Clinical Efficacy of Ribavirin in Adults Hospitalized With Severe Covid-19: A Retrospective Analysis of 208 Patients

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Abstract

Background: Coronavirus disease-2019 (COVID-19) spreads rapidly throughout the world. So far, no therapeutics have yet been proven to be effective. Ribavirin was recommended for the treatment of COVID-19 because of its in vitro activity. However, evidence supporting its clinical use with good efficacy is still lacking.

Methods: A total of 208 confirmed severe or critical COVID-19 patients who were hospitalized in Wuhan Union West Campus between 1 February 2020 and 10 March 2020 were enrolled in the retrospective study. Patients were divided into two groups based on the use of ribavirin. The primary endpoint was the time to clinical improvement. The secondary endpoints included mortality, survival time, time to throat swab SARS-CoV-2 nucleic acid negative conversion, and hospital duration.

Results: 68 patients were treated with ribavirin while 140 not. There were no significant between-group differences in demographic characteristics, baseline laboratory test results, treatment, and distribution of ordinal scale scores at enrollment, except coexisting diseases especially cancer (ribavirin group vs no ribavirin group, $P = 0.014$). Treatment with ribavirin was not associated with a difference in the time to clinical improvement ($P = 0.483$, HR = 0.884, 95% CI = 0.627-1.247). There were also no significant differences between-group in the number of patients with SARS-CoV-2 nucleic acid negative conversion, mortality, survival time, and hospital duration.

Conclusion: In hospitalized adult patients with severe or critical COVID-19, no significant benefit was observed with ribavirin treatment.

Background

Coronavirus disease 2019 (COVID-19), which was declared by the World Health Organization (WHO) as a public health emergency of international concern on 30 January 2020, was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The full spectrum of COVID-19 ranged from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death [1]. It was very transmissible, with each new infected case producing an average of 2.68 new secondary cases [2]. Up to 11 March 2020, COVID-19 swept into at least 114 countries and killed more than 4,000 people, which was officially a pandemic by WHO. So far, almost every country was struck by COVID-19 with 8708008 cases and 461715 deaths [3].

With the increasing understanding of the disease and the accumulation of treatment experience, the diagnosis and treatment schemes for COVID-19 are continually updated. The National Health Committee of the People's Republic of China has issued 8 versions of the New Coronavirus Infected Pneumonia Diagnosis and Treatment Plan, which includes the usage of anti-viral drugs, antibiotics, respiratory support, symptomatic support, and corticosteroid, etc. However, there are still no specific therapeutic agents for coronavirus infections at present.

Ribavirin was prominent on the list of potential COVID-19 treatments from the 5th version of the New Coronavirus Infected Pneumonia Diagnosis and Treatment Plan. Ribavirin was recommended to use with interferon alfa or lopinavir-ritonavir for COVID-19 [4]. Ribavirin has activity both in vitro and in an animal model, against Middle East respiratory syndrome coronavirus (MERS-CoV), and case reports have suggested that the combination of ribavirin with interferon alfa resulted in virologic clearance and survival [5, 6]. However, the results were still controversial [7]. The data on the convincing evidence from clinical trials supporting the use of ribavirin with good efficacy for the treatment of COVID-19 are still lacking.

In the study, we extracted the clinical data on 208 confirmed severe cases of COVID-19 with definite outcomes from a COVID-19 designated hospital in Hubei province, and depicted their clinical characteristics and treatment regimens through a retrospective study. We particularly explored the use of ribavirin in different patients, committing to provide new testimony for the clinical remedy of COVID-19.

Methods

Patient inclusion

There were 208 confirmed COVID-19 patients included in the study. All subjects were enrolled from Union Hospital West Campus, Tongji Medical College, Huazhong University of Science and Technology between 1 February 2020 and 10 March 2020. Inclusion criteria: 1. Diagnosed with COVID-19 by laboratory confirmation according to the New Coronavirus Infected Pneumonia

Diagnosis and Treatment Plan (Trial Version 6) promulgated by the National Health Committee of the People's Republic of China; 2. Fit the criteria of severe type or critical type according to the New Coronavirus Infected Pneumonia Diagnosis and Treatment Plan (Trial Version 6); 3. Patients with clear clinical outcomes (discharged or dead). Exclusion criteria: 1. Pregnancy; 2. Hospital length of stay ≤ 48 hours; 3. Age ≤ 18 years. The study was approved by the institution of the research ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology ([2020-0104]).

Data collection

All data including epidemiological, clinical, laboratory and treatment information were mainly collected from the electronic medical record. The details are following: Demographic data: age, sex, exposure history, chronic medical histories (hypertension, cardiovascular disease, diabetes, liver disease, kidney disease, malignancy); Signs and symptoms: fever, cough, expectoration, dyspnoea, and diarrhea from onset to hospital admission; Laboratory parameters: white blood cell count, neutrophil count, lymphocyte count, platelet count, C-reactive protein, procalcitonin, erythrocyte sedimentation rate, prothrombin time, activated partial thromboplastin time, troponin, blood urea nitrogen, serum creatinine concentration, direct bilirubin, indirect bilirubin, albumin, sodium, potassium, blood glucose at confirmation of disease type; Therapeutic regimen: anti-viral therapy, anti-biotic therapy, Traditional Chinese Drugs, corticosteroids, and respiratory support (mask breathing, non-invasive respiratory support, invasive respiratory support, and ECMO); Chest radiology: Chest x-

rays and/or chest CT. Patients were assessed on a seven-category ordinal scale from day 0 to day 28, hospital discharge, or death. The seven-category ordinal scale as following: 1. Not hospitalized with resumption of normal activities; 2. Not hospitalized, but unable to resume normal activities; 3. Hospitalized, not requiring supplemental oxygen; 4. Hospitalized, requiring supplemental oxygen; 5. Hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6. Hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7. Death [8].

Statistical Analysis

Continuous variables were expressed as median (interquartile range [IQR]), and categorical variables were expressed as number (proportion). The Student t-test or one-way ANOVA was employed for group comparison of continuous data that are normally distributed; otherwise, the Mann-Whitney U test or Kruskal-Wallis test was used. Chi-square test or the Fisher exact test was used to compare the categorical data. The time to clinical improvement, SARS-CoV-2 nucleic acid negative conversion or survival curves was portrayed by the Kaplan-Meier plot and compared with a log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated by means of the Cox proportional-hazards model. Statistical analyses were performed using SPSS (Version 23.0). All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Result

Demographic and Clinical Characteristics

A total of 208 severe patients with COVID-19 were included in this study. Based on whether treated with ribavirin, patients were divided into two groups. The ribavirin group has 68 patients. Among them, 29 patients were treated with the regimen of ribavirin and interferon, and 26 patients received the regimen of ribavirin and lopinavir/ritonavir. There were 140 patients without ribavirin treatment.

The median age of patients was 62 years (IQR, 52-70 years), and 51.4% of the patients were men. 121 (58.2%) patients had chronic illness: 66 (31.7%) had hypertension, 53 (25.5%) had diabetes, 34 (16.4%) had heart disease, 19 (9.1%) had cancer. A few patients had liver or kidney disease. The most common symptoms before admission were fever (78.4%), cough (70.2%), expectoration (30.8%) and dyspnea (58.2%), and diarrhea (13.5%). Demographic and clinical features are shown in Table 1 and Supplementary Table 1. The median interval time between symptom onset and admission was 12 days (IQR, 7 to 15 days). There were no significant between-group differences in demographic characteristics, baseline laboratory test results, distribution of ordinal scale scores at enrollment, except coexisting diseases especially cancer (ribavirin group vs no ribavirin group, $P = 0.014$). In terms of treatment approaches, most of them received the treatment of arbidol, respiratory support, antibiotic agents, expectorants, and immunopotentiators. Some were given with chloroquine, Lianhua Qingwen, XUE BI JING injection, and glucocorticoid. There were no between-group differences in treatment (Table 2).

Outcome

The time to clinical improvement, defined as the time from admission to an improvement of two points on the seven-category ordinal scale, was used as the primary endpoint to assess the primary outcome of treatments [9]. Patients with failure to reach clinical improvement or death before day 28 were considered as right-censored at day 28. The median time to clinical improvement was 22 days in the ribavirin group, 23 days in the ribavirin and lopinavir/ritonavir group, 27 days in the ribavirin and interferon group, as compared with 22 days in the no ribavirin group ($P = 0.483$; $P = 0.562$; $P = 0.483$) (Table 3). There were no differences in the cumulative improvement rate between-group (ribavirin group vs no ribavirin group: $P = 0.483$, HR = 0.884, 95% CI = 0.627-1.247; ribavirin and lopinavir/ritonavir group vs no ribavirin group: $P = 0.560$, HR = 0.862, 95% CI = 0.522-1.421; ribavirin and interferon group vs no ribavirin group: $P = 0.483$, HR = 0.239, 95% CI = 0.457-1.216) (Figure 1). No significant differences were observed in the score on a seven-category scale at day 7, 14 (Table 3).

The time from admission to throat swab SARS-CoV-2 nucleic acid negative conversion was used to assess the secondary outcome of different treatments. A total of 167 patients reached a negative conversion of the SARS-CoV-2 virus. The median duration for a patient with positive SARS-CoV-2 from admission was 10 days in the ribavirin group, 13 days in the ribavirin and lopinavir/ritonavir group, 13 days in the ribavirin and interferon group, as compared with 10 days in the no ribavirin group ($P = 0.533$; $P = 0.764$; $P = 0.255$) (Table 3). There were no differences in the cumulative conversion of SARS-CoV-2 nucleic acid between-group (ribavirin group vs no ribavirin group: $P = 0.533$, HR = 1.111, 95% CI = 0.797-1.549; ribavirin and lopinavir/ritonavir group vs no ribavirin group: $P = 0.764$, HR = 1.080, 95% CI = 0.653-1.786; ribavirin and interferon group vs no ribavirin group: $P = 0.255$, HR = 0.766, 95% CI = 0.484-1.212) (Figure 2). No significant differences were observed between-group in the number of patients with SARS-CoV-2 nucleic acid negative conversion at day 7, 14 and 28 (Table 3).

There were 16 (23.53%) deaths in the ribavirin group, 8 (30.77%) deaths in the ribavirin and lopinavir/ritonavir group, 6 (20.69%) deaths in the ribavirin and interferon group, and 25 (17.86%) deaths in the no ribavirin group. There were no differences in the survival rate (ribavirin group vs no ribavirin group: $P = 0.437$, HR = 1.282, 95% CI = 0.685-2.402; ribavirin and lopinavir/ritonavir group vs no ribavirin group: $P = 0.196$, HR = 1.692, 95% CI = 0.763-3.751; ribavirin and interferon group vs no ribavirin group: $P = 0.794$, HR = 1.126, 95% CI = 0.462-2.745) (Figure 3). The mortality at day 7, 14 and 28, duration of hospitalization and clinical symptoms during inpatient were no differences between-group (Table 3).

Discussion

This retrospective study included 208 patients who were hospitalized in the designed hospital for severe or critical COVID-19 patients. Among them, 68 patients were treated with ribavirin. The finding did not provide evidence to support an increase in the probability of clinical improvement, negative conversion of SARS-Cov-2 conferred by ribavirin treatment even the combination of ribavirin and lopinavir/ritonavir or interferon. Neither was a decrease in the probability of mortality or hospital duration.

Ribavirin, a guanosine analog, not only interferes with the replication of RNA and DNA viruses and RNA capping but also promotes the destabilization of viral RNA. Ribavirin was combined with lopinavir/ritonavir for the treatment of SARS-Cov patients, who showed a favorable clinical response [10]. The combination

of ribavirin and interferon- α 2b or - α 2a was found to block MERS-CoV viral replication and reduce ICU admission [11, 12]. The pathology of COVID-19 resembles that of the 2013 MERS-CoV and 2003 SARS-CoV infections. Ribavirin showed in vitro direct-acting anti-viral activity by binding to the RNA-dependent RNA polymerase of SARS-CoV-2, which established the basis for its clinical use against the SARS-CoV-2 [13, 14]. With its potency toward SARS-CoV-2 and availability, ribavirin was recommended for the treatment of COVID-19. However, the clinical evidence supporting the use of ribavirin for COVID-19 is still lacking. Our retrospective study did not support that ribavirin significantly improved clinical symptoms, decrease the time to SARS-CoV-2 nucleic acid negative conversion and mortality. A number of studies found that no evidence of a strong antiviral activity or clinical benefit of hydroxychloroquine for the treatment of our hospitalised patients with severe COVID-19 despite of its strong antiviral activity against SARS-CoV-2 in vitro [15-17]. Cao B et al. found that no benefit was observed with lopinavir/ritonavir treatment beyond standard care for those adult patients with severe COVID-19 [9]. Remdesivir was not associated with statistically significant clinical benefits in adult patients admitted to hospital for severe COVID-19 [18]. Though tocilizumab and administration of convalescent plasma containing neutralizing antibody might improve the clinical outcome in severe and critical COVID-19 patients, the sample size was so small that these observations required further evaluations in clinical trials [19, 20].

Ribavirin was recommended to use with interferon alfa or lopinavir–ritonavir for COVID-19. We compared the outcomes of the combination of ribavirin and interferon alfa or lopinavir–ritonavir with no ribavirin. However, no significant differences were found. Molina J.M. et al. found that there was no evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection [21]. One prospective study indicated that mild or moderate COVID-19 patients with the triple combination of ribavirin, lopinavir/ritonavir, and interferon might have a shorter duration of viral shedding and hospital stay compared with lopinavir-ritonavir alone [22]. So far prospective, randomized, controlled clinical trials to obtain robust clinical data of therapeutic efficacy and safety for ribavirin and its combination with lopinavir-ritonavir or interferon may be still imperative in severe or critical COVID-19 patients.

It should not be ignored that the present study had some limitations. First, the study was retrospective and non-randomized. It was inevitable that selection and unmeasured confounding bias might exist. What's more, only severe or critical patients were hospitalized in the designed hospital, which might affect the therapy regimen. Though we carefully selected control patients to ensure their clinical characteristics and treatment interventions other than ribavirin, the complications especially cancer was higher in the ribavirin group. Second, because of the lack of serial viral load measurement in lower respiratory tract samples, it was impossible to explore the association between temporal viral load changes and antiviral therapy. Last but not least, the sample of the study was relatively small, which might limit the interpretation of our findings.

Conclusion

We found that ribavirin treatment did not significantly accelerate clinical improvement, reduce mortality, the time to SARS-CoV-2 nucleic acid negative conversion, or hospital duration in patients with severe or critical COVID-19. The prospective, randomized, controlled clinical trials of the use of ribavirin and its combination with lopinavir-ritonavir or interferon for severe COVID-19 may be imperative.

Abbreviations

COVID-19: coronavirus disease-2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; WHO: World Health Organization; IQR: interquartile range; HR: hazard ratios; CI: confidence intervals.

Declarations

Acknowledgement

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Authors' contributions

YZ and WJG conceived and designed the study; SLW, JLY, JQX, XFC, and YYS had roles in clinical management, patient recruitment, formulated the treatment regimens; WJG, TZ, SLW, JLY, JQX, XFC, YYS, YNL, and FZ contributed to data collections and data entry. WJG performed the statistics; WJG and TZ wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of the institution of the research ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology ([2020-0104]).

Consent for publication

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Tables

Table 1: Demographic and Clinical Characteristics of the Patients at Baseline.

Characristic	Total(N=208)	Ribavirin (N=68)	Ribavirin+Interferon (N=29)	Ribavirin+Lopinavir/Ritonavir (N=26)	No Ribavirin (N=140)	<i>P</i> Value ^a	<i>P</i> Value ^b
Male sex-no. (%)	107(51.4)	38(55.9)	20(69.0)	17(65.4)	69(49.3)	0.372	0.053
Age, median(IQR)-yr	62(52,70)	63(53,70)	60(55,68)	62(48,71)	62(52,70)	0.418	0.711
<65	116(55.8)	38(55.9)	19(65.6)	15(57.7)	78(55.7)	0.982	0.331
≥65	92(44.2)	30(44.1)	10(34.5)	11(42.3)	62(44.3)		
Coexisting conditions-no. (%)	121(58.2)	49(72.1)	17(58.6)	15(57.7)	72(51.4)	0.005	0.480
Hypertension	66(31.7)	26(38.2)	9(31.0)	9(34.6)	40(28.6)	0.160	0.790
Diabetes	53(25.5)	23(33.8)	10(34.5)	7(26.9)	30(21.4)	0.054	0.132
Heart Diseases	34(16.4)	10(14.7)	4(13.8)	3(11.5)	24(17.2)	0.656	0.659
Liver Diseases	9(4.3)	3(4.4)	1(3.5)	1(3.8)	6(4.3)	0.967	0.837
Kidney Diseases	10(4.8)	4(5.9)	0(0.0)	3(11.5)	6(4.3)	0.614	0.256
Cancer	19(9.1)	11(16.2)	3(10.3)	2(7.7)	8(5.7)	0.014	0.358
Clinical symptoms before admission							
Fiver-no. (%)	163(78.4)	56(82.4)	22(75.9)	19(73.1)	107(76.4)	0.330	0.948
Cough-no. (%)	146(70.2)	50(73.5)	23(79.3)	18(69.2)	96(68.6)	0.463	0.249
Expectoration-no. (%)	64(30.8)	15(22.1)	6(20.7)	7(26.9)	49(35.0)	0.058	0.134
Dyspnea-no. (%)	121(58.2)	36(52.9)	18(62.1)	13(50.0)	85(60.7)	0.286	0.892
Diarrhea-no. (%)	28(13.5)	12(17.6)	4(13.8)	7(26.9)	16(11.4)	0.218	0.720
White-cell count (×10 ⁹ /L) – median (IQR)	5.63(4.40,7.44)	5.44(4.40,7.59)	5.58(4.11,7.42)	5.56(4.50,7.80)	5.75(4.40,7.36)	0.528	0.587
4–10 ×10 ⁹ /L – no. (%)	161(77.4)	55(80.9)	23(79.3)	22(84.6)	111(79.3)	0.472	0.964
<4 ×10 ⁹ /L – no. (%)	20(9.6)	4(5.9)	3(10.3)	0(0.0)	16(11.4)		
>10 ×10 ⁹ /L – no. (%)	26(12.5)	9(13.2)	3(10.3)	4(15.4)	17(12.1)		
Absolute Neutrophil count (×10 ⁹ /L) – median (IQR)	4.00(2.96,5.84)	4.11(3.15,5.95)	3.85(2.71,5.88)	4.23(2.90,6.90)	3.99(2.94,5.56)	0.526	0.547
1.80–6.30 ×10 ⁹ /L – no. (%)	150(72.1)	50(70.5)	21(72.4)	18(69.2)	100(71.4)	0.388	0.652
<1.80 ×10 ⁹ /L – no. (%)	13(6.2)	2(2.9)	1(3.4)	0(0.0)	11(7.9)		
>6.30 ×10 ⁹ /L – no. (%)	43(20.7)	15(22.1)	7(24.1)	8(30.8)	28(20.0)		
Lymphocyte count	0.97(0.66,1.31)	1.00(0.68,1.30)	1.08(0.67,1.35)	1.02(0.69,1.32)	0.96(0.64,1.33)	0.850	0.847

($\times 10^9/L$) – median (IQR)							
1.1-3.2 $\times 10^9/L$ – no. (%)	78(37.5)	28(41.2)	14(48.3)	12(46.2)	50(35.7)	0.468	0.215
<1.10 $\times 10^9/L$ – no. (%)	129(62.0)	40(58.8)	15(51.7)	14(53.8)	89(63.6)		
Eosinophil count ($\times 10^9/L$) – median (IQR)	0.04(0.01,0.11)	0.04(0.01,0.13)	0.06(0.00,0.15)	0.02(0.01,0.07)	0.04(0.01,0.10)	0.485	0.189
0.02-0.52 $\times 10^9/L$ – no. (%)	114(54.8)	32(47.1)	10(34.5)	13(50.0)	82(58.6)	0.244	0.039
<0.02 $\times 10^9/L$ – no. (%)	71(34.1)	26(38.2)	13(44.8)	10(38.5)	45(32.1)		
>0.52 $\times 10^9/L$ – no. (%)	23(11.1)	10(14.7)	6(20.7)	3(11.5)	13(9.3)		
Hemoglobin (g/L) – median (IQR)	125(115,135)	126(120,134)	128(121,137)	126(120,142)	124(113,135)	0.258	0.055
110-150(female) or 120-165(male) g/L – no. (%)	166(79.8)	58(85.3)	27(93.1)	22(84.6)	108(77.1)	0.362	0.179
<110(female) or 120 (male) g/L – no. (%)	38(19.3)	9(13.2)	2(6.9)	3(11.5)	29(20.7)		
>150(female) or 165 (male) g/L – no. (%)	2(1.0)	1(1.5)	0(0.0)	1(3.8)	1(0.7)		
Platelet count ($\times 10^9/L$) – median (IQR)	215(153,292)	214(159,286)	207(155,252)	211(120,142)	217(147,292)	0.945	0.394
125-350 $\times 10^9/L$ – no. (%)	168(80.8)	59(86.8)	25(86.2)	23(88.5)	109(77.9)	0.276	0.487
<125 $\times 10^9/L$ – no. (%)	21(10.0)	4(5.9)	3(10.3)	1(3.8)	17(12.1)		
>350 $\times 10^9/L$ – no. (%)	19(9.1)	5(7.4)	1(3.4)	2(7.7)	14(10.0)		
C-reactive protein (mg/L) – median (IQR)	15.95(3.58,53.25)	16.69(3.75,67.09)	16.69(2.16,53.53)	16.23(4.34,70.08)	15.73(3.60,42.56)	0.310	0.888
$\leq 10\text{mg/}$ – no. (%)	87(41.8)	26(38.2)	13(44.8)	10(38.5)	61(43.6)	0.438	0.976
$> 10\text{mg/}$ – no. (%)	117(56.3)	41(60.3)	16(55.2)	15(57.7)	76(54.3)		

IQR interquartile range;

^a The ribavirin group compared with the no ribavirin group;

^b The ribavirin+interferon group compared with the no ribavirin group;

^c The ribavirin+ lopinavir/ritonavir group compared with the no ribavirin group.

Table 2: Patients' Status and Treatments Received at or after Enrollment

Characteristic	Total (N=208)	Ribavirin (N=68)	Ribavirin+Interferon (N=29)	Ribavirin+Lopinavir/Ritonavir (N=26)	No Ribavirin (N=140)	<i>P</i> Value ^a	<i>P</i> Value ^b	<i>P</i> Value ^c
Seven-category scale at day 1								
3: Hospitalization, not requiring supplemental oxygen — no. (%)	41(19.7)	10(14.7)	4(13.8)	2(7.7)	31(22.1)	0.068	0.425	0.077
4: Hospitalization, requiring supplemental oxygen — no. (%)	128(61.5)	41(60.3)	20(69.0)	15(57.7)	87(62.1)			
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation — no. (%)	37(17.8)	16(23.5)	5(17.2)	8(30.8)	21(15.0)			
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both — no. (%)	2(1.0)	1(1.5)	0(0.0)	1(3.8)	1(0.7)			
Days from illness onset to inpatient — median (IQR)	12(7,15)	12(7,15)	13(7,16)	12(7,15)	12(7,15)	0.583	0.549	0.875
Earlier (≤12 days of symptom onset) — no. (%)	110(52.8)	35(51.5)	14(48.3)	14(53.8)	75(53.6)	0.694	0.564	0.998
Later (>12 days of symptom onset) — no. (%)	90(43.7)	31(45.6)	14(48.3)	11(42.3)	59(42.1)			
Treatments during inpatient								
Chloroquine — no. (%)	32(15.4)	12(17.6)	5(17.2)	5(19.2)	20(14.3)	0.528	0.683	0.517
Arbidol — no. (%)	188(90.4)	60(88.6)	22(75.9)	22(84.6)	128(91.4)	0.464	0.016	0.280
Lianhua Qingwen — no. (%)	84(40.4)	23(33.8)	5(17.2)	12(46.2)	61(43.6)	0.179	0.008	0.808
XUE BI JING injection — no. (%)	51(24.5)	17(25.0)	8(27.6)	7(26.9)	34(24.3)	0.911	0.708	0.775
Antibiotic agent — no. (%)	180(86.5)	58(85.3)	26(89.7)	20(76.9)	122(87.1)	0.714	0.709	0.174
Expectorants — no. (%)	127(61.1)	39(57.4)	20(69.0)	15(57.7)	88(62.9)	0.445	0.533	0.618
Immunopotentiator — no. (%)	106(51.0)	29(42.6)	12(41.4)	12(46.2)	77(55.0)	0.095	0.181	0.406
Anticoagulant drugs — no. (%)	41(19.7)	15(22.1)	7(24.1)	9(34.6)	26(18.6)	0.553	0.491	0.066
Anti-platelet drugs — no. (%)	13(6.2)	6(8.8)	1(3.4)	2(7.7)	7(5.0)	0.285	0.720	0.578
Glucocorticoid therapy — no. (%)	70(33.6)	28(41.2)	13(44.8)	12(46.2)	42(30.0)	0.110	0.121	0.106

^a The ribavirin group compared with the no ribavirin group;

^b The ribavirin+interferon group compared with the no ribavirin group;

^c The ribavirin+ lopinavir/ritonavir group compared with the no ribavirin group.

Table 3: Outcomes of the treatment

Characteristic	Total N=208	Ribavirin (N=68)	Ribavirin+Interferon (N=29)	Ribavirin+Lopinavir/Ritonavir (N=26)	No Ribavirin (N=140)	<i>P</i> Value ^a	<i>P</i> Value ^b	<i>P</i> Value ^c			
Time to clinical improvement – median no. of days (IQR)	22(19,28)	22(19,28)	27(19,28)	23(19,28)	22(19,28)	0.483	0.562	0.483			
Score on seven-category scale at day 7 – no.of patients (%) on seven-category scale at day 7 – no.of patients (%)											
2: Not hospitalized, but unable to resume normal activities	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.145	0.474	0.075			
3: Hospitalization, not requiring supplemental oxygen	25(12.0)	5(7.4)	3(10.3)	2(7.7)	20(14.3)						
4: Hospitalization, requiring supplemental oxygen	130(62.5)	43(63.2)	18(62.1)	14(53.8)	87(62.1)						
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	40(19.2)	14(20.6)	5(17.2)	6(23.1)	26(18.6)						
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	11(5.3)	6(8.8)	3(10.3)	4(15.4)	5(3.6)						
7: Death	2(1.0)	0(0.0)	0(0.0)	0(0.0)	2(1.4)	0.792	0.747	0.510			
Score on seven-category scale at day 14 – no.of patients (%) seven-category scale at day 14 – no.of patients (%)											
2: Not hospitalized, but unable to resume normal activities	20(9.6)	9(13.2)	3(10.3)	4(15.4)	11(7.9)						
3: Hospitalization, not requiring supplemental oxygen	39(18.8)	9(13.2)	4(13.8)	2(7.7)	30(21.4)						
4: Hospitalization, requiring supplemental oxygen	102(49.0)	33(48.5)	15(51.7)	12(46.2)	69(49.3)						
5: Hospitalization, requiring HFNC or noninvasive mechanical ventilation	13(6.2)	4(5.9)	2(6.9)	1(3.8)	9(6.4)						
6: Hospitalization, requiring ECMO, invasive mechanical ventilation, or both	15(7.2)	9(13.2)	4(13.8)	6(23.1)	6(4.3)	0.533	0.764	0.255			
7: Death	19(9.1)	4(5.9)	1(3.4)	1(3.8)	15(10.7)						
Time to SARS-CoV-2 nucleic acid negative – median no. of days (IQR)	10(7,14)	10(7,13)	13(10,16)	13(9,14)	10(7,15)						
SARS-CoV-2 nucleic acid negative – no. (%)	167(80.3)	52(76.5)	23(79.3)	18(69.2)	115(82.1)	0.250	0.720	0.272			
Day 7	46(27.5)	14(26.9)	4(17.4)	3(16.7)	32(27.8)	0.712	0.278	0.194			
Day 14	130(82.8)	45(86.5)	16(69.6)	16(88.9)	85(73.9)	0.445	0.580	0.937			
Day 28	166(99.4)	51(98.1)	22(95.6)	18(100.0)	115(100.0)	0.229	0.432	0.237			
Time from admission to death – median no. of days (IQR)	16(11,20)	20(16,23)	18(16,20)	20(19,23)	14(11,17)	0.035	0.364	0.047			
Mortality – no. (%)	41(19.7)	16(23.5)	6(20.7)	8(30.8)	25(17.9)	0.250	0.720	0.272			
Day 7	2(4.9)	0(0.0)	0(0.0)	0(0.0)	2(8.0)	0.999	0.999	0.999			
Day 14	19(46.3)	4(25.0)	1(16.7)	1(14.3)	15(60.0)	0.256	0.312	0.471			
Day 28	40(97.6)	15(93.8)	6(100.0)	7(100.0)	25(100.0)	0.471	0.720	0.593			
Hospital stay – median no. of days (IQR)	20(16,24)	20(17,23)	20(18,27)	20(17,23)	20(16,24)	0.411	0.135	0.767			
Clinical symptoms During											

inpatient									
Fiver-no. (%)	33(15.9)	11(16.2)	6(20.7)	2(7.7)	22(15.7)	0.932	0.512	0.285	
Cough-no. (%)	120(57.7)	38(55.9)	17(58.6)	12(46.2)	82(58.6)	0.713	0.996	0.241	
Expectoration -no. (%)	57(27.4)	13(19.1)	4(13.8)	5(19.2)	44(31.4)	0.062	0.055	0.210	
Dyspnea-no. (%)	90(43.3)	29(42.6)	8(27.6)	10(38.5)	61(43.6)	0.900	0.111	0.629	
Diarrhea-no. (%)	16(7.7)	6(8.8)	2(6.9)	4(8.2)	10(7.1)	0.670	0.962	0.165	

^a The ribavirin group compared with the no ribavirin group;

^b The ribavirin+interferon group compared with the no ribavirin group;

^c The ribavirin+ lopinavir/ritonavir group compared with the no ribavirin group.

Figures

Figure 1

Time to clinical improvement for hospitalized COVID-19 patients from admission. (a) ribavirin group vs no ribavirin group ($P = 0.483$, $HR = 0.884$, 95% $CI = 0.627-1.247$); (2) ribavirin and lopinavir/ritonavir group vs no ribavirin group ($P = 0.560$, $HR = 0.862$, 95% $CI = 0.522-1.421$); (3) ribavirin and interferon group vs no ribavirin group ($P = 0.483$, $HR = 0.239$, 95% $CI = 0.457-1.216$).

Figure 2

Overall negative conversion curve in COVID-19 patients from admission. (a) ribavirin group vs no ribavirin group ($P = 0.608$, $HR = 0.918$, $95\% \text{ CI} = 0.661-1.274$) ; (2) ribavirin and lopinavir/ritonavir group vs no ribavirin group ($P = 0.198$, $HR = 0.721$, $95\% \text{ CI} = 0.439-1.186$); (3) ribavirin and interferon group vs no ribavirin group ($P = 0.447$, $HR = 0.840$, $95\% \text{ CI} = 0.537-1.316$).

Figure 3

Kaplan-Meier curve for hospitalized COVID-19 patients from admission. (a) ribavirin group vs no ribavirin group ($P = 0.437$, $HR = 1.282$, $95\% CI = 0.685-2.402$); (2) ribavirin and lopinavir/ritonavir group vs no ribavirin group ($P = 0.196$, $HR = 1.692$, $95\% CI = 0.763-3.751$); (3) ribavirin and interferon group vs no ribavirin group ($P = 0.794$, $HR = 1.126$, $95\% CI = 0.462-2.745$).

Supplementary Files

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- [SupplementaryTable1.docx](#)