Supporting information

Table S1. Demographic and Clinical Characteristics of the Moderate and Severe Patients at Baseline.

Characteristics	Moderate		Severe	
	Hydroxychloroquine (N=31)	Chloroquine (N=32)	Hydroxychloroquine (N=9)	Chloroquine (N=8)
Age, year, *n* (SD)	59.70 (14.46)	60.59 (11.72)	60 (14.01)	72 (8.71)
Male, *n* (%)	18 (58.06)	21 (65.63)	5 (55.56)	4 (50.00)
Days from symptom onset to hospitalization, mean (SD)	16.63 (10.75)	17.77 (11.96)	17.75 (13.63)	15.87 (11.89)
Days from symptom onset to randomization, mean (SD)	28.43 (7.63)	29.20 (8.59)	28.81 (13.50)	27.20 (12.08)
Co-morbidities, *n* (%)	24 (77.42)	22 (68.75)	7 (77.78)	5 (62.50)
Hypertension, *n* (%)	15 (48.39)	9 (28.13)	4 (44.44)	4(50.00)
Coronary artery disease, *n* (%)	6 (19.35)	2 (6.25)	1 (11.11)	0 (0.00)
Diabetes, *n* (%)	11(35.48)	4 (12.50)	1 (11.11)	0 (0.00)
Body temperature, ℃, *n* (SD)	36.45 (0.36)	36.66(0.73)	36.79 (1.05)	36.64 (0.32)
Fever, *n* (%)	6 (19.35)	9 (28.13)	1 (11.11)	1(12.5)
Cough, *n* (%)	24 (77.42)	25(78.13)	8 (88.89)	6 (75.00)
Respiratory rate > 24 /min, *n* (%)	1 (3.23)	1 (3.13)	2 (22.22)	5 (62.50)
Respiratory rate > 30 /min, *n* (%)	0 (0.00)	0 (0.00)	0 (0.00)	4(50.00)
Systolic blood pressure < 90 mmHg, *n* (%)	0 (0.00)	1 (3.13)	0 (0.00)	0(0.00)
Oxygen saturation* ≤ 93%, *n* (%)	0 (0.00)	3 (9.38)	2 (22.22)	7 (87.50)
White blood cell count (×10^9/L), mean (SD)	6.21 (2.50)	6.67 (3.06)	7.69 (4.25)	7.21 (2.63)
4-10, *n* (%)	26 (83.87)	25 (78.13)	7 (77.78)	6 (75.00)
<4, *n* (%)	2 (6.45)	2 (6.25)	0 (0.00)	1 (12.50)
>10, *n* (%)	3 (9.67)	5 (15.63)	2 (22.22)	1 (12.50)
Lymphocyte count (× 10^9/L), mean (SD)	1.55 (0.64)	1.33 (0.52)	1.17 (0.50)	0.96 (0.75)
≥ 1.0, *n* (%)	26 (83.87)	24 (75.00)	5 (55.56)	2 (25.00)
< 1.0, *n* (%)	5 (16.13)	8 (25.00)	4 (44.44)	6 (75.00)
Lymphocyte percentage (%), mean (SD)	27.02 (11.32)	23.33 (10.12)	19.28 (12.09)	13.94 (9.03)
20-50, *n* (%)	22 (70.97)	20 (62.50)	4 (44.44)	1 (12.50)
< 20, *n* (%)	9 (29.03)	12 (37.50)	5 (55.56)	7 (87.50)
> 50, *n* (%)	0(0.00)	0(0.00)	0 (0.00)	0 (0.00)
Platelet count (× 10^9/L), mean (SD)	228.00 (103.26)	218.19 (87.01)	223.44 (143.40)	215.62 (81.72)
≥ 100, *n* (%)	31 (100.00)	31 (96.88)	8 (88.89)	8 (100.00)
< 100, *n* (%)	0(0.00)	1 (3.13)	1 (11.11)	0 (0.00)
Serum creatinine (μmol/L), mean (SD)	74.80 (18.85)	69.00 (21.86)	71.96 (17.56)	78.71 (29.71)
≤ 133, *n* (%)	30 (96.77)	32 (100.00)	7 (77.78)	6 (75.00)
> 133, *n* (%)	1 (3.22)	0(0.00)	0 (0.00)	1(12.50)
Aspartate aminotransferase (U/L), mean (SD)	24.00 (10.48)	26.94 (12.12)	26.22 (11.65)	24.87 (8.02)
≤ 40, *n* (%)	28 (90.32)	27 (84.38)	8 (88.89)	7 (87.50)
> 40, *n* (%)	3 (9.67)	5 (15.63)	1 (11.11)	1 (12.50)
Alanine aminotransferase (U/L), mean (SD)	33.123(22.86)	36.19 (23.86)	32.22 (20.96)	29.12 (9.50)
≤ 50, *n* (%)	25 (80.65)	25 (78.13)	7 (77.78)	8 (100.00)
> 50, *n* (%)	6 (19.35)	7 (21.88)	2 (22.22)	0 (0.00)
Lactate dehydrogenase (U/L), mean (SD)	210.37 (39.21)	240.31 (94.56)	257.00(124.60)	315.00 (117.47)
≤ 245, *n* (%)	25 (80.65)	24 (75.00)	6 (66.67)	3 (37.5)
> 245, *n* (%)	5 (16.13)	8 (25.00)	1 (11.11)	5 (62.5)
γ-glutamyl transpeptidase (U/L), mean (SD)	36.7(27.35)	51.78 (41.87)	79.44(65.39)	39.71(24.40)
6-42, *n* (%)	22(70.97)	19 (59.38)	3 (33.33)	5 (62.50)
<6, *n* (%)	0 (0.00)	1 (3.13)	0 (0.00)	0 (0.00)
>42, *n* (%)	9 (29.03)	12 (37.50)	6 (66.67)	2 (25.00)
Total bilirubin, μmol/L, mean (SD)	9.43 (5.83)	9.6 (6.29)	9.43 (3.46)	10.18 (6.50)
≤21, *n* (%)	30 (96.77)	29 (90.63)	9 (100.00)	7 (87.50)
>21, *n* (%)	1 (3.23)	3 (9.38)	0 (0.00)	1 (12.50)
Direct Bilirubin, μmol/L, mean (SD)	3.68 (1.82)	3.76 (2.22)	4.66 (2.45)	5.24 (3.07)
≤8, *n* (%)	30 (96.77)	30 (93.75)	8 (88.89)	7 (87.50)
>8, *n* (%)	1 (3.23)	2 (6.25)	1 (11.11)	1 (12.50)
Creatine kinase (U/L), mean (SD)	60.44 (41.41)	75.05 (100.97)	57.7 (82.58)	14.3 (9.61)
≤ 185, *n* (%)	17 (54.84)	19 (59.38)	5 (55.56)	5 (62.5)
> 185, *n* (%)	1 (3.23)	1 (3.13)	0 (0.00)	0 (0.00)

COVID-19 treatments between hospitalization and randomization				
Previously used drugs, n (%)	25 (80.65)	25 (78.13)	6 (66.67)	6 (75.00)
Arbidol, *n* (%)	22 (70.97)	18 (56.25)	5 (55.56)	4 (50.00)
Kaletra, *n* (%)	5 (16.13)	9 (28.13)	1 (11.11)	2 (25.00)
Ribavirin, *n* (%)	1 (3.23)	1 (3.13)	1 (11.11)	1 (12.50)
Lianhua Qingwen**, *n* (%)	14 (45.16)	13 (40.63)	5 (55.56)	3 (37.50)
Xuebijing**, *n* (%)	3 (9.68)	4 (12.50)	3 (33.33)	1 (12.50)
The percentage of patients who had taken at least one of drugs mentioned above, *n* (%)	25 (80.65)	25 (78.13)	6 (66.67)	6 (75.00)
The percentage of patients who had taken at least two of drugs mentioned above, *n* (%)	13 (41.94)	12 (37.50)	5 (55.56)	3 (37.50)
Type of antiviral drug used before randomization, *n* (min, max)	2 (1, 4)	2 (1, 4)	3 (1,4)	2 (1,3)

Note. Numbers in parenthesis correspond to interquartile range observed value for continuous variables and to percentages for indicator variables

*All severe patients were under oxygen therapy when oxygen saturation was measured.

** Traditional Chinese medicine

Table S2. Laboratory outcomes in the Moderate and Severe patients in RCT.

Outcomes	Moderate (N=63)				Severe (N=17)			
	Hydroxychloroquine (N=31)	Chloroquine (N=32)	Difference (95%CI)	*P* Value*	Hydroxychloroquine (N=9)	Chloroquine (N=8)	Difference (95%CI)	*P* Value*
Change from baseline in lymphocyte counts at day5	-0.07±0.26	-0.04±0.50	-0.08 (-0.29, 0.13)	0.44	-0.30±0.45	0.10±0.35	-0.38 (-0.73, -0.03)	**0.04**
Change from baseline in lymphocyte counts at day10	-0.18±0.31	-0.33±0.57	0.07 (-0.24, 0.39)	0.64	-0.18±0.32	-0.16±0.49	-0.00 (-0.37, 0.36)	0.99
Change from baseline in Ferritin at day5	79.24±145.78	-27.25±155.65	97.05 (4.83, 189.27)	**0.04**	-6.57±271.79	-15.03±380.68	-2.52 (-438.16,433.13)	0.99
Change from baseline in Ferritin at day10	104.96±91.55	-5.19±155.15	106.71 (-5.67,219.08)	0.06	95.58±293.58	35.82±551.73	13.36 (-687.11,713.83)	0.97
Change from baseline in C-Reactive Protein at day5	5.53±11.68	4.26±17.76	3.58 (-3.57, 10.73)	0.32	28.79±38.94	2.42±51.63	24.81 (-21.36, 70.99)	0.26
Change from baseline in C-Reactive Protein at day10	10.88±19.38	15.73±28.94	2.21 (-3.48, 7.89)	0.43	19.38±35.96	19.78±29.73	0.78 (-30.48, 32.04)	0.96

* The adjusted *p* value was derived from the general linear regression analysis results. The group was taken as the independent variable and the baseline value of the indicator was included as the covariable.

Table S3: Inflammatory cytokines Outcomes in Moderate and Severe patients in RCT.

Outcomes	Moderate (N=63)				Severe (N=17)			
	HCQ (N=31)	CQ (N=32)	Difference (95%CI)	*P* Value	HCQ (N=9)	CQ (N=8)	Difference (95%CI)	*P* Value
Change from baseline on IL-1 at day 5	-0.50 ±1.59	-5.08 ±18.18	1.79 (-16.34,19.91)	0.83*	NA	NA	NA	NA[#]
Change from baseline on IL-1 at day 10	-9.31 ±18.61	2.72 ±5.49	-11.08 (-26.83,4.67)	0.15*	NA	NA	NA	NA[#]
Change from baseline on IL-2 at day 5	-0.17[#]	-0.09 ±0.12	NA[#]	NA[#]	NA	NA	NA	NA[#]
Change from baseline on IL-2 at day 10	0.33[#]	-0.22 ±0.52	NA[#]	NA[#]	NA	NA	NA	NA[#]
Change from baseline on IL-6 at day 5	7.91 ±33.28	9.33 ±27.26	0.98 (-5.90,7.86)	0.78*	1.58 ±11.38	-292.90 ±790.99	-147.68 (-430.63,135.26)	0.28*
Change from baseline on IL-6 at day 10	4.72 ±14.12	9.54 ±31.24	4.24 (-3.71,12.18)	0.29*	-34.72 ±58.52	26.88 ±37.24	-60.36 (-128.59,7.87)	0.08*
Change from baseline on IL-8 at day 5	-5.48 ±17.62	1.34 ±13.00	-2.55 (-12.68,7.58)	0.61*	-4.40 ±13.17	-3.95 ±14.78	-1.01 (-23.28,21.25)	0.92*
Change from baseline on IL-8 at day 10	0.41 ±5.71	-65.93 ±192.69	12.34 (-103.83,128.52)	0.83*	-3.86 ±14.01	-6.74 ±18.95	2.19 (-23.37,27.75)	0.85*
Change from baseline on IL-10 at day 5	1.57 ±2.00	-2.53 ±6.20	4.41 (-1.74,10.56)	0.14*	23.00 ±32.53	9.50 [#]	NA[#]	NA[#]
Change from baseline on IL-10 at day 10	1.17 ±2.30	0.47 ±1.54	0.48 (-1.54,2.51)	0.60*	-107.10 ±184.38	12.00 [#]	NA[#]	NA[#]
Change from baseline on TNF-α at day 5	-0.22 ±4.05	1.72 ±6.23	-0.38 (-2.98,2.22)	0.77*	1.00 ±3.37	-1.04 ±7.09	4.94 (-2.73,12.61)	0.17*
Change from baseline on TNF-α at day 10	0.04 ±4.16	-0.49 ±5.65	2.37 (-0.63,5.37)	0.12*	-1.50 ±3.11	0.13 ±4.90	0.94 (-2.46,4.34)	0.51*

Abbreviation: HCQ: Hydroxychloroquine; CQ: chloroquine NA, not applicable because of missing data.

*The adjusted *p* value was derived from the general linear regression analysis results. The group was taken as the independent variable and the baseline value of the indicator was included as the covariable.

[#] Sample size less than 3, relevant parameters not calculated.

Table S4. Secondary Outcomes in Moderate and Severe patients in RCT.

Outcomes	Moderate (N=63)				Severe (N=17)			
	Hydroxychloroquine (N=31)	Chloroquine (N=32)	Difference (95%CI)	*P* Value*	Hydroxychloroquine (N=9)	Chloroquine (N=8)	Difference (95%CI)	*P* Value*
Change from baseline in lymphocyte counts at day5	-0.07±0.26	-0.04±0.50	-0.08 (-0.29, 0.13)	0.44	-0.30±0.45	0.10±0.35	-0.38 (-0.73, -0.03)	**0.04**
Change from baseline in lymphocyte counts at day10	-0.18±0.31	-0.33±0.57	0.07 (-0.24, 0.39)	0.64	-0.18±0.32	-0.16±0.49	-0.00 (-0.37, 0.36)	0.99
Change from baseline in Ferritin at day5	79.24±145.78	-27.25±155.65	97.05 (4.83, 189.27)	**0.04**	-6.57±271.79	-15.03±380.68	-2.52 (-438.16,433.13)	0.99
Change from baseline in Ferritin at day10	104.96±91.55	-5.19±155.15	106.71 (-5.67,219.08)	0.06	95.58±293.58	35.82±551.73	13.36 (-687.11,713.83)	0.97
Change from baseline in C-Reactive Protein at day5	5.53±11.68	4.26±17.76	3.58 (-3.57, 10.73)	0.32	28.79±38.94	2.42±51.63	24.81 (-21.36, 70.99)	0.26
Change from baseline in C-Reactive Protein at day10	10.88±19.38	15.73±28.94	2.21 (-3.48, 7.89)	0.43	19.38±35.96	19.78±29.73	0.78 (-30.48, 32.04)	0.96

* The adjusted p value was derived from the general linear regression analysis results. The group was taken as the independent variable and the baseline value of the indicator was included as the covariable.

Table S5. Baseline Characteristics of the matched RCT and RWS patients.

Outcomes	RCT (N=14)	RWS (N=14)
Age, yr, mean (SD)	56.57 (16.43)	54.29 (13.18)
Male, n (%)	10 (71.43)	9 (64.29)
Days from symptom onset to hospitalization, mean (SD)	10 (5.41)	20.21 (12.65)
Days from symptom onset randomization, mean (SD)	20.86 (6.63)	NA
Co-morbidities, n (%)	7 (50.00)	5 (35.71)
Hypertension, n (%)	6 (42.86)	2 (14.29)
Coronary artery disease, n (%)	2 (14.29)	1 (7.14)
Diabetes, n (%)	2 (14.29)	3(21.43)
Body temperature, ℃, n (SD)	36.65 (0.93)	36.73 (0.65)
Fever, n (%)	12 (85.71)	10 (71.43)
Cough, n (%)	9 (64.29)	12 (85.71)
Respiratory rate > 24 /min, n (%)	1 (7.14)	4 (28.57)
Respiratory rate > 30 /min, n (%)	0(0.00)	1(7.14)
Systolic blood pressure < 90 mmHg, n (%)	0 (0.00)	0 (0.00)
Oxygen saturation ≤ 93%, n (%)	1(7.14)	1(7.14)
White blood cell count (×10^9/L)		
4-10, n (%)	11 (78.57)	10 (71.43)
< 4, n (%)	1 (7.14)	2 (14.29)
> 10, n (%)	2 (14.29)	1 (7.14)
Lymphocyte count (×10^9/L)		
≥ 1.0, n (%)	12 (85.71)	8 (57.14)
< 1.0, n (%)	2 (14.29)	5 (35.71)
Lymphocyte percentage (%)		
20-50, n (%)	9 (64.29)	9 (64.29)
< 20, n (%)	5 (35.71)	4 (28.57)
> 50, n (%)	0 (0.00)	0 (0.00)
Platelet count (×10^9/L)		
≥ 100, n (%)	13 (92.86)	13 (92.86)
< 100, n (%)	1 (7.14)	0 (0.00)
Serum creatinine (μmol/L)		
≤ 133, n (%)	13 (92.86)	14 (100.00)
> 133, n (%)	0 (0.00)	0 (0.00)
Aspartate aminotransferase (U/L)		
≤ 40, n (%)	14 (100.00)	12 (85.71)
> 40, n (%)	0 (0.00)	1 (7.14)
Alanine aminotransferase (U/L)		
≤ 50, n (%)	14 (100.00)	11 (78.57)
> 50, n (%)	0(0.00)	2 (14.29)
Lactate dehydrogenase (U/L)		
≤ 245, n (%)	11(78.57)	7 (50.00)
> 245, n (%)	3 (21.43)	6 (42.86)
γ-glutamyl transpeptidase (U/L)		
6-42, n (%)	9 (64.29)	10 (71.43)
< 6, n (%)	0 (0.00)	0 (0.00)
> 42, n (%)	5 (35.71)	3 (21.43)
Total bilirubin, μmol/L		
≤ 21, n (%)	13 (92.86)	13 (92.86)
> 21, n (%)	1 (7.14)	0 (0.00)
Direct Bilirubin, μmol/L		
≤ 8, n (%)	13 (92.86)	12 (85.71)
> 8, n (%)	1 (7.14)	1 (7.14)
Creatine kinase (U/L)		
≤ 185, n (%)	7 (50.00)	11 (78.57)
> 185, n (%)	1 (7.14)	0 (0.00)

Abbreviation: RCT：Randomized control trial; RWS: Real world study.

Table S6. Laboratory Outcomes in the RCT and RWS patients.

Outcomes	RCT (N=14)	RWS (N=14)	Difference (95%CI)	*P* Value*
Change from baseline on lymphocyte counts at day 5	-0.14 ±0.45	-0.15 ±0.36	0.00 (-0.38, 0.39)	0.99
Change from baseline on lymphocyte counts at day 10	-0.32 ±0.29	-0.39 ±0.37	-0.01 (-0.29, 0.27)	0.96
Change from baseline on Ferritin at day 5	-93.04 ±182.81	-46.75 ±145.95	-96.83 (-317.94,124.28)	0.35
Change from baseline on Ferritin at day 10	-14.24 ±197.17	106.67 ±65.23	-137.09 (-414.92,140.74)	0.28
Change from baseline on C-Reactive Protein at day 5	21.21 ±21.32	-0.12 ±6.84	9.27 (-6.52, 25.07)	0.23
Change from baseline on C-Reactive Protein at day 10	30.50 ±25.77	5.09 ±8.99	5.90 (0.20, 11.60)	**0.04**

Abbreviation: RCT：Randomized control trial; RWS: Real world study

*The adjusted p value was derived from the general linear regression analysis results. The group was taken as the independent variable and the baseline value of the indicator was included as the covariable.

Table S7. Coagulation-related parameters of RCT and RWS patients.

	Baselines		Day10	
	RCT (N=14)	**RWS (N=14)**	**RCT (N=14)**	**RWS (N=14)**
PT, mean（SD）	13.29（1.06）	13.63（0.97）	13.35（1.25）	13.70（0.55）
>12.8, n (%)	10（76.92）	10（83.33）	8（72.72）	6（85.71）
8.8-12.8, n (%)	3（23.08）	2（16.67）	3（27.27）	1（14.29）
<8.8, n (%)	0（0）	0（0）	0（0）	0（0）
TT, mean（SD）	17.36（2.15）	16（2.64）	16.68（0.62）	14.50（NA）
>18, n (%)	2（15.38）	1（20）	0（0）	0（0）
12-18, n (%)	11（84.62）	4（80）	11（100）	1（100）
<12, n (%)	0（0）	0（0）	0（0）	0（0）
FIB, mean（SD）	4.40（1.23）	3.62（0.97）	3.69（0.94）	4.33（NA）
>4.4, n (%)	6（46.15）	2（40）	3（27.27）	0（0）
2.0-4.4, n（%）	7（53.85）	3（60）	8（72.72）	1（100）
<2.0, n（%）	0（0）	0（0）	0（0）	0（0）
INR, mean（SD）	1.05（0.07）	1.03（0.07）	1.03（0.07）	0.94（NA）
>1.2, n (%)	0（0）	0（0）	0（0）	0（0）
0.8-1.2, n (%)	13（100）	6（100）	11（100）	1（100）
<0.8, n (%)	0（0）	0（0）	0（0）	0（0）
APTT, mean（SD）	37.43（7.48）	36.88（4.31）	34.93（9.35）	37.19（2.53）
>42, n (%)	2（15.38）	1（8.33）	4（36.36）	0（0）
28-42, n (%)	9（69.23）	11（91.67）	5（45.45）	7（100）
<28, n (%)	2（15.38）	0（0）	2（18.18）	0（0）
D-dimer, mean（SD）	3.57（9.51）	0.99（0.91）	1.36（1.71）	1.08（0.67）
>0.3, n (%)	9（64.29）	2（14.29）	9（64.29）	2（14.29）
≤0.3, n (%)	3（21.43）	0（0）	2（14.29）	0（0.00）

Abbreviation: PT: prothrombin time, TT: thrombin time, FIB: fibrinogen, INR: international normalized ratio, APTT: activated partial thromboplastin time.

Table S8. Summary of Adverse Events in the Moderate and Severe patients in RCT.

Adverse Events	Moderate		Severe	
	Hydroxychloroquine (N=31)	Chloroquine (N=33)	Hydroxychloroquine (N=11)	Chloroquine (N=10)
	number of patients (TEAEs percent/ DRAEs percent)			
QT prolongation*	1 (3.23/3.23)	5 (15.15/15.15)	2 (18.18/18.18)	1 (10.00/10.00)
I degree atrioventricular block	0	4 (12.10/3.03)	0	0
Ventricular premature beats**			1 (9.09/9.09)	1 (10.00/10.00)
Diarrhea	4 (12.90/12.90)	2 (6.06/6.06)	1 (9.09/9.09)	1 (10.00/10.00)
Stomachache	0	0	0	1 (10.00/10.00)
Vomiting	0	2 (6.06/6.06)	0	0
Anorexia	0	1 (3.03/3.03)	0	0
Nausea	0	1 (3.03/3.03)	0	0
Bitter taste	1 (3.23/3.23)	0	0	0
Hypoglycemia	0	1 (3.03/0)	0	0
Blurred vision	1 (3.23/0)	1 (3.03/0)	0	0
Anxiety	0	1 (3.03/0)	0	0
Rash	2 (6.45/6.45)	0	0	0

Abbreviations: TEAE: Treatment emergent adverse event. DRAE: Drug-related adverse event. AEs judged by the investigators according to the CTCAE5.0. All AEs were in Grade 1 and could be recovered spontaneously. There were no serious adverse events.

*There were no drug discontinuations due to prolonged QT intervals and no ventricular arrhythmias due to prolonged QT. Seven patients with extended QT intervals ranged from 500 to 530 ms, and another two patients were 562 ms and 566 ms, respectively.

** The AE was not accompanied by prolonged QT interval.