3 ± 2.80.132Concerular filtration rate ()93.1 ± 25.996.6 ± 18.10.733AIT (U/L)41.6 ± 38.532.6 ± 18.30.739AIT (U/L)41.7 ± 21.137.4 ± 18.90.289ACT (U/L)37.7 ± 166.631.9 ± 160.20.901Crossolid tive pulmonary opacities13 (19.1)10 (24.4)Roond-glass opacity53 (77.9)30 (73.2)0.901Crossolid tive pulmonary opacities13 (13.1)3 (97.1)34 (6.6)0 (0.00)444 (6.6)2 (6.5)5577.938 (86.4)9.99Smokes or previously smoked65 (91.5)40 (90.9)Smokes or previously smoked65 (91.5)40 (90.9)Smokes or previously smoked65 (91.5)41 (40.00)Yes6 (69.3)41 (40.00)<   | Fever <sup>b</sup>                   |                          |                            | 0.231           |
| $\begin{array}{c c c c c c c } & 0.5 \pm 0.5 & 1.0 \pm 0.6 & 0.592 \\ leakcyte count (\times 10^9 lL) & 49 \pm 3.8 & 3.8 \pm 2.6 & 0.113 \\ haemoglobin (g L) & 127.6 \pm 18.7 & 122.0 \pm 17.2 & 0.119 \\ latelet count (\times 10^9 lL) & 197.3 \pm 88.8 & 188.9 \pm 7.5.9 & 0.611 \\ Prothrombin time (s) & 13.5 \pm 1.3 & 14.0 \pm 2.1 & 0.140 \\ aPTT (s) & 41.1 \pm 11.5 & 39.8 \pm 6.5 & 0.503 \\ Procalcitonin (ng L) & 0.2 \pm 0.3 & 0.3 \pm 0.5 & 0.324 \\ Creactive protein (mg/L) & 67.4 \pm 49.1 & 65.4 \pm 61.6 & 0.853 \\ ESR (mm/h) & 47.8 \pm 32.7 & 48.3 \pm 25.6 & 0.934 \\ Serum creatinine (nmol/L) & 52 \pm 3.1 & 43 \pm 2.8 & 0.132 \\ Glomerular fitration rate () & 93.1 \pm 25.9 & 94.6 \pm 18.1 & 0.733 \\ ALT (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.1 & 0.733 \\ AST (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.1 & 0.733 \\ Croundrigas opacity & 53 (7.7.5 & 38 (86.4) & 0.909 \\ Croundrigas opacity & 54 (7.7.5 & 38 (86.4) & 0.909 \\ Never smoked & 64 (90.1) & 40 (90.9) & 0.892 \\ Never drinks & 64 (90.1) & 40 (90.9) & 0.892 \\ Never drinks & 64 (90.1) & 61 (3.6) & 0.700 \\ Never drinks & 64 (93.0) & 44 (100.0) & 0.892 \\ No & 61 (85.9) & 38 (86.4) & 0.901 \\ No & 5 (7.0) & 0 (0.0) & 0.001 \\ Dinks or previously drak & 65 (91.5) & 42 (95.5) & 0.700 \\ No & 61 (85.9) & 38 (86.4) & 0.700 \\ No & 61 (85.9) & 38 (86.4) & 0.700 \\ N$ | No                                   | 2 (3.3)                  | 0 (0.0)                    |                 |
| icuikoryie count (× 10 <sup>9</sup> /L)         49 ± 3.8         3.8 ± 2.6         0.113           Haemoglobin (g/L)         127 £ ± 18.7         12.20 ± 17.2         0.119           Platelet count (× 10 <sup>9</sup> /L)         197.3 ± 88.8         188.9 ± 75.9         0.611           Prothrombin time (s)         13.5 ± 1.3         14.0 ± 2.1         0.140           aPTT (s)         41.1 ± 11.5         39.8 ± 6.5         0.503           Procalcitonin (µg/L)         0.2 ± 0.3         0.3 ± 0.5         0.324           Cr-ractive protein (mg/L)         67.4 ± 49.1         63.8 ± 25.6         0.334           Serum creatinine (µmol/L)         75.5 ± 27.9         69.3 ± 19.4         0.213           BUN (mmol/L)         52.8 ± 3.1         4.3 ± 2.8         0.132           Glomerular filtration rate ()         93.1 ± 25.9         94.6 ± 18.1         0.733           ALT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.159           ALT (U/L)         41.7 ± 21.1         37.4 ± 18.9         0.289           Lactate dehydrogenase (U/L)         37.7 4 ± 166.6         38.19 ± 160.2         0.901           Consolidative pulmonary opacities         13 (19.1)         10 (24.4)         0.902           Ground-glass opacity         53 (77.9)         30 (73.2)         0  | Yes                                  | 59 (96.7)                | 43 (100.0)                 |                 |
| Haemoglobin (glL)127.6 ± 18.7122.0 ± 17.20.119Platelet count (× 10 <sup>9</sup> /L)197.3 ± 88.8188.9 ± 75.90.611Prothrombin time (s)13.5 ± 1.314.0 ± 2.10.140aPTT (s)41.1 ± 11.539.8 ± 6.50.503Procalcitonin (ng/L)0.2 ± 0.30.3 ± 0.50.324Creactive protein (mg/L)67.4 ± 49.165.4 ± 61.60.853ESR (mm/h)47.8 ± 32.748.3 ± 25.60.934Serum creatinine (µmol/L)75.5 ± 77.969.3 ± 19.40.213BUN (mmol/L)52.2 ± 3.143.4 ± 2.61.132Clonerular filtration rate ()93.1 ± 25.994.6 ± 18.10.733ALT (U/L)41.6 ± 38.532.6 ± 18.30.159AST (U/L)17.7 ± 1.177.4 ± 18.90.289Lactar dehydrogenase (U/L)37.7 ± 166.638.19 ± 160.20.901CT imagin findings <sup>b</sup>   | Lymphocyte count ( $\times 10^9/L$ ) | $0.9\pm0.5$              | $1.0 \pm 0.6$              | 0.592           |
| Plateler count (× 10 <sup>4</sup> /L)         197.3 ± 88.8         188.9 ± 75.9         0.611           Prothrombin time (s)         13.5 ± 1.3         14.0 ± 2.1         0.140           Prothrombin time (s)         41.1 ± 11.5         39.8 ± 6.5         0.503           Procalcitonin (µg L)         0.2 ± 0.3         0.3 ± 0.5         0.324           C-reactive protein (mg L)         67.4 ± 49.1         65.4 ± 61.6         0.853           ESR (mm/h)         47.8 ± 32.7         48.3 ± 25.6         0.334           Serum creatinine (µmol/L)         52.5 ± 3.1         43.2 ± 2.8         0.132           Glomerular filtration rate ()         31.1 ± 2.5         32.6 ± 18.3         0.159           ALT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.159           ALT (U/L)         41.7 ± 21.1         37.4 ± 18.9         0.289           Lactare dehydrogenase (U/L)         37.7 ± 1 166.6         31.9 ± 160.2         0.901           Cround-glass opacity         53 (77.9)         30 (73.2)         -           Consolidative pulmonary opacities         13 (19.1)         10 (24.4)         -           No. of infected lung lobes <sup>b</sup> 0         0.00         -         -           Q         6 (9.8)         1 (3.2)         -         -<  |                                      | 4.9 ± 3.8                | $3.8 \pm 2.6$              | 0.113           |
| Protrombin time (s)         13.5 ± 1.3         14.0 ± 2.1         0.40           aPTT (s)         0.2 ± 0.3         0.3 ± 0.5         0.503           Procalcitonin (µg/L)         0.2 ± 0.3         0.3 ± 0.5         0.324           C-reactive protein (mg/L)         67.4 ± 49.1         65.4 ± 61.6         0.853           ESR (mm/h)         47.8 ± 32.7         48.3 ± 25.6         0.934           Serum creatinine (µmol/L)         75.5 ± 27.9         69.3 ± 19.4         0.13           Glomenlar filtration rate ()         93.1 ± 25.9         94.6 ± 18.1         0.733           ALT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.159           Lactate dehydrogenase (U/L)         41.7 ± 21.1         37.4 ± 18.9         0.289           Lactate dehydrogenase (U/L)         35 (77.9)         30 (73.2)         Consolidative pulmonary opacities         13 (19.1)         10 (24.4)           No         for infected lung lobes b         (6.6)         0 (0.0)         4         4 (6.6)         2 (6.5)           5         5 (77.9)         30 (73.2)         Consolidative pulmonary opacities         1.3 (19.1)         10 (24.4)         5           Smoker previously smoked         6 (9.8)         1 (3.2)         -         5         6   |                                      | $127.6 \pm 18.7$         |                            | 0.119           |
| aPTT (s)       41.1 ± 11.5       39.8 ± 6.5       0.503         Procalcitomin (µg/L)       67.4 ± 49.1       65.4 ± 61.6       0.853         ESR (mm/h)       47.8 ± 32.7       48.3 ± 25.6       0.934         Serum creatinine (µmol/L)       75.5 ± 27.9       69.3 ± 19.4       0.213         BUN (mmol/L)       52.4 ± 3.1       43.4 ± 2.8       0.132         Glomerular filtration rate ()       93.1 ± 25.9       94.6 ± 18.1       0.733         AST (U/L)       41.6 ± 38.5       32.6 ± 18.3       0.159         AST (U/L)       41.7 ± 21.1       37.4 ± 18.9       0.289         AST (U/L)       41.7 ± 21.1       37.4 ± 18.9       0.289         No lesion       2 (2.9)       1 (2.4)       6000         Ground-glass opacity       53 (77.9)       30 (73.2)       0.509         No efficiend lung lobes <sup>10</sup> 2 (3.3)       1 (3.2)       0.509         0       6 (9.8)       1 (3.2)       1       0.509         1       6 (9.8)       1 (3.2)       1       0.509         0       5 (77.9)       3 (9.7)       2       0.509         1       6 (9.8)       4 (9.1)       0.906       0.906         Smoking history       0.906   |                                      |                          |                            |                 |
| Procalicioni (µg/L)         0.2 ± 0.3         0.3 ± 0.5         0.324           C-reactive protein (µg/L)         67.4 ± 49.1         65.4 ± 61.6         0.833           Serum creatinine (µmol/L)         75.5 ± 27.9         69.3 ± 19.4         0.132           Gomerular filtration rate ()         93.1 ± 25.9         94.6 ± 18.1         0.733           ADT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.153           ADT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.153           ADT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.159           AST (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.159           AST (U/L)         41.7 ± 21.1         37.4 ± 18.9         0.289           Lactate dehydrogenase (U/L)         37.7 ± 166.6         381.9 ± 160.2         0.901           Cround-glas opacity         53 (77.9)         30 (73.2)         0           Consolidative pulmonary opacities         13 (19.1)         10 (24.4)         0           No         in facted lung lobes <sup>b</sup>  |                                      |                          |                            |                 |
| C-reactive protein (mg/L)         67.4 ± 9.1         65.4 ± 61.6         0.853           ESR (mm/h)         47.8 ± 32.7         48.3 ± 25.6         0.934           BUN (mmol/L)         5.5 ± 27.9         69.3 ± 19.4         0.213           BUN (mmol/L)         5.2 ± 3.1         4.3 ± 2.8         0.132           Colomerular filtration rate ()         93.1 ± 25.6         94.6 ± 18.1         0.733           ALT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.159           AST (U/L)         41.7 ± 21.1         37.4 ± 18.9         0.289           Lactate dehydrogenase (U/L)         37.7 ± 166.6         31.9 ± 160.2         0.01           Cround-glass opacity         53 (77.9)         30 (73.2)         0.034           Consolidative pulmonary opacities         13 (19.1)         10 (24.4)         0.509           No of infected lung lobes <sup>b</sup> (6.98)         1 (32.2)         1           2         8 (13.1)         3 (97.7)         3         0.00           4         (6.66)         2 (6.5)         5         0.90         4           No of infected lung lobes <sup>b</sup> (69.91)         40 (90.9)         0.906           Smoking history         0.900         2         0.900         0.900 </td <td></td> <td></td> <td></td> <td></td>   |                                      |                          |                            |                 |
| Impl(h)       47.8 ± 32.7       48.3 ± 25.6       0.934         Serum creatinine (µmol/L)       75.5 ± 27.9       69.3 ± 19.4       0.213         BUN (mmol/L)       5.2 ± 3.1       4.3 ± 2.8       0.132         Glomerular filtration rate ()       93.1 ± 25.9       94.6 ± 18.1       0.733         ALT (U/L)       41.6 ± 38.5       32.6 ± 18.3       0.159         AST (U/L)       41.7 ± 21.1       37.4 ± 18.9       0.289         Lactate dehydrogenase (U/L)       37.7 ± 166.6       381.9 ± 160.2       0.901         CT imaging findings   |                                      |                          |                            |                 |
| Serum creatinine (μmol/L)         75.5 ± 27.9         69.3 ± 19.4         0.213           BUN (mmol/L)         5.2 ± 3.1         4.3 ± 2.8         0.132           Clomerular filtration rate ()         93.1 ± 25.9         94.6 ± 18.1         0.733           ALT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.159           AST (U/L)         41.7 ± 21.1         37.4 ± 160.2         0.901           Clamerular fibration rate ()         37.7 ± 166.6         381.9 ± 160.2         0.901           Clamerular fibration rate ()         37.7 ± 166.6         381.9 ± 160.2         0.901           Clamerular fibration rate ()         37.7 ± 166.6         381.9 ± 160.2         0.901           Clamerular fibration rate ()         37.7 ± 166.6         381.9 ± 160.2         0.901           Clamerular fibration rate ()         53 (77.9)         30 (73.2)         0         5.05           Consolidative pulmonary opacities         13 (9.1)         1 (32.0)         1         1 (3.2)         1           0.0         finfected lung lobes b         0 (6.8)         1 (3.2)         1         3.0         9.71           3         4 (6.6)         2 (6.5)         5         5         3 (6.7)         8 (8.0)         1         9.90           S  |                                      |                          |                            |                 |
| BUN (mmol/L)         52 ± 3.1         4.3 ± 2.8         0.132           Glomerular filtration rate ()         93.1 ± 25.9         94.6 ± 18.1         0.733           ALT (U/L)         41.6 ± 38.5         32.6 ± 18.3         0.159           AST (U/L)         41.7 ± 21.1         37.4 ± 18.9         0.289           AST (U/L)         41.7 ± 21.1         37.4 ± 18.9         0.804           No lesion         2 (2.9)         1 (2.4)         0.804           No lesion         2 (3.3)         1 (3.2)         0.509           Consolidative pulmonary opacities         13 (19.1)         10 (24.4)         0.509           No. of infected lung lobes b         0         2 (3.3)         1 (3.2)         1           1         6 (9.8)         1 (3.2)         1         3 (9.7)         3           3         4 (6.6)         0 (0.0)         4         4 (6.6)         2 (6.5)           5         3 7 (60.7)         24 (77.4)         9         9         9           Smokes or previously smoked         65 (91.5)         40 (90.9)         9         9           Drinks or previously smoked         64 (90.1)         40 (90.1)         9         9           Mo         67 (93.0)         38 (86.4)  |                                      |                          |                            |                 |
| $\begin{array}{c c c c c c } \mbox{Cl} Intraction rate () & 93.1 \pm 25.9 & 94.6 \pm 18.1 & 0.733 \\ ALT (U/L) & 41.6 \pm 38.5 & 32.6 \pm 18.3 & 0.159 \\ AST (U/L) & 41.7 \pm 21.1 & 37.4 \pm 18.9 & 0.289 \\ Lactate dehydrogenase (U/L) & 37.4 \pm 166.6 & 381.9 \pm 160.2 & 0.901 \\ CT imaging findings b & & & & & & & & & & & & & & & & & & $  |                                      |                          |                            |                 |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$  |                                      |                          |                            |                 |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$  |                                      |                          |                            |                 |
| Lactate dehydrogenase (U/L) $377.4 \pm 166.6$ $381.9 \pm 160.2$ $0.901$<br>$0.804$ CT imaging findings b2 (2.9)1 (2.4) $0.804$ No lesion2 (2.9)30 (73.2) $0.804$ Consolidative pulmonary opacities13 (19.1)10 (24.4) $0.509$ No. of infected lung lobes b2 (3.3)1 (3.2) $1.5000000000000000000000000000000000000$   |                                      |                          |                            |                 |
| CT imaging findings b       0.804         No lesion       2 (2.9)       1 (2.4)         No lesion       30 (75.2)         Consolidative pulmonary opacities       13 (19.1)       10 (24.4)         No. of infected lung lobes b       0       0.509         0       1 (3.2)       1       13 (2)         1       6 (9.8)       1 (3.2)       1         2       8 (13.1)       3 (9.7)       2         3       4 (6.6)       0 (0.0)       4         4       4 (6.6)       2 (6.5)       5         5       37 (80.7)       24 (77.4)       0.906         Smoking history        0.892       0.906         Never smoked       65 (91.5)       40 (90.9)       0.892         Drinking history        0.892       0.892         No       55 (77.5)       38 (86.4)       0.238         Ves       16 (22.5)       6 (13.6)       0.92   |                                      |                          |                            |                 |
| No lesion         2 (2.9)         1 (2.4)           Ground-glass opacity         53 (77.9)         30 (73.2)           Consolidative pulmoary opacities         13 (19.1)         10 (24.4)           No. of infected lung lobes b         (2.3.3)         1 (3.2.)           0         2 (3.3)         1 (3.2.)           1         6 (9.8)         1 (3.2.)           2         8 (13.1)         3 (9.7.)           3         4 (6.6)         2 (6.5.)           5         37 (60.7)         24 (77.4)           Smoking history         0         0.906           Never smoked         65 (91.5.)         4 (9.1)           Drinking history         0.892           Never smoked         64 (90.1)         40 (90.9)           Smokes or previously smoked         6 (25.5)         4 (9.1)           Priver drinks         7 (9.9)         4 (9.1)           Hypertension         0.238           No         66 (93.0.0)         6 (13.6)           Yes         16 (22.5.)         6 (13.6)           Cardiovascular disease         0.946           No         5 (7.0.)         0 (0.0.)           Yes         10 (14.1)         6 (13.6)           Yes   |                                      | 577.4 ± 100.0            | 501.5 ± 100.2              |                 |
| Ground-glass opacity53 (77.9)30 (73.2)Consolidative pulmonary opacities13 (19.1)10 (24.4)No. of infected lung lobes b0.50902 (3.3)1 (3.2)16 (9.8)1 (3.2)16 (9.8)1 (3.2)28 (13.1)3 (9.7)34 (6.6)0 (0.0)44 (6.6)2 (6.5)53 (97.7)2 (77.4)Smoking history0.906Never smoked65 (91.5)40 (90.9)Smokes or previously smoked64 (90.1)40 (90.9)Drinking history0.380.38Never drinks64 (90.1)40 (90.9)Drinking reviously drank7 (9.9)40 (90.9)Drinking history0.380.38No55 (77.5)38 (86.4)Yes6 (6 (93.0)44 (100.0)Yes0 (0.0)0.907Diabetes mellitus0.972No65 (91.5)42 (95.5)Yes10 (14.1)6 (13.6)Carcer0.730No6 (8.5)2 (9.5)Yes6 (8.5)2 (9.5)Yes6 (8.5)2 (9.5)Yes0 (98.6)3 (97.7)Yes1 (1.4)1 (2.3)No52 (75.4)34 (82.9)   |                                      | 2 (2.9)                  | 1 (2.4)                    | 0.001           |
| Consolidative pulmonary opacities13 (19.1)10 (24.4)No. of infected lung lobes b0.50902 (3.3)1 (3.2)16 (9.8)1 (3.2)28 (13.1)3 (9.7)34 (6.6)2 (6.5)537 (60.7)24 (77.4)Smoking history0.906Never smoked65 (91.5)40 (90.9)Smokes or previously smoked6 (8.5)4 (9.1)Drinking history0.892Never drinks64 (90.1)40 (90.9)Drinks or previously drank7 (9.9)4 (9.1)Hypertension0.238No55 (77.5)38 (86.4)Yes66 (93.0)44 (100.0)Yes0.072No61 (85.9)38 (86.4)Yes0.014.116 (13.6)Cardiovascular disease0.946No65 (91.5)42 (95.5)Yes65 (91.5)42 (95.5)Yes65 (91.5)42 (95.5)Yes70 (98.6)43 (97.7)Yes1 (1.4)1 (2.3)No70 (98.6)43 (97.7)Yes   |                                      |                          |                            |                 |
| No. of infected lung lobes b0.50902 (3.3)1 (3.2)16 (9.8)1 (3.2)28 (13.1)3 (9.7)34 (6.6)0 (0.0)44 (6.6)2 (6.5)537 (60.7)24 (77.4)Smoking history0.906Never smoked65 (91.5)40 (90.9)Smokes or previously smoked6 (8.5)4 (9.1)Drinking history0.892Never drinks64 (90.1)40 (90.9)Drinks or previously drank7 (9.9)4 (9.1)Hypertension0.238No55 (77.5)38 (86.4)Yes66 (93.0)44 (100.0)Yes0.072Diabetes mellitus0.946No61 (85.9)38 (86.4)Yes0.10 (14.1)6 (13.6)Carciovascular disease0.424No65 (91.5)42 (95.5)Yes6 (8.5)2 (4.5)No65 (91.5)43 (97.7)Yes1 (1.4)1 (2.3)No70 (98.6)43 (97.7)Yes1 (1.4)1 (2.3)Negative conversion time for SARS-CoV-2 test (days)14 (1.2)No52 (75.4)34 (82.9)  |                                      |                          |                            |                 |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$  |                                      |                          |                            | 0.509           |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$  | 0                                    | 2 (3.3)                  | 1 (3.2)                    |                 |
| 3       4 (6.6)       0 (0.0)         4       4 (6.6)       2 (6.5)         5       37 (60.7)       24 (77.4)         Smoking history       0.906         Never smoked       65 (91.5)       40 (90.9)         Smokes or previously smoked       66 (8.5)       4 (9.1)         Drinking history       0.892         Never drinks       64 (90.1)       40 (90.9)         Drinks or previously drank       7 (9.9)       4 (9.1)         Hypertension       0.238         No       55 (77.5)       38 (86.4)         Yes       16 (22.5)       6 (13.6)         Cardiovascular disease       0.072         No       65 (93.0)       44 (100.0)         Yes       5 (7.0)       0 (0.0)         Diabetes mellitus       0.946         No       61 (85.9)       38 (86.4)         Yes       10 (14.1)       6 (13.6)         Carcior       0.424       0.424         No       65 (91.5)       42 (95.5)         Yes       6 (8.5)       2 (4.5)         Carcer       0.730         No       6 (8.5)       2 (4.5)         Yes       6 (93.6)       43 (97.7)  | 1                                    | 6 (9.8)                  | 1 (3.2)                    |                 |
| 446.6)26.5)53760.7)2477.4)Smoking history0.906Never smoked6591.5)40Smokes or previously smoked68.5)49.1)Drinking history0.8920.8920.892Never drinks6490.1)4090.9)Drinks or previously drank79.9)49.1)Hypertension0.2380.2380.238No5577.5)3886.4)0.72Yes1662.5)613.6)0.72No6693.0)44100.0)0.72No6693.0)44100.0)0.946No6185.9)3886.4)10Yes1014.1)613.6)0.424No6591.5)242.95.5)6Yes1014.1)613.6)0.424No6591.5)245.938Yes1014.1)613.6)0.424No6591.5)245.936Yes1014.1)11.231.41No7098.6)4397.7)12.84.10.314No7098.6)4397.7)1.411.284.10.314No7098.6)4397.7)1.411.284.10.314No7098.6) <td>2</td> <td>8 (13.1)</td> <td>3 (9.7)</td> <td></td>   | 2                                    | 8 (13.1)                 | 3 (9.7)                    |                 |
| 5 $37$ ( $60.7$ ) $24$ ( $7.4$ )         Smoking history       0.906         Never smoked $65$ ( $91.5$ ) $40$ ( $90.9$ )         Smokes or previously smoked $6$ ( $8.5$ ) $4$ ( $9.1$ )         Drinking history       0.892         Never drinks $64$ ( $90.1$ ) $40$ ( $90.9$ )         Drinks or previously drank $7$ ( $9.9$ ) $4$ ( $9.1$ )         Hypertension       0.238         No $55$ ( $77.5$ ) $38$ ( $86.4$ )         Yes       16 ( $22.5$ ) $6$ ( $13.6$ )         Cardiovascular disease       0.072         No $66$ ( $93.0$ ) $44$ ( $100.0$ )         Yes $5$ ( $7.0$ ) $0$ ( $0.0$ )         Diabetes mellitus       0.946         No $61$ ( $85.9$ ) $38$ ( $86.4$ )         Yes $10$ ( $14.1$ ) $6$ ( $13.6$ )         Cancer       0.424         No $61$ ( $85.9$ ) $38$ ( $86.4$ )         Yes $24$ ( $95.5$ ) $2$ ( $4.5$ )         Cancer $0.424$ $0.730$ No $61$ ( $85.9$ ) $24$ ( $95.5$ )         Yes $2(4.5)$ $-730$ No $70$ ( $98.6$ ) <td>3</td> <td>4 (6.6)</td> <td>0 (0.0)</td> <td></td>  | 3                                    | 4 (6.6)                  | 0 (0.0)                    |                 |
| Smoking history       0.906         Never smoked       65 (91.5)       40 (90.9)         Smokes or previously smoked       6 (8.5)       4 (9.1)         Drinking history       0.892         Never drinks       64 (90.1)       40 (90.9)         Drinks or previously drank       7 (9.9)       4 (9.1)         Hypertension       0.238         No       55 (77.5)       38 (86.4)         Yes       66 (93.0)       44 (100.0)         Cardiovascular disease       0.072         No       55 (7.0)       0 (0.0)         Pises mellitus       0.946         No       66 (93.0)       44 (100.0)         Yes       5 (7.0)       0 (0.0)         Diabetes mellitus       0.946         No       61 (85.9)       38 (86.4)         Yes       10 (14.1)       61 (36.)         Cancer       0.424         No       65 (91.5)       42 (95.5)         Yes       6 (8.5)       2 (4.5)         Cerebrovascular disease       0.730         No       70 (98.6)       43 (97.7)         Yes       6 (8.5)       2 (4.5)         No       70 (98.6)       43 (97.7)         <  | 4                                    | 4 (6.6)                  | 2 (6.5)                    |                 |
| Never smoked65 (91.5)40 (90.9)Smokes or previously smoked6 (8.5)4 (9.1)Drinking history0.892Never drinks64 (90.1)40 (90.9)Drinks or previously drank7 (9.9)4 (9.1)Hypertension0.238No55 (77.5)38 (86.4)Yes16 (22.5)6 (13.6)Cardiovascular disease0.072No66 (93.0)44 (100.0)Yes5 (7.0)0 (0.0)Diabetes mellitus0.946No61 (85.9)38 (86.4)Yes10 (14.1)6 (13.6)Cancer0.424No65 (91.5)42 (95.5)Yes6 (8.5)2 (4.5)Cerebrovascular disease0.730No70 (98.6)43 (97.7)Yes1 (1.4)1 (2.3)Negative conversion time for SARS-CoV-2 test (days)14.1 ± 3.512.8 ± 4.1No52 (75.4)34 (82.9)  |                                      | 37 (60.7)                | 24 (77.4)                  |                 |
| Smokes or previously smoked6 (8.5)4 (9.1)0.892Drinking history0.8920.892Never drinks64 (90.1)40 (90.9)Drinks or previously drank7 (9.9)4 (9.1)Hypertension0.238No55 (77.5)38 (86.4)Yes16 (22.5)6 (13.6)Cardiovascular disease0.072No66 (93.0)44 (100.0)Yes5 (7.0)0 (0.0)Diabetes mellitus0.946No61 (85.9)38 (86.4)Yes10 (14.1)6 (13.6)Cancer0.424No65 (91.5)42 (95.5)Yes6 (8.5)2 (4.5)Oko70 (98.6)43 (97.7)Yes1 (1.4)1 (2.3)No70 (98.6)43 (97.7)Yes1 (1.4)1 (2.3)No52 (75.4)34 (82.9)   | 0                                    |                          |                            | 0.906           |
| Drinking history       0.892         Never drinks       64 (90.1)       40 (90.9)         Drinks or previously drank       7 (9.9)       4 (9.1)         Hypertension       0.238         No       55 (77.5)       38 (86.4)         Yes       16 (22.5)       6 (13.6)         Cardiovascular disease       0.072         No       66 (93.0)       44 (100.0)         Yes       5 (7.0)       0 (0.0)         Diabetes mellitus       0.946         No       61 (85.9)       38 (86.4)         Yes       10 (14.1)       6 (13.6)         Carcer       0.946         No       65 (91.5)       42 (95.5)         Yes       6 (8.5)       2 (4.5)         Cerebrovascular disease       0.730         No       65 (91.5)       42 (95.5)         Yes       6 (8.5)       2 (4.5)         Yes       6 (8.5)       2 (4.5)         No       70 (98.6)       43 (97.7)         Yes       1 (1.4)       1 (2.3)         Negative conversion time for SARS-CoV-2 test (days)       14.1 ± 3.5       0.314         Death <sup>c</sup> 0.314       0.314         Death <sup>c</sup> 0.34 (82.9)   |                                      |                          | . ,                        |                 |
| Never drinks64 (90.1)40 (90.9)Drinks or previously drank7 (9.9)4 (9.1)Hypertension0.238No55 (77.5)38 (86.4)Yes16 (22.5)6 (13.6)Cardiovascular disease0.072No66 (93.0)44 (100.0)Yes5 (7.0)0 (0.0)Pes5 (7.0)0 (0.0)Diabetes mellitus0.946No61 (85.9)38 (86.4)Yes10 (14.1)6 (13.6)Carcer0.424No65 (91.5)42 (95.5)Yes6 (8.5)2 (4.5)Cerebrovascular disease0.730No70 (98.6)43 (97.7)Yes1 (1.4)1 (2.3)Negative conversion time for SARS-CoV-2 test (days)14.1 $\pm$ 3.512.8 $\pm$ 4.10.314Death <sup>c</sup> 052 (75.4)34 (82.9)  |                                      | 6 (8.5)                  | 4 (9.1)                    |                 |
| $\begin{array}{ccccccc} Drinks or previously drank & 7 (9.9) & 4 (9.1) \\ Hypertension & 0.238 \\ No & 55 (77.5) & 38 (86.4) \\ Yes & 16 (22.5) & 6 (13.6) \\ Cardiovascular disease & 0.072 \\ No & 66 (93.0) & 44 (100.0) \\ Yes & 5 (7.0) & 0 (0.0) \\ \end{array}$  |                                      | 64 (00.4)                | 40 (00 0)                  | 0.892           |
| Hypertension       0.238         No       55 (77.5)       38 (86.4)         Yes       16 (22.5)       6 (13.6)         Cardiovascular disease       0.072         No       66 (93.0)       44 (100.0)         Yes       5 (7.0)       0 (0.0)         Diabetes mellitus       0.946         No       61 (85.9)       38 (86.4)         Yes       10 (14.1)       6 (13.6)         Cancer       0.424         No       65 (91.5)       42 (95.5)         Yes       6 (8.5)       2 (4.5)         Cerebrovascular disease       0.730         No       70 (98.6)       43 (97.7)         Yes       1 (1.4)       1 (2.3)         Negative conversion time for SARS-CoV-2 test (days)       14.1 ± 3.5       12.8 ± 4.1       0.314         Death <sup>c</sup> 0.475       0.475       0.475         No       52 (75.4)       34 (82.9)       0.475  |                                      |                          |                            |                 |
| No55 (77.5)38 (86.4)Yes16 (22.5)6 (13.6)Cardiovascular disease0.072No66 (93.0)44 (100.0)Yes5 (7.0)0 (0.0)Diabetes mellitus $0.946$ No61 (85.9)38 (86.4)Yes10 (14.1)6 (13.6)Cancer $0.424$ No65 (91.5)42 (95.5)Yes6 (8.5)2 (4.5)Cencer0.730No70 (98.6)43 (97.7)Yes1 (1.4)1 (2.3)Negative conversion time for SARS-CoV-2 test (days)14.1 ± 3.512.8 ± 4.1No52 (75.4)34 (82.9)  |                                      | 7 (9.9)                  | 4 (9.1)                    | 0.220           |
| Yes16 (22.5)6 (13.6)Cardiovascular disease0.072No66 (93.0)44 (100.0)Yes5 (7.0)0 (0.0)Diabetes mellitus $0.946$ No61 (85.9)38 (86.4)Yes10 (14.1)6 (13.6)Cancer $0.424$ No65 (91.5)42 (95.5)Yes6 (8.5)2 (4.5)Cerebrovascular disease $0.730$ No70 (98.6)43 (97.7)Yes1 (1.4)1 (2.3)Negative conversion time for SARS-CoV-2 test (days)14.1 ± 3.512.8 ± 4.1No52 (75.4)34 (82.9)   | 51                                   |                          | 28 (86.4)                  | 0.238           |
| $\begin{array}{c c} \mbox{Cardiovascular disease} & 0.072 \\ \hline No & 66 (93.0) & 44 (100.0) \\ \hline Yes & 5 (7.0) & 0 (0.0) \\ \hline Diabetes mellitus & 0.946 \\ \hline No & 61 (85.9) & 38 (86.4) \\ \hline Yes & 10 (14.1) & 6 (13.6) \\ \hline Cancer & 0.424 \\ \hline No & 65 (91.5) & 42 (95.5) \\ \hline Yes & 6 (8.5) & 2 (4.5) \\ \hline Cerebrovascular disease & 0.730 \\ \hline No & 70 (98.6) & 43 (97.7) \\ \hline Yes & 1 (1.4) & 1 (2.3) \\ \hline Negative conversion time for SARS-CoV-2 test (days) & 14.1 \pm 3.5 \\ \hline No & 52 (75.4) & 34 (82.9) \\ \hline \end{array}$   |                                      |                          |                            |                 |
| $\begin{array}{cccc} No & 66 (93.0) & 44 (100.0) \\ Yes & 5 (7.0) & 0 (0.0) \\ \hline Diabetes mellitus & & 0.946 \\ No & 61 (85.9) & 38 (86.4) \\ Yes & 10 (14.1) & 6 (13.6) \\ \hline Cancer & & 0.424 \\ No & 65 (91.5) & 42 (95.5) \\ Yes & 6 (8.5) & 2 (4.5) \\ \hline Cerebrovascular disease & & 0.730 \\ \hline No & 70 (98.6) & 43 (97.7) \\ Yes & 1 (1.4) & 1 (2.3) \\ \hline Negative conversion time for SARS-CoV-2 test (days) & 1(1.4) & 1.28 \pm 4.1 & 0.314 \\ Death^c & & 0.475 \\ \hline No & 52 (75.4) & 34 (82.9) \\ \hline \end{array}$  |                                      | 16 (22.5)                | 6 (13.6)                   | 0.072           |
| $\begin{array}{cccc} Yes & 5 (7.0) & 0 (0.0) \\ \hline Diabetes mellitus & & 0.946 \\ No & 61 (85.9) & 38 (86.4) \\ Yes & 10 (14.1) & 6 (13.6) \\ \hline Cancer & & 0.424 \\ No & 65 (91.5) & 42 (95.5) \\ Yes & 6 (8.5) & 2 (4.5) \\ \hline Cerebrovascular disease & & 0.730 \\ No & 70 (98.6) & 43 (97.7) \\ Yes & 1 (1.4) & 1 (2.3) \\ \hline Negative conversion time for SARS-CoV-2 test (days) & 14.1 \pm 3.5 & 12.8 \pm 4.1 & 0.314 \\ Death^c & & 0.475 \\ \hline No & 52 (75.4) & 34 (82.9) \\ \hline \end{array}$  |                                      | 66 (02.0)                | 44 (100.0)                 | 0.072           |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $  |                                      |                          | . ,                        |                 |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$  |                                      | 5 (1.0)                  | 0 (0.0)                    | 0.946           |
| $\begin{array}{cccc} Yes & 10 (14.1) & 6 (13.6) \\ \hline Cancer & 0.424 \\ No & 65 (91.5) & 42 (95.5) \\ Yes & 6 (8.5) & 2 (4.5) \\ \hline Cerebrovascular disease & 0.730 \\ No & 70 (98.6) & 43 (97.7) \\ Yes & 1 (1.4) & 1 (2.3) \\ \hline Negative conversion time for SARS-CoV-2 test (days) & 14.1 \pm 3.5 & 12.8 \pm 4.1 & 0.314 \\ Death^c & 0.475 \\ \hline No & 52 (75.4) & 34 (82.9) \end{array}$   |                                      | 61 (85.9)                | 38 (86.4)                  | 0.540           |
| $\begin{array}{c c} Cancer & 0.424 \\ No & 65 (91.5) & 42 (95.5) \\ Yes & 6 (8.5) & 2 (4.5) \\ Cerebrovascular disease & 0.730 \\ No & 70 (98.6) & 43 (97.7) \\ Yes & 1 (1.4) & 1 (2.3) \\ Negative conversion time for SARS-CoV-2 test (days) & 14.1 \pm 3.5 & 12.8 \pm 4.1 & 0.314 \\ Death^c & 0.475 \\ No & 52 (75.4) & 34 (82.9) \end{array}$  |                                      |                          |                            |                 |
| $\begin{array}{cccc} No & 65 & (91.5) & 42 & (95.5) \\ Yes & 6 & (8.5) & 2 & (4.5) \\ \hline Cerebrovascular disease & & & & & & & & & \\ No & 70 & (98.6) & 43 & (97.7) & & & & \\ Yes & 1 & (1.4) & 1 & (2.3) & & & & \\ Negative conversion time for SARS-CoV-2 test (days) & 14.1 \pm 3.5 & 12.8 \pm 4.1 & 0.314 \\ Death^c & & & & & & & & & \\ No & 52 & (75.4) & 34 & (82.9) & & & & \\ \end{array}$   |                                      |                          |                            | 0.424           |
| $\begin{array}{cccc} Yes & 6 & (8.5) & 2 & (4.5) \\ \hline Cerebrovascular disease & & & & & & & & & & & & & & & & & & &$   |                                      | 65 (91.5)                | 42 (95.5)                  |                 |
| $\begin{array}{c c} Cerebrovascular disease \\ No \\ Yes \\ Ves \\ Negative conversion time for SARS-CoV-2 test (days) \\ Death^c \\ No \\ \end{array} \begin{array}{c c} 70 (98.6) \\ 11 (1.4) \\ 11 (2.3) \\ 14.1 \pm 3.5 \\ 12.8 \pm 4.1 \\ 0.314 \\ 0.475 \\ 0.475 \\ 34 (82.9) \\ \end{array}$   |                                      |                          |                            |                 |
| $\begin{array}{cccc} No & 70 & (98.6) & 43 & (97.7) \\ Yes & 1 & (1.4) & 1 & (2.3) \\ Negative conversion time for SARS-CoV-2 test (days) & 14.1 \pm 3.5 & 12.8 \pm 4.1 & 0.314 \\ Death^c & & 0.475 \\ No & 52 & (75.4) & 34 & (82.9) \end{array}$   |                                      | <u> </u>                 |                            | 0.730           |
| Yes       1 (1.4)       1 (2.3)         Negative conversion time for SARS-CoV-2 test (days) $14.1 \pm 3.5$ $12.8 \pm 4.1$ $0.314$ Death <sup>c</sup> 0.475         No       52 (75.4)       34 (82.9)   |                                      | 70 (98.6)                | 43 (97.7)                  |                 |
| Negative conversion time for SARS-CoV-2 test (days) $14.1 \pm 3.5$ $12.8 \pm 4.1$ $0.314$ Death <sup>c</sup> 0.475           No         52 (75.4)         34 (82.9)   |                                      | . ,                      |                            |                 |
| Death <sup>c</sup> 0.475           No         52 (75.4)         34 (82.9)   |                                      |                          |                            | 0.314           |
| No 52 (75.4) 34 (82.9)  | Death <sup>c</sup>                   |                          |                            |                 |
|   | No                                   | 52 (75.4)                | 34 (82.9)                  |                 |
|   | Yes                                  | 17 (24.6)                | 7 (17.1)                   |                 |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; aPTT, activated partial thromboplastin time; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography.

<sup>a</sup> Data are presented as the n (%) or mean  $\pm$  standard deviation.

<sup>b</sup> There were missing data for dyspnoea, fever, CT imaging findings and number of infected lung lobes.

<sup>c</sup> Two participants in the control group and three participants in the treatment group were still receiving treatment in hospital at the end of the study.

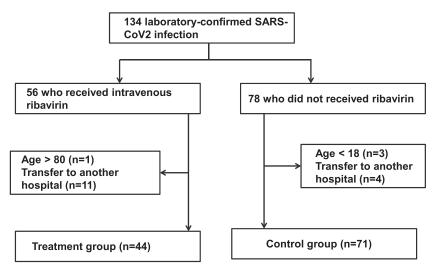


Fig. 1. Flow diagram for study inclusion. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2

| Support measures offered | l during the course o | of SARS-CoV-2 infection <sup>a</sup> |
|--------------------------|-----------------------|--------------------------------------|
|--------------------------|-----------------------|--------------------------------------|

| Support measure        | Control group $(n = 71)$     | Ribavirin group $(n = 44)$ | P-value |
|------------------------|------------------------------|----------------------------|---------|
| Immunoglobulin therapy |                              |                            | 0.143   |
| No                     | 46 (64.8)                    | 33 (75.0)                  |         |
| Yes                    | 25 (35.2)                    | 11 (25.0)                  |         |
| Non-invasive vent      | ilation support              |                            | 0.750   |
| No                     | 53 (74.6)                    | 34 (77.3)                  |         |
| Yes                    | 18 (25.4)                    | 10 (22.7)                  |         |
| Invasive ventilatio    | Invasive ventilation support |                            |         |
| No                     | 64 (90.1)                    | 42 (95.5)                  |         |
| Yes                    | 7 (9.9)                      | 2 (4.5)                    |         |
| Corticosteroid the     | rapy <sup>b</sup>            |                            | 0.288   |
| No                     | 45 (65.2)                    | 30 (75.0)                  |         |
| Yes                    | 24 (34.8)                    | 10 (25.0)                  |         |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup> Data are presented as *n* (%).

<sup>b</sup> There were missing data for immunoglobulin therapy and corticosteroid therapy.

# Table 3

Laboratory parameters following therapy for severe COVID-19 a

| Parameter                            | Control group $(n = 71)$ | Ribavirin group $(n = 44)$ | P-value |
|--------------------------------------|--------------------------|----------------------------|---------|
| Haemoglobin (g/L)                    | 115.8 ± 19.8             | $116.0 \pm 16.7$           | 0.952   |
| Haemoglobin change (g/L)             | $-10.4 \pm 12.6$         | $-5.3 \pm 13.5$            | 0.051   |
| Leukocyte count ( $\times 10^9/L$ )  | $6.4 \pm 3.6$            | $5.7 \pm 3.0$              | 0.283   |
| Lymphocyte count ( $\times 10^9$ /L) | $1.1 \pm 0.6$            | $1.1 \pm 0.5$              | 0.720   |
| C-reactive protein (mg/L)            | 39.1 ± 48.1              | $28.2\pm37.9$              | 0.233   |
| Platelet count ( $\times 10^9/L$ )   | $243.3 \pm 103.8$        | $263.4 \pm 128.2$          | 0.367   |
| Serum creatinine ( $\mu$ mol/L)      | $69.7 \pm 26.8$          | $63.3 \pm 21.4$            | 0.195   |
| BUN (mmol/L)                         | $5.8 \pm 4.3$            | $4.4 \pm 2.7$              | 0.068   |
| ALT (U/L)                            | 62.1 ± 187.3             | 35.8 ± 17.7                | 0.372   |
| AST (U/L)                            | $56.9\pm145.9$           | $34.3 \pm 21.7$            | 0.327   |

COVID-19, coronavirus disease 2019; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

<sup>a</sup> Data are presented as the mean  $\pm$  standard deviation.

promote the recovery of patients infected with SARS-CoV [13,14]. A retrospective cohort study showed that ribavirin and interferon alfa-2a therapy improved survival at 14 days but not at 28 days in patients with severe MERS-CoV infection [4]. It should also be pointed out that a large, retrospective, multicentre study on different types of interferon with ribavirin to treat critically ill MERS cases did not improve survival [6]. Therefore, we should consider to remove the suggestion that patients with COVID-19 be treated with ribavirin.

This study is limited by its single-centre, retrospective and nonrandomised nature. Inevitably, selection bias cannot be completely ruled out. Incontrovertibly, new interventions should be evaluated in randomised controlled clinical trials. However, such an approach is generally accepted in emerging diseases such as SARS-CoV-2 infection. In addition, the sample size required to achieve 90% power of test is approximately 1048 patients. Thus, the sample size in the current study is limited and it is possible that small effects were missed. Nevertheless, the results can provide a reference for further studies based on a larger sample size randomised clinical trial or other populations.

In conclusion, severe COVID-19 is associated with a relatively high mortality rate. Intravenous ribavirin therapy is not associated with improved negative conversion time for SARS-CoV2 test or a reduced mortality rate. Ribavirin therapy was well tolerated and there were no significant adverse effects. These results should be verified in randomised controlled clinical trials. The role of ribavirin in patients with mild SARS-CoV-2 infection also requires further study.

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