Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2019014

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Supplementary Appendix
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Supplemental Methods

Additional Details on Participants

We enrolled adults who were hospitalized with suspected or confirmed COVID-19. Suspected cases were defined based on the Brazilian Ministry of Health criteria: patients with fever and at least 1 respiratory sign or symptom (cough, shortness of breath, nasal congestion, sore throat, peripheral oxygen saturation <95%, cyanosis, dyspnea); those from an endemic region or traveling from an endemic region in the last 14 days; or those in contact in the last 14 days with someone with a suspected or confirmed COVID-19 diagnosis.

The initial list of inclusion and exclusion criteria is provided below.

Inclusion Criteria (Initial):

1. Patients who were 18 years of age or older and were hospitalized with suspected or confirmed COVID-19.
2. Fewer than 14 days since symptom onset.
3. Time between hospital admission and inclusion ≤ 48 hours

Exclusion Criteria (Initial):

1. Need for oxygen supplementation >4 L/min via nasal cannula or ≥40% via Venturi mask;
2. Need for oxygen supplementation via high-flow nasal cannula;
3. Need for non-invasive ventilation;
4. Need for invasive mechanical ventilation;
5. History of severe ventricular cardiac arrhythmia or electrocardiogram with corrected QT interval (QTc) ≥480 ms;
6. History of liver cirrhosis;
7. Chronic renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m2);
8. Known retinopathy or macular degeneration;
9. History of pancreatitis;
10. Less than 18 years of age;

11. Known allergy to chloroquine or hydroxychloroquine.

The inclusion and exclusion criteria were revised on May 13th, 2020. Below we provide the final list.

Inclusion Criteria (Final):

1. Patients who were 18 years of age or older and were hospitalized with suspected or confirmed COVID-19.
2. Fewer than 14 days since symptom onset.

Exclusion Criteria (Final):

1. Need for oxygen supplementation >4 L/min via nasal cannula or ≥40% via Venturi mask;
2. Need for oxygen supplementation via high-flow nasal cannula;
3. Need for non-invasive ventilation;
4. Need for invasive mechanical ventilation;
5. Previous use of chloroquine, hydroxychloroquine, azithromycin, or any other macrolide for more than 24 hours before enrollment;
6. History of severe ventricular cardiac arrhythmia or electrocardiogram with corrected QT interval (QTc) ≥480 ms;
7. History of liver cirrhosis;
8. Chronic renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m2);
9. Known retinopathy or macular degeneration;
10. History of pancreatitis;
11. Less than 18 years of age;
12. Known allergy to chloroquine or hydroxychloroquine;
13. Known allergy to azithromycin;
14. Pregnancy or breastfeeding.

In the May 13 amended version of the trial enrollment criteria, the inclusion criterion stating that the time from hospital admission to inclusion needed to be 48 hours or less was removed. We removed this inclusion criterion because we assumed that the most important potential modifier of treatment effect would be duration of disease, which is reflected in the second inclusion criterion. We assumed that duration of hospitalization, by itself, would not modify treatment effect.

Prior Use of Hydroxychloroquine or Azithromycin

The intention of the investigators was to enroll patients who had not had prior use of either hydroxychloroquine or azithromycin. However, this was not specified in the original version of the trial protocol as an exclusion criterion, and at the time of enrollment of the first patient (on March 29, 2020), the case report forms did not request information about prior use of these drugs.

During the course of the trial, it became evident that use of hydroxychloroquine, azithromycin, or both was widespread in Brazil, and some patients enrolled in the trial were already receiving these drugs at the time of randomization. Beginning on April 13, 2020, a revised version of the case report form was used in the trial. This revised form requested data on prior use of hydroxychloroquine or azithromycin, but it did not request information about the duration of prior use. Beginning on May 13, 2020, a specific exclusion criterion was adopted (and incorporated in the case report form) specifying that patients could not be enrolled in the trial if they had received chloroquine, hydroxychloroquine, azithromycin, or any other macrolide for more than 24 hours.

For patients who had been enrolled prior to these changes in the case report form, data concerning prior use and duration of prior use were collected retrospectively. As indicated in Table 1 in the main article, 9.3% of trial participants had prior use of hydroxychloroquine and 36.1% had prior use of azithromycin. As indicated in Table S7, 99.7% of patients had either no use of hydroxychloroquine prior to randomization or less than 48 hours of prior use; 96.7% of patients had either no use of azithromycin prior to randomization or less than 48 hours of prior use.

Additional Details on the Randomization Procedure

The trial statistician, not involved with patient enrolment or care, generated the randomization table in R software (R Core Team, 2019) and implemented in the RedCap. The study treatment was revealed to investigators only after patients were registered in the RedCap, ensuring proper concealment of the allocation sequence.

Additional Details on Interventions

The treatment and control groups received the current standard of care treatment for COVID-19, which included daily monitoring with clinical assessment by the attending physician, routine laboratory tests (blood count, urea, creatinine, liver enzymes and bilirubin, c-reactive protein) at the discretion of the attending physician, respiratory therapy and motor physiotherapy, surveillance of vital parameters according to the patient's location (inpatient unit or ICU) at least once per period (which may be more frequent in some situations and institutions), addition of ventilatory support measures, such as increased oxygen flow, use of non-invasive positive pressure ventilation or oxygen supplementation via high-flow nasal cannula, as recommended by the attending physician, prophylaxis of stress ulcers (if indicated) and venous thromboembolism according to the protocol of each institution and addition of other therapies such as antibiotics, corticosteroids, other immunomodulators (e.g., tocilizumab), other antivirals (e.g., oseltamivir for suspected influenza coinfection), as recommended by the attending physician. Remdesivir was not available in Brazil during the trial and was not used.

Additional Details on Outcomes

The secondary outcome of clinical status on day 7 was assessed using a 6-level ordinal scale, defined as follows: 1, not hospitalized; 2, hospitalized and not using supplemental oxygen; 3, hospitalized and using supplemental oxygen; 4, hospitalized and using oxygen supplementation via high-flow nasal cannula or non-invasive ventilation; 5, hospitalized and on mechanical ventilation; 6, death. Thromboembolic

complications included stroke, myocardial infarction, and deep vein thrombosis. Acute kidney injury was defined as an increase in creatinine above 1.5 times the baseline value.

Secondary safety outcomes included nausea and vomiting; prolongation of the QT interval (defined as QTc ≥480 ms); liver toxicity (defined as an increase in alanine aminotransferase or aspartate aminotransferase greater than three-fold the upper limit of normal for the local laboratory or any increase in serum bilirubin); ventricular arrhythmia; severe hypoglycemia (blood glucose ≤40 mg/dL); acute cardiomyopathy (defined as an ejection fraction below 40% in a patient with no previous history of ventricular dysfunction confirmed by echocardiography); loss of hearing or visual acuity; and hematological abnormalities (anemia, leukopenia, and thrombocytopenia).

All secondary outcomes were assessed by site investigators, who were not blinded to treatment assignment. We did not adjudicate primary or secondary outcomes. We conducted source data verification of the 15-day medical assessment form and the hospital discharge summary form for all patients at sites enrolling 5 or fewer patients, and randomly selected patients (20% of those enrolled at the site or up to 10) at sites enrolling more than 5 patients. If any discrepancy was noted between source data verification and CRF data, then we would assess 100% of patients at that site.

Events that are classified as primary or secondary study outcomes are not reported as adverse events.

Additional Details on Changes in Protocol During Study

Classification of patients with RT-PCR or serologic tests negative for SARS-CoV-2

An independent committee classified all cases with RT-PCR tests negative for COVID into the following categories:

- Probable COVID-19: if only one RT-PCR test for SARS-CoV-2 was performed and it is negative, but both the clinical information and chest computerized tomography (CT) are typical of COVID-

19. Cases with absent or negative RT-PCR tests, but with positive serologic tests were also classified as probable COVID-19.

- Possible COVID-19: if two RT-PCR tests for SARS-CoV-2 were performed and are negative, but both the clinical information and chest CT are typical of COVID-19; or, if only one RT-PCR for SARSCoV-2 was performed and is negative, and either the clinical information or the chest CT is typical, but the other is atypical for COVID-19.
- Probably not COVID-19: if two or more RT-PCR tests for SARS-CoV-2 are negative, and both the clinical information and chest CT are not typical; or when two or more RT-PCR tests for SARS-CoV-2 are negative and an alternative diagnosis explains clinical and CT findings.

Day 15 follow-up

Initially, we had planned to follow patients only up to hospital discharge. We assumed that patients discharged home before 15 days were alive at home on day 15, although we were not able to discriminate whether patients were at home with or without limitations on activities. Thus, for the primary outcome, we used the 6-level ordinal scale, whose first level is "patient not hospitalized".

On April 10, 2020, and before the first patient was about to complete 15-day follow up, we established the capability to conduct 15-day outpatient follow-up via telephone calls. Researchers from a central office (Hospital Moinhos de Vento), blinded to treatment assigned, performed the calls following a standard script. The primary outcome was changed from the 6-level ordinal scale to the 7-level ordinal scale in a protocol revision on May 13, 2020. A total of 581 patients had been enrolled and 288 patients had already reached or passed day 15 when this change was made.

For patients who were still hospitalized by day 15, the 15-day status was assessed exactly on that day. For patients who had been discharged before 15 days, we aimed to assess the 15-day status by phone calls between day 15 and 17. When initial calls were unsuccessful (10 attempts), we asked site investigators for additional phone numbers, e-mail addresses, and addresses and attempted again to contact the patient or a

relative (10 attempts). If these attempts were also unsuccessful, we asked the site investigators and social assistants to try contacting the patient or relatives. As a last resource, for patients living in São Paulo, we sent a trained person to visit the patient's house and obtain follow-up data. In all cases, researchers contacting the patient collected information regarding their status on day 15 after randomization.

Change in primary outcome and sample size calculation

Originally, we planned to include 630 patients, using the intention-to-treat (ITT) analysis population, with a 6-level ordinal scale for the primary outcome defined as follows: 1, not hospitalized; 2, hospitalized and not using supplemental oxygen; 3, hospitalized and using supplemental oxygen; 4, hospitalized and using oxygen supplementation via high-flow nasal cannula or non-invasive ventilation; 5, hospitalized and on mechanical ventilation; 6, death. We determined that, using the 6-level ordinal outcome with probabilities of 35%, 15%, 20%, 10%,10%, and 10%, a sample of 210 cases per arm (630 cases) would have 80% power to detect an average odds ratio of 0.57 on pairwise comparison between arms with a 5% significance level, with Bonferroni adjustment for multiple comparisons.

Before the first data monitoring committee analysis, we proposed to change the primary end point from the 6-level ordinal scale to days alive and free of oxygen support at 15 days (DAFOR15). We approached regulatory agencies in Brazil with the following proposal, after agreement in the steering committee and in agreement with the data monitoring committee:

1. Change the primary analysis from ITT to mITT
2. Change the primary end point from the 6-level ordinal scale to days alive and free of oxygen support (DAFOR15). Considering the overall outcome data for the first 120 patients enrolled in the trial, we calculated that with 510 patients we would have 80% power to detect a difference as small as 1.5 days between groups. Reductions in DAFOR15 of less than 1 day would probably be less useful in increasing bed turnover. Considering that ~20% of patients would have negative RT-PCR for COVID-19, the initial planned sample size of 630 patients would still be sufficient.

3. Use of 7 levels (instead of the 6-level scale) for a key secondary end point (with Bonferroni correction, as required by the regulatory agency in Brazil) due to the ability to obtain this information at 15 days.

The National Health Regulatory Agency in Brazil agreed with proposals 1 and 3, but not with the second proposal. Instead, the Agency preferred the alternative approach of changing the primary end point from the 6- to the 7-level ordinal scale at 15 days. We, therefore, proceeded with changing the primary outcome to the 7-level ordinal scale at 15 days.

Additional Details on Statistical Analyses

Odds proportionality was assessed using the method of Lipsitz.[1] We assessed whether the assumption of proportional hazards held for the Cox proportional-hazards assessment of in-hospital mortality by examining plots of Schoenfeld's residuals.[2]

In post hoc analyses, we also assessed treatment effects on the risk of thromboembolic events within 15 days and acute kidney injury within 15 days accounting for the competing risk of death using ordinal logistic regression models. These models were not adjusted for baseline covariates and did not model sites as random effects.

Missing data for the secondary outcomes of 6-level ordinal outcome scale at 7 days and days free from respiratory support within 15 days were imputed using multivariate imputation by chained equations using baseline age, supplemental oxygen and the 7-level ordinal outcome scale at 15 days.[2]

Three prespecified subgroup analyses were performed for the primary outcome, based on time from onset of symptoms to randomization (≤7 days versus > 7 days), age (<60 years versus ≥60 years), and use of supplemental oxygen at randomization (no versus yes). In addition, three post hoc subgroup analyses were performed to determine whether the prior use of hydroxychloroquine or azithromycin by some trial

participants would influence the results. These included analyses based on prior use of hydroxychloroquine (no versus yes), prior use of azithromycin (no versus yes), and randomization date (before April 13 versus on or after April 13). The last of these analyses was performed to take into account the fact that data on prior use of hydroxychloroquine or azithromycin was collected prospectively on or after April 13, but retrospectively before April 13, with the potential for the information to be less accurate. For all of the subgroup analyses, it was not possible to adjust proportional odds ratio models with interaction for the subgroup variables for the 7-level ordinal scale because of the low number of cases in some cells. Therefore, as prespecified in our statistical analysis plan, we grouped the 7-level variables in two categories: patients who were at home versus patients who died or were at hospital at day 15.

Table S1. List of sites and number of randomized patients per site

Site	Number of patients randomized
Hospital São Camilo	107
HCor	44
Hospital Moriah	44
Secretaria Municipal de Saúde - SMS/SP (Gripário Pacaembu)	37
Hospital SEPACO	34
Hospital Santa Paula	31
BP - A Beneficência Portuguesa de São Paulo	28
Hospital Naval Marcílio dias	25
Hospital Israelita Albert Einstein	20
Hospital Giselda Trigueiro	19
Hospital Tacchini/ Instituto Tacchini de Pesquisa em Saúde	18
Hospital Bruno Born	18
Hospital Baía Sul - Baía Sul Medical Center	14
Hospital Regional Hans Dieter Schmidt	13
AngioCor Blumenau	13
Hospital e Clínica São Roque	12
Hospital de Clínicas de Porto Alegre	12
Centro Hospitalar Unimed	11
Hospital BP Mirante - Real e Benemérita Associação Portuguesa de Beneficência	10
Hospital Sírio-Libanês	10
Hospital Moinhos de Vento	10
Hospital Alemão Oswaldo Cruz	10
Hospital Evangélico de Vila Velha -	10
Casa de Saúde Santa Marcelina	9
Instituto de Pesquisa Clínica de Campinas	8
Hospital de Urgência e Emergência de Rio Branco - HUERB	8
Hospital Universitário de Londrina	7
Hospital Estadual Jayme dos Santos Neves	7
Santa Casa de Misericórdia de Passos	6
Hospital de Brasília	6
Hospital São José – Criciúma	5
Hospital da Cidade	5
Faculdade de Medicina de Botucatu, UNESP	5
Hospital Municipal São Jose	5
Associação Evangélica Beneficente de Londrina	4
Hospital Dona Helena	4
Casa de Caridade de Carangola	4

Hospital Maternidade São Vicente de Paulo	4
Hospital de Amor - Unidade Barretos (Fundação PIO XII)	3
Hospital Unimed Cariri	3
Santa Casa de Misericórdia de Votuporanga	3
Santa Casa de Misericórdia de São João Del Rei	2
Hospital Cardio Pulmonar	2
Hospital Maternidade Promater	2
CEPON - Secretaria de Estado da Saúde de Santa Catarina	2
Hospital Florianopolis - Secretaria de Estado da Saúde de Santa Catarina	2
Hospital São Paulo - UNIFESP	1
Hospital Nereu Ramos	1
Hospital Geral de Caxias do Sul	1
Hospital Vila da Serra	1
Hospital Universitário Regional de Maringá	1
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Table S2. Additional characteristics of the intention-to-treat population at baseline*

Baseline information	Hydroxychloroquine plus Azithromycin (n=217)	Hydroxychloroquine (n=221)	Control (n=227)	Overall (n=665)
Diagnostic classification				
Definitive	172 (79.3)	159 (71.9)	173 (76.2)	504 (75.8)
Probable	8 (3.7)	13 (5.9)	13 (5.7)	34 (5.1)
Possible	21 (9.7)	27 (12.2)	22 (9.7)	70 (10.5)
Unlikely	16 (7.4)	22 (10.0)	19 (8.4)	57 (8.6)
Randomization site				
Emergency/Ward	187 (86.2)	189 (85.5)	197 (86.8)	573 (86.2)
ICU	30 (13.8)	32 (14.5)	30 (13.2)	92 (13.8)
Vital signs				
Systolic blood pressure, mm Hg	125±18	127±20	123±17	125±18
Diastolic blood pressure, mm Hg	76±11	78±11	76±12	77±11
Heart rate, beats/min	87±15	87±15	88±14	87±15
Respiratory rate, breaths/min	20±4	20±4	20±5	20±4
Peripheral saturation O_2, %	96±3	95±3	96±3	96±3
Laboratory tests				
Creatinine, mg/dL	0.9±0.3	0.9±0.3	0.9±0.6	0.9±0.4
D-dimer, ng/mL	703±770	709±739	785±817	733±775
Hemoglobin, g/dL	13.7±1.6	13.8±1.5	13.8±1.6	13.7±1.6
Leukocyte, 10^3/mL	6.8±3.0	6.8±3.1	7.0±3.8	6.9±3.3
Platelets, $10^3/mm^3$	206±68	206±70	207±81	206±73
Lymphocyte, 10^3/mL	1.4±0.6	1.5±1.1	1.6±1.4	1.5±1.1
Vasopressor use, no. (%)				
None	217 (100)	220 (99.5)	227 (100)	664 (99.8)
Norepinephrine	0	1 (0.5)	0	1 (0.2)
In-hospital medications, no. (%)				
Ceftriaxone	116 (53.5)	118 (53.4)	125 (55.1)	359 (54.0)
Ceftaroline	1 (0.5)	2 (0.9)	5 (2.2)	8 (1.2)

Piperacillin/Tazobactam	8 (3.7)	2 (0.9)	2 (0.9)	12 (1.8)
Quinolone	12 (5.5)	18 (8.1)	26 (11.5)	56 (8.4)
Oseltamivir	51 (23.5)	64 (29.0)	74 (32.6)	189 (28.4)
Lopinavir/Ritonavir	0	0	0	0
Corticosteroids	6 (2.8)	6 (2.7)	11 (4.8)	23 (3.5)
None	43 (19.8)	35 (15.8)	30 (13.2)	108 (16.2)

* Plus-minus values are mean and standard deviation. The upper limit of normal for D-dimer is 500 ng/mL. Values shown are based on available data. The number of patients with laboratory values available for each exam was: creatinine, 601 patients; D-dimer, 396 patients; hemoglobin, 623 patients; leukocyte, 618 patients; platelets, 615 patients; lymphocyte, 587 patients. ICU denotes intensive care unit.

Table S3. Characteristics of patients with RT-PCR confirmed COVID-19 (modified intention-to-treat population) at baseline*

Baseline information	Hydroxychloroquine plus Azithromycin (n=172)	Hydroxychloroquine (n=159)	Control (n=173)	Overall (n=504)
Age, mean ± SD	49.5 ± 13.4	50.1 ± 13.5	50.5 ± 14.7	50 ± 13.9
Male sex	105 (61.0)	105 (66.0)	93 (53.8)	303 (60.1)
Comorbidities				
Hypertension	66 (38.4)	64 (40.3)	71 (41.0)	201 (39.9)
Diabetes	37 (21.5)	33 (20.8)	36 (20.8)	106 (21.0)
Current or former smoker	9 (5.2)	4 (2.5)	7 (4.0)	20 (4.0)
Obesity	23 (13.4)	32 (20.1)	32 (18.5)	87 (17.3)
Cancer	4 (2.3)	1 (0.6)	5 (2.9)	10 (2.0)
Heart failure	2 (1.2)	1 (0.6)	3 (1.7)	6 (1.2)
COPD	1 (0.6)	0	1 (0.6)	2 (0.4)
AIDS	1 (0.6)	0	1 (0.6)	2 (0.4)
Chronic renal disease	2 (1.2)	1 (0.6)	2 (1.2)	5 (1.0)
Asthma	11 (6.4)	3 (1.9)	10 (5.8)	24 (4.8)
Previous medications				
Corticosteroids	3 (1.7)	0	3 (1.7)	6 (1.2)
ACE inhibitors	13 (7.6)	12 (7.5)	9 (5.2)	34 (6.7)
Angiotensin II receptor antagonists	34 (19.8)	26 (16.4)	37 (21.4)	97 (19.2)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	6 (3.5)	6 (3.8)	7 (4.0)	19 (3.8)
Clinical data, mean ± SD				
SBP, mm Hg	125 ± 19	126 ± 19 (n=157)	123 ± 16	125 ± 18 (n=502)
DBP, mm Hg	76 ± 11	77 ± 11 (n=157)	76 ± 12	76 ± 11 (n=502)
Heart rate, beats/min	86 ± 15	87 ± 14	87 ± 14	87 ± 14
Respiratory rate, breaths/min	20 ± 4	20 ± 3 (n=158)	20 ± 5 (n=170)	20 ± 4 (n=500)
Peripheral saturation O_2,	96 ± 3	95 ± 3	95 ± 3	96 ± 3
Score on 7-level ordinal scale				
3. Hospitalized and not using supplemental oxygen	90 (52.3)	88 (55.3)	99 (57.2)	277 (55.0)
4. Hospitalized and using supplemental oxygen	82 (47.7)	71 (44.7)	74 (42.8)	227 (45.0)
Vasopressors use				
None	170/170 (100)	157/158 (99.4)	173/173 (100)	500/501 (99.8)
Norepinephrine	0	1/158 (0.6)	0	1/501 (0.2)
Laboratorial, mean ± SD				
Creatinine, mg/dL	0.9 ± 0.3 (n=150)	0.9 ± 0.3 (n=150)	1 ± 0.6 (n=157)	0.9 ± 0.4 (n=457)

D-dimer, ng/mL	684 ± 698 (n=98)	588.1 ± 411.7 (n=108)	731.6 ± 760.3 (n=107)	667.2 ± 640 (n=313)
Hemoglobin, g/dL	13.8 ± 1.6 (n=157)	14 ± 1.4 (n=151)	13.9 ± 1.5 (n=165)	13.9 ± 1.5 (n=473)
Leukocyte, 10^3/mL	6.2 ± 2.4 (n=156)	6.2 ± 2.5 (n=152)	6.3 ± 2.6 (n=164)	6.3 ± 2.5 (n=472)
Platelets, 10^3/mm³	199.9 ± 66.4 (n=156)	204 ± 74.1 (n=151)	199.5 ± 67.6 (n=163)	201.1 ± 69.2 (n=470)
Lymphocyte, 10^3/mL	1.3 ± 0.6 (n=146)	1.4 ± 0.6 (n=147)	1.5 ± 1.4 (n=154)	1.4 ± 1 (n=447)
Previous use of study medication				
Hydroxychloroquine	13 (7.6)	13 (8.2)	12 (6.9)	38 (7.5)
Azithromycin	57 (33.1)	55 (34.6)	68/172 (39.5)	180/503 (35.8)
In hospital medications				
Ceftriaxone	93 (54.1)	88 (55.3)	96 (55.5)	277 (55)
Ceftaroline	1 (0.6)	1 (0.6)	4 (2.3)	6 (1.2)
Piperacillin/Tazobactam	5 (2.9)	1 (0.6)	2 (1.2)	8 (1.6)
Quinolone	12 (7)	14 (8.8)	22 (12.7)	48 (9.5)
Oseltamivir	37 (21.5)	38 (23.9)	51 (29.5)	126 (25)
Lopinavir/Ritonavir	0	0	0	0
Corticosteroids	5 (2.9)	5 (3.1)	8 (4.6)	18 (3.6)
None	36 (20.9)	30 (18.9)	23 (13.3)	89 (17.7)
Days from admission to randomization, median [IQR]	1 [0 - 1]	1 [0 - 1]	1 [0 - 1]	1 [0 - 1]
Days from symptoms onset to randomization, median [IQR]	8 [5 - 10]	7 [5 - 8]	7 [5 - 9]	7 [5 - 9]

* Data are presented as no. (%) unless indicated otherwise. The upper limit of normal for D-dimer is 500 ng/mL. Information on comorbidities were obtained from the medical records. ACE denotes angiotensin converting enzyme; AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ICU, intensive care unit; IQR, interquartile range; RT-PCR, polymerase chain reaction; SBP, systolic blood pressure; SD, standard deviation.

Table S4. Comparison between patients with positive RT-PCR for COVID-19 and those with negative or unavailable RT-PCR testing for COVID-19*

Baseline information	Negative or Unavailable RT-PCR for COVID-19 (n=161)	Positive RT-PCR for COVID-19 (n=504)	Overall (n=665)
Allocated intervention			
Hydroxychloroquine plus Azithromycin	45 (28)	172 (34.1)	217 (32.6)
Hydroxychloroquine	62 (38.5)	159 (31.5)	221 (33.2)
Control	54 (33.5)	173 (34.3)	227 (34.1)
Diagnostic classification			
Definitive	16 (9.9)	504 (100)	520 (78.2)
Probable	24 (14.9)	0	24 (3.6)
Possible	68 (42.2)	0	68 (10.2)
Unlikely	53 (32.9)	0	53 (8)
Age, mean ± SD	51.1 ± 16.6	50.0 ± 13.9	50.3 ± 14.6
Male sex, n ()	85 (52.8)	303 (60.1)	388 (58.3)
Comorbidities			
Hypertension	57 (35.4)	201 (39.9)	258 (38.8)
Diabetes	21 (13)	106 (21)	127 (19.1)
Current or former smoker	24 (14.9)	20 (4)	44 (6.6)
Obesity	16 (9.9)	87 (17.3)	103 (15.5)
Cancer	9 (5.6)	10 (2)	19 (2.9)
Heart failure	4 (2.5)	6 (1.2)	10 (1.5)
COPD	10 (6.2)	2 (0.4)	12 (1.8)
AIDS	2 (1.2)	2 (0.4)	4 (0.6)
Chronic renal disease	0	5 (1)	5 (0.8)
Asthma	16 (9.9)	24 (4.8)	40 (6)
Previous medications			
Corticosteroids	2 (1.2)	6 (1.2)	8 (1.2)
ACE inhibitors	14 (8.7)	34 (6.7)	48 (7.2)
Angiotensin II receptor antagonists	19 (11.8)	97 (19.2)	116 (17.4)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	10 (6.2)	19 (3.8)	29 (4.4)
Clinical data, mean ± SD			
SBP, mm Hg	127 ± 19	125 ± 18 (n=502)	125 ± 18 (n=663)
DBP, mm Hg	77 ± 12	76 ± 11 (n=502)	77 ± 11 (n=663)

Heart rate, beats/min	89 ± 17	87 ± 14 (n=504)	87 ± 15 (n=665)
Respiratory rate, breaths/min	21 ± 4 (n=159)	20 ± 4 (n=500)	20 ± 4 (n=659)
Peripheral saturation O_2,	95 ± 3	96 ± 3 (n=504)	96 ± 3 (n=665)
Score on 7-level ordinal scale, no. (%)			
3. Hospitalized and not using supplemental oxygen	110 (68.3)	277 (55)	387 (58.2)
4. Hospitalized and using supplemental oxygen	51 (31.7)	227 (45)	278 (41.8)
Vasopressors use			
None	160/160 (100)	500/501 (99.8)	660/661 (99.8)
Norepinephrine	0	1/501 (0.2)	1/661 (0.2)
Laboratorial			
Creatinine, mg/dL, mean ± SD	0.9 ± 0.3 (n=144)	0.9 ± 0.4 (n=457)	0.9 ± 0.4 (n=601)
D-dimer, ng/dL, median [IQR]	497 [357 - 1058.5] (n=83)	500 [302 - 742] (n=313)	500 [303.5 - 830.5] (n=396)
Hemoglobin, g/dL, mean ± SD	13.3 ± 1.7 (n=150)	13.9 ± 1.5 (n=473)	13.7 ± 1.6 (n=623)
Leukocyte, 10^3/mL, mean ± SD	8.8 ± 4.7 (n=146)	6.3 ± 2.5 (n=472)	6.9 ± 3.3 (n=618)
Platelets, $10^3/mm^3$, mean ± SD	224 ± 83.1 (n=145)	201.1 ± 69.2 (n=470)	206.5 ± 73.3 (n=615)
Lymphocyte, 10^3/mL, median [IQR]	1.5 [1.0 – 2.0] (n=140)	1.3 [1.0 – 1.7] (n=447)	1.3 [1.0 – 1.8] (n=587)
Previous use of study medication			
Hydroxychloroquine	24 (14.9)	38 (7.5)	62 (9.3)
Azithromycin	60 (37.3)	180/503 (35.8)	240/664 (36.1)
In hospital medications			
Ceftriaxone	82 (50.9)	277 (55)	359 (54)
Ceftaroline	2 (1.2)	6 (1.2)	8 (1.2)
Piperacillin/Tazobactam	4 (2.5)	8 (1.6)	12 (1.8)
Quinolone	8 (5)	48 (9.5)	56 (8.4)
Oseltamivir	63 (39.1)	126 (25)	189 (28.4)
Lopinavir/Ritonavir	0	0	0
Corticosteroids	5 (3.1)	18 (3.6)	23 (3.5)
None	19 (11.8)	89 (17.7)	108 (16.2)
Days from admission to randomization, median [IQR]	1 [0 - 1]	1 [0 - 1]	1 [0 - 1]
Days from symptoms onset to randomization, median [IQR]	5 [3 - 8]	7 [5 - 9] (n=503)	7 [4 - 9] (n=664)

* Data are presented as no. (%) and p-values are Fisher exact tests unless indicated otherwise. If data are presented as mean and standard deviation, p-values refers to t-test, and if data are presented as median [IQR], p-values refers to Mann-Whitney test. ACE denotes angiotensin converting enzyme; AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ICU, intensive care unit; IQR, interquartile range; RT-PCR, reverse-transcription-polymerase-chain-reaction; SBP, systolic blood pressure; SD, standard deviation.

Table S5. In-hospital trial drug use in the modified intention to treat population

Day	Hydroxychloroquine plus Azithromycin (n=172)	Hydroxychloroquine (n=159)	Control (n=173)
Daily use of hydroxychloroquine			
1	162/172 (94.2)	150/159 (94.3)	10/173 (5.8)
2	161/171 (94.2)	151/158 (95.6)	13/169 (7.7)
3	156/164 (95.1)	145/153 (94.8)	14/158 (8.9)
4	143/155 (92.3)	139/150 (92.7)	13/150 (8.7)
5	127/147 (86.4)	126/140 (90.0)	9/133 (6.8)
6	114/138 (82.6)	111/131 (84.7)	8/126 (6.3)
7	86/126 (68.3)	90/126 (71.4)	7/120 (5.8)
Rate of hydroxychloroquine within 7 days per 100 patients-day	949/1073 (88.4)	912/1017 (89.7)	74/1029 (7.2)
Use of at least one dose of hydroxychloroquine within 7 days	165/172 (95.9)	154/159 (96.9)	20/173 (11.6)
Number of days using hydroxychloroquine, median (IQR)	6 (4 – 7)	7 (5 – 7)	0 (0 – 0)
Daily use of azithromycin			
1	170/172 (98.8)	18/159 (11.3)	29/173 (16.8)
2	167/171 (97.7)	13/158 (8.2)	24/169 (14.2)
3	158/164 (96.3)	14/153 (9.2)	22/158 (13.9)
4	145/155 (93.5)	12/150 (8.0)	17/150 (11.3)
5	135/147 (91.8)	9/140 (6.4)	13/133 (9.8)
6	119/138 (86.2)	7/131 (5.3)	10/126 (7.9)
7	88/126 (69.8)	5/126 (4.0)	8/120 (6.7)
Rate of azithromycin within 7 days per 100 patients-day	982/1073 (91.5)	78/1017 (7.7)	123/1029 (12.0)
Use of at least one dose of azithromycin within 7 days	170/172 (98.8)	22/159 (13.8)	35/173 (20.2)
Number of days using azithromycin, median (IQR)	6 (5 – 7)	0 (0 – 0)	0 (0 – 0)
Patients using at least one dose of hydroxychloroquine and azithromycin within 7 days	165/172 (95.9)	17/159 (10.7)	14/173 (8.1)
Number of days using hydroxychloroquine and azithromycin, median (IQR)	6 (4 – 7)	0 (0 – 0)	0 (0 – 0)

***** Data are presented as no./total no. (%) unless indicated otherwise

Table S6. Use of other medications during hospital stay in the modified intention-to-treat population from randomization up to day 15*

Medication	Hydroxychloroquine + azithromycin n=172	Hydroxychloroquine n=159	Control n=173
Ceftriaxone	99 (57.6)	86 (54.1)	99 (57.2)
Ceftaroline	11 (6.4)	11 (6.9)	17 (9.8)
Piperaciline/Tazobactan	12 (7.0)	8 (5.0)	15 (8.7)
Oxacillin	0	0	1 (0.6)
Vancomycin	9 (5.2)	1 (0.6)	4 (2.3)
Carbapenem	9 (5.2)	6 (3.8)	3 (1.7)
Quinolone	17 (9.9)	22 (13.8)	28 (16.2)
Oseltamivir	40 (23.3)	38 (23.9)	51 (29.5)
Lopinavir/Ritonavir	0	0	0
Aciclovir	1 (0.6)	1 (0.6)	0
Corticosteroids	34 (19.8)	31 (19.5)	35 (20.2)
Other antibiotics	40 (23.3)	47 (29.6)	43 (24.9)
No other antiviral, antibiotics or corticosteroids†	33 (19.2)	21 (13.2)	18 (10.4)

* Data are presented as no. (%).
† Except hydroxychloroquine or azithromycin

Table S7. Duration of prior use of hydroxychloroquine or azithromycin*

Hydroxychloroquine (N = 665)			**Azithromycin (N = 664)**		
No. of days	No. of pts.	%	No. of days	No. of pts.	%
0	603	90.7	0	424	63.9
1	57	8.6	1	181	27.3
2	5	0.7	2	42	6.3
missing	0	0.0	3	7	1.1
			4	2	0.3
			5 or more	5	0.8
			missing	3	0.5

***** Use of hydroxychloroquine or azithromycin was determined for 67 patients retrospectively and for 598 patients prospectively; 1 patient had missing data for prior azithromycin use. Duration of use of hydroxychloroquine or azithromycin was determined for 597 patients retrospectively and for 68 patients prospectively; 3 patients had missing data for duration of prior azithromycin use.

Table S8. Primary outcome analysis model*

Coefficients	Estimate	Std. Error	z value	p value†
Group (Hydroxychloroquine)	0.18	0.23	0.80	0.42
Group (Hydroxychloroquine plus Azithromycin)	-0.01	0.23	-0.05	0.96
Oxygen support at randomization	0.43	0.20	2.11	0.03
Age (years)	0.031	0.007	4.16	<0.01
Threshold coefficients				
1|2	2.55	0.44	5.79	
2|3	3.43	0.45	7.54	
3|4	4.05	0.47	8.60	
4|5	4.45	0.48	9.23	
5|6	4.58	0.49	9.40	
6|7	5.61	0.54	10.40	
Intercept random effects standard deviation	0.37			

* Mixed ordinal logistic regression considering proportional odds ratios with random intercept by site adjusted for age and oxygen support at randomization

† P-values are not adjusted for multiple comparisons

Table S9. Primary and secondary outcomes for the intention-to-treat population*

Outcomes	Hydroxychloroquine + Azithromycin (HCQA) (n=217)	Hydroxychloroquine (HCQ) (n=221)	Control (n=227)	HCQA vs. Cont Effect measure (95% CI)	HCQ vs. Cont Effect measure (95% CI)	HCQA vs. HCQ Effect measure (95% CI)
Ordinal outcome at 15 days, median (IQR)	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	OR 0.81 (0.54 - 1.23)	OR 0.96 (0.64 - 1.43)	OR 0.85 (0.56 - 1.28)
Death	3 (1.4)	7 (3.2)	6 (2.6)			
Patient on mechanical ventilation.	10 (4.6)	6 (2.7)	7 (3.1)			
Patient in hospital on noninvasive ventilation or HFNC	0 (0)	3 (1.4)	2 (0.9)			
Patient in hospital, with oxygen.	5 (2.3)	6 (2.7)	6 (2.6)			
Patient in hospital, without oxygen.	15 (6.9)	14 (6.3)	11 (4.8)			
Patient not hospitalized but with limitations on activities	27 (12.4)	33 (14.9)	42 (18.5)			
Patient not hospitalized with no limitations on activities	157 (72.4)	152 (68.8)	153 (67.4)			
Secondary outcomes						
Ordinal outcome at 7 days, median (IQR)	1 (1 – 2) (n=216)	2 (1 – 2) (n=219)	1 (1 - 2.5)	OR 0.86 (0.59 - 1.25)	OR 1.02 (0.71 - 1.48)	OR 0.84 (0.58 - 1.22)
Death	1 (0.5)	3 (1.4)	3 (1.3)			
Patient on mechanical ventilation.	15 (6.9)	11 (5.0)	10 (4.4)			
Patient in hospital on noninvasive ventilation or HFNC	3 (1.4)	3 (1.4)	4 (1.8)			
Patient in hospital, with oxygen.	31 (14.4)	32 (14.6)	40 (17.6)			
Patient in hospital, without oxygen.	46 (21.3)	63 (28.8)	53 (23.3)			
Patient not hospitalized	120 (55.6)	107 (48.9)	117 (51.5)			
Days free from respiratory support in 15 days, mean (SD)	11.7 ± 4.6 (n=213)	11.5 ± 4.8 (n=219)	11.6 ± 4.6 (n=225)	MD 0.1 (-0.7 – 0.9)	MD -0.1 (-0.9 - 0.7)	MD 0.2 (-0.6 - 1.1)
Need of HFNC or NIV within 15 days	17 (7.8)	19 (8.6)	20 (8.8)	OR 0.95 (0.54 - 1.66)	OR 0.94 (0.54 - 1.65)	OR 1.01 (0.57 - 1.78)
Need of mechanical ventilation within 15 days,	20 (9.2)	16 (7.2)	13 (5.7)	OR 1.79 (0.85 - 3.74)	OR 1.30 (0.60 - 2.82)	OR 1.37 (0.68 - 2.76)
Length of hospital stay, days, mean (SD)	9.4 ± 7.8	8.9 ± 6.2	8.8 ± 7.0	MD 0.7 (-0.4 - 1.7)	MD 0.2 (-0.8 - 1.2)	MD 0.5 (-0.6 - 1.6)
In-hospital death	5 (2.3)	9 (4.1)	8 (3.5)	HR 0.58 (0.18 - 1.82)	HR 1.25 (0.47 - 3.31)	HR 0.46 (0.15 - 1.43)
Thromboembolic complications within 15 days	2 (0.9)	3 (1.4)	2 (0.9)	OR 0.95 (0.37 - 2.43)	OR 1.38 (0.59 - 3.25)	OR 0.69 (0.29 - 1.63)
Renal failure within 15 days	6 (2.8)	4 (1.8)	6 (2.6)	OR, 1.05 [0.42 - 2.61]	OR, 0.66 [0.24 - 1.82]	OR, 1.58 [0.58 - 4.33]

*Data are presented as no. (%) unless indicated otherwise. CI denotes confidence interval; HCQ, hydroxychloroquine; HCQA, hydroxychloroquine + azithromycin; HFNC, high-flow nasal cannula; HR, hazard ratio; IQR, interquartile range; MD, mean difference; NIV, non-invasive ventilation; OR, odds ratio; SD, standard deviation.

Table S10. Sensitivity analyses for the primary outcome*

7-level Ordinal Scale at 15 Days	Hydroxychloroquine plus Azithromycin (HCQA)	Hydroxychloroquine (HCQ)	Control	Effect Size		
				HCQA vs. Cont	HCQ vs. Cont	HCQA vs. HCQ
				Proportional OR (95% CI)	Proportional OR (95% CI)	Proportional OR (95% CI)
Definitive, probable or possible COVID-19 population	1 [1 - 2] (n=202)	1 [1 - 2] (n=200)	1 [1 - 2] (n=210)	0.9 (0.59 - 1.38)	0.94 (0.62 - 1.43)	0.97 (0.63 - 1.49)
Definitive or probable COVID-19 population	1 [1 - 2] (n=181)	1 [1 - 2] (n=175)	1 [1 - 2] (n=188)	1.04 (0.66 - 1.62)	1.14 (0.73 - 1.78)	0.91 (0.58 - 1.42)
Only patients who used at least one dose of allocated medication	1 [1 - 2] (n=168)	1 [1 - 2] (n=163)	1 [1 - 2] (n=177)	1.03 (0.65 - 1.63)	1.11 (0.70 - 1.75)	0.93 (0.59 - 1.47)
Per protocol (only patients who used at least one dose of allocated medication and did not crossover)	1 [1 - 2] (n=168)	1 [1 - 2] (n=146)	1 [1 - 2] (n=135)	1.10 (0.67 - 1.79)	1.04 (0.63 - 1.73)	1.05 (0.65 - 1.69)

*CI denotes confidence interval; HCQ, hydroxychloroquine; HCQA, hydroxychloroquine plus azithromycin; OR, odds ratio.

Table S11. Prespecified subgroup analyses for the primary outcome*

Subgroup	Outcome at 15 Days	Hydroxychloroquine plus Azithromycin (HCQA)	Hydroxychloroquine (HCQ)	Control	Effect Size		
					HCQA vs. Cont OR (95% CI)	HCQ vs. Cont OR (95% CI)	HCQA vs. HCQ OR (95% CI)
Days from symptoms onset to randomization							
≤ 7 days					1.12 (0.51 - 2.45)	0.97 (0.46 – 2.07)	1.15 (0.53 - 2.50)
	In hospital or dead	20/84 (23.8)	21/100 (21.0)	21/99 (21.2)			
	At home	64/84 (76.2)	79/100 (79.0)	78/99 (78.8)			
> 7 days					2.53 (0.74 - 8.57)	2.70 (0.73 – 10.0)	0.94 (0.32 – 2.72)
	In hospital or dead	12/88 (13.6)	8/58 (13.8)	6/74 (8.1)			
	At home	76/88 (86.4)	50/58 (86.2)	68/74 (91.9)			
Age							
< 60 years					1.45 (0.68 - 3.12)	1.50 (0.69 - 3.23)	0.97 (0.48 - 1.98)
	In hospital or dead	20/130 (15.4)	20/123 (16.3)	14/129 (10.9)			
	At home	110/130 (84.6)	103/123 (83.7)	115/129 (89.1)			
≥ 60 years					0.95 (0.37 - 2.43)	0.96 (0.36 - 2.58)	0.99 (0.36 - 2.69)
	In hospital or dead	12/42 (28.6)	10/36 (27.8)	13/44 (29.5)			
	At home	30/42 (71.4)	26/36 (72.2)	31/44 (70.5)			
Supplemental oxygen at randomization							
No					1.53 (0.60 - 3.92)	1.28 (0.50 - 3.29)	1.20 (0.48 - 3.01)
	In hospital or dead	14/90 (15.6)	13/88 (14.8)	12/99 (12.1)			
	At home	76/90 (84.4)	75/88 (85.2)	87/99 (87.9)			
Yes					1.33 (0.59 - 2.99)	1.47 (0.64 - 3.38)	0.09 (0.41 - 1.98)
	In hospital or dead	18/82 (22.0)	17/71 (23.9)	15/74 (20.3)			
	At home	64/82 (78.0)	54/71 (76.1)	59/74 (79.7)			

* Data are presented as no./total no. (%) unless indicated otherwise. It was not possible to adjust proportional odds ratio models with interaction for the subgroup variables for the 7-ordinal scale because of low number of cases in some cells. Therefore, as prespecified in our statistical analysis plan, we grouped the 7-level variables in two categories: patients who were at home versus patients who died or were at hospital at day 15. CI denotes confidence interval; HCQ, hydroxychloroquine; HCQA, hydroxychloroquine plus azithromycin; OR, odds ratio.

Table S12. Post hoc subgroup analyses for the primary outcome

Subgroup	Outcome at 15 Days	Hydroxychloroquine plus Azithromycin (HCQA)	Hydroxychloroquine (HCQ)	Control	Effect Size		
					HCQA vs. Cont OR (95% CI)	HCQ vs. Cont OR (95% CI)	HCQA vs. HCQ OR (95% CI)
Hydroxychloroquine use before randomization							
No					1.15 [0.64 - 2.05]	1.12 [0.61 - 2.02]	1.03 [0.57 - 1.84]
	In hospital or dead	30/159 (18.9)	27/146 (18.5)	27/161 (16.8)			
	At home	129/159 (81.1)	119/146 (81.5)	134/161 (83.2)			
Yes					-	-	0.28 [0.01 - 15.59]
	In hospital or dead	2/13 (15.4)	3/13 (23.1)	0/12 (0)			
	At home	11/13 (84.6)	10/13 (76.9)	12/12 (100)			
Azithromycin use before randomization							
No					1.27 [0.64 - 2.52]	1.22 [0.6 - 2.47]	1.04 [0.53 - 2.02]
	In hospital or dead	24/115 (20.9)	21/104 (20.2)	18/104 (17.3)			
	At home	91/115 (79.1)	83/104 (79.8)	86/104 (82.7)			
Yes					1.06 [0.38 - 2.98]	1.28 [0.46 - 3.53]	0.83 [0.29 - 2.37]
	In hospital or dead	8/57 (14)	9/55 (16.4)	9/68 (13.2)			
	At home	49/57 (86)	46/55 (83.6)	59/68 (86.8)			
Randomization date							
Before April 13th 2020					0.76 [0.13 - 4.51]	2.74 [0.5 - 15.15]	0.28 [0.05 - 1.54]
	In hospital or dead	3/20 (15.0)	6/16 (37.5)	3/16 (18.8)			
	At home	17/20 (85.0)	10/16 (62.5)	13/16 (81.2)			
On or after April 13th 2020					1.29 [0.71 - 2.35]	1.10 [0.59 - 2.06]	1.17 [0.64 - 2.14]
	In hospital or dead	29/152 (19.1)	24/143 (16.8)	24/157 (15.3)			
	At home	123/152 (80.9)	119/143 (83.2)	133/157 (84.7)			

* Data are presented as no./total no. (%) unless indicated otherwise. It was not possible to adjust proportional odds ratio models with interaction for the subgroup variables for the 7-ordinal scale because of low number of cases in some cells. Therefore, as prespecified in our statistical analysis plan, we grouped the 7-level variables in two categories: patients who were at home versus patients who died or were at hospital at day 15.

CI denotes confidence interval; HCQ, hydroxychloroquine; HCQA, hydroxychloroquine + azithromycin; OR, odds ratio.

Table S13. Treatment effect on thromboembolic events within 15 days and acute kidney injury within 15 days assessed with prespecified ordinal logistic regression model and post hoc ordinal logistic regression model with adjustment for the competing risk of death

Secondary outcomes	Hydroxychloroquine plus Azithromycin (n=172)	Hydroxychloroquine (n=159)	Control (n=173)		Effect Size		
					Hydroxychloroquine plus Azithromycin vs. Control	Hydroxychloroquine vs. Control	Hydroxychloroquine plus Azithromycin vs. Hydroxychloroquine
					Effect estimate (95% CI)	Effect estimate (95% CI))	Effect estimate (95% CI)
Thromboembolic complications within 15 days, no. (%)	2 (1.2)	3 (1.9)	2 (1.2)	Pre-specified model, odds ratio	0.89 (0.31 - 2.54)	1.39 (0.53 - 3.65)	0.64 (0.24 - 1.68)
				Competing risk model, hazard ratio	1.03 (0.15 – 7.33)	1.66 (0.28 - 9.93)	0.62 (0.10 – 3.74)
Acute kidney injury, within 15 days, no. (%)	6 (3.5)	4 (2.5)	5 (2.9)	Pre-specified model, odds ratio	1.18 (0.44 - 3.2)	0.88 (0.29 - 2.63)	1.35 (0.47 - 3.84)
				Competing risk model, hazard ratio	1.07 (0.34 – 3.32)	0.69 (0.19 – 2.44)	1.56 (0.44 – 5.54)

* Prespecified models were mixed ordinal logistic regression considering proportional odds ratios with random intercept by site and adjustment for Age and use of supplemental oxygen at baseline. Post hoc competing risk effects was estimated by Cause-Specific Cox proportional hazard models competing with death adjusted for age and use of supplemental oxygen at baseline.

Table S14. Marginal effects for primary and secondary outcomes for the modified intention-to-treat population*

Outcomes	Hydroxychloroquine plus Azithromycin (n=172)	Hydroxychloroquine (n=159)	Control (n=173)	Marginal Effects		
				Hydroxychloroquine plus Azithromycin vs. Control	Hydroxychloroquine vs. Control	Hydroxychloroquine plus Azithromycin vs. Hydroxychloroquine
				Effect estimate (95% CI)	Effect estimate (95% CI)	Effect estimate (95% CI)
Primary outcome						
Ordinal outcome at 15 days, median (IQR)†	1 (1 - 2)	1 (1 - 2)	1 (1 - 2)	OR, 0.99 (0.63–1.56)	OR, 1.18 (0.75–1.85)	OR, 0.84 (0.53–1.32)
Secondary outcomes						
Ordinal outcome at 7 days, median (IQR) ‡	2 (1 - 3)	2 (1 - 2)	2 (1 - 3)	OR, 0.84 (0.57–1.26)	OR, 0.95 (0.64–1.41)	OR, 0.89 (0.59–1.34)
Days free from respiratory support within 15 days§	11.1±4.9	11.2±4.9	11.1±4.9	MD, -0.1 (-1.1, 0.8)	MD, -0.2 (-1.2, 0.8)	MD, 0.1 (-0.9, 1.1)
Need for high-flow nasal cannula or non-invasive ventilation within 15 days, no. (%)	16 (9.3)	17 (10.7)	16 (9.2)	OR, 1.06 (0.51–2.22)	OR, 1.22 (0.59–2.54)	OR, 0.87 (0.42–1.80)
Need for mechanical ventilation within 15 days, no. (%)	19 (11.0)	12 (7.5)	12 (6.9)	OR, 1.77 (0.81–3.89)	OR, 1.15 (0.49–2.72)	OR, 1.54 (0.70–3.36)
Length of hospital stay, days‖	10.3±8.4	9.6±6.5	9.5±7.2	MD, 0.9 (-0.7, 2.5)	MD, 0.1 (-1.4, 1.6)	MD, 0.8 (-0.9, 2.4)
In-hospital mortality, no. (%)‖	5 (2.9)	7 (4.4)	6 (3.5)	HR, 0.83 (0.25–2.72)	HR, 1.28 (0.43–3.80)	HR, 0.65 (0.21–2.05)
Thromboembolic complications within 15 days, no. (%)	2 (1.2)	3 (1.9)	2 (1.2)	OR, 0.94 (0.13–6.81)	OR, 1.59 (0.26–9.69)	OR, 0.59 (0.10–3.61)
Acute kidney injury within 15 days, no. (%)	6 (3.5)	4 (2.5)	5 (2.9)	OR, 1.23 (0.36–4.19)	OR, 0.89 (0.23–3.44)	OR, 1.38 (0.38–5.04)

CI denotes confidence interval; IQR, interquartile range; OR, odds ratio; MD, mean difference; and HR, hazard ratio.

*Plus-minus values are mean and standard deviation. Odds ratio values for the ordinal outcome at 7 and at 15 days lower than 1 indicate a benefit for treatment groups compared to control.

†Ordinal outcome assessed at 15 days has seven levels: (1) not hospitalized with no limitations on activities; (2) not hospitalized but with limitations on activities; (3) hospitalized and not using supplemental oxygen; (4) hospitalized and using supplemental oxygen; (5) hospitalized and using high-flow nasal cannula or non-invasive ventilation; (6) hospitalized and on mechanical ventilation; (7) death. Odds ratio values lower than 1 indicate treatment benefit.

‡Ordinal outcome assessed at 7 days has six levels: 1) not hospitalized; (2) hospitalized and not using supplemental oxygen; (3) hospitalized and using supplemental oxygen; (4) hospitalized and using high-flow nasal cannula or non-invasive ventilation; (5) hospitalized and on mechanical ventilation; (6) death. Data were available for 171 patients in the hydroxychloroquine plus azithromycin group, 157 patients in the hydroxychloroquine group and 173 in the control group. Odds ratio values lower than 1 indicate treatment benefit

§Data were available for 169 patients in the hydroxychloroquine plus azithromycin group, 157 patients in the hydroxychloroquine group and 171 in the control group.

‖ As of June 4, 2020, 21 patients were still in the hospital (length of follow-up from 22 to 49 days): 8 patients in the hydroxychloroquine plus azithromycin group, 5 patients in the hydroxychloroquine group and 8 in the control group. These patients were considered as discharged alive.

Table S15. Adverse events in the intention-to-treat population*

	Hydroxychloroquine plus Azithromycin (n=217)	Hydroxychloroquine (n=221)	Control (n=227)	Total (n=665)	p†
Reported Serious Adverse Events	3 (1.4)	3 (1.4)	3 (1.3)	9 (1.4)	1
SAE classification					
Risk of life	1 (0.5)	1 (0.5)	0 (0)	2 (0.3)	
Extension of hospitalization	2 (0.9)	0 (0)	1 (0.4)	3 (0.5)	
Clinically significant	0 (0)	1 (0.5)	1 (0.4)	2 (0.3)	
Death	0 (0)	1 (0.5)	1 (0.4)	2 (0.3)	
Adverse events					
Patients with any reported adverse events	82 (37.8)	74 (33.5)	61 (26.9)	217 (32.6)	0.047
QTc > 480 within 7 days	19/126 (15.1)	21/134 (15.7)	6/96 (6.2)	46/356 (12.9)	0.06
Arrhythmia	3 (1.4)	3 (1.4)	1 (0.4)	7 (1.1)	0.58
Bradycardia	2 (0.9)	1 (0.5)	1 (0.4)	4 (0.6)	
Supraventricular tachycardia	1 (0.5)	2 (0.9)	0 (0)	3 (0.5)	
Ventricular tachycardia	0	0	0	0	
Myocardial infarction	0 (0)	0 (0)	1 (0.4)	1 (0.2)	1
Abdominal hemorrhage	0 (0)	1 (0.5)	0 (0)	1 (0.2)	0.66
Pulmonary embolism	2 (0.9)	0 (0)	0 (0)	2 (0.3)	0.11
Pneumothorax	0 (0)	1 (0.5)	0 (0)	1 (0.2)	0.66
Bronchospasm	0 (0)	0 (0)	1 (0.4)	1 (0.2)	1
Epistaxis	2 (0.9)	0 (0)	0 (0)	2 (0.3)	0.11
Bloodstream infection	0 (0)	1 (0.5)	0 (0)	1 (0.2)	0.66
Itching	0 (0)	1 (0.5)	0 (0)	1 (0.2)	0.66
Nausea	6 (2.8)	9 (4.1)	2 (0.9)	17 (2.6)	0.08
Severe vomiting	0 (0)	0 (0)	1 (0.4)	1 (0.2)	1
Anemia	22 (10.1)	15 (6.8)	16 (7)	53 (8)	0.38
ALT or AST elevation	23 (10.6)	20 (9)	8 (3.5)	51 (7.7)	0.008
Hypoglycemia	0 (0)	1 (0.5)	0 (0)	1 (0.2)	0.66
Bilirubin elevation	0 (0)	3 (1.4)	5 (2.2)	8 (1.2)	0.11
Leukopenia	5 (2.3)	3 (1.4)	6 (2.6)	14 (2.1)	0.63
Decreased lymphocytes	20 (9.2)	19 (8.6)	25 (11)	64 (9.6)	0.68
Thrombocytopenia	11 (5.1)	16 (7.2)	23 (10.1)	50 (7.5)	0.13
Hypoacusia	0 (0)	0 (0)	0 (0)	0 (0)	1

*Data are presented as no. (%). ALT denotes alanine aminotransferase; AST, aspartate aminotransferase; QTc, corrected QT interval; SAE, serious adverse event.
†Fisher exact test.

Table S16. Adverse events in patients with confirmed COVID-19 (modified intention-to-treat population)*

	Hydroxychloroquine plus Azithromycin (n=172)	Hydroxychloroquine (n=159)	Control (n=173)	Total (n=504)	p†
Reported Serious Adverse Events	3 (1.7)	2 (1.3)	3 (1.7)	8 (1.6)	1
SAE classification					
Risk of life	1 (0.6)	1 (0.6)	0	2 (0.4)	
Extension of hospitalization	2 (1.2)	0	1 (0.6)	3 (0.6)	
Clinically significant	0	0	1 (0.6)	1 (0.2)	
Death	0	1 (0.6)	1 (0.6)	2 (0.4)	
Adverse events					
Patients with any adverse events	68 (39.5)	53 (33.3)	49 (28.3)	170 (33.7)	0.09
QTc > 480 within 7 days	14/85 (16.5)	11/77 (14.3)	1/58 (1.7)	26/220 (11.8)	0.009
Arrhythmia	1 (0.6)	2 (1.3)	1 (0.6)	4 (0.8)	0.70
Bradycardia	1 (0.6)	1 (0.6)	1 (0.6)	3 (0.6)	
Supraventricular tachycardia	0	1 (0.6)	0	1 (0.2)	
Ventricular tachycardia	0	0	0	0	
Myocardial infarction	0	0	1 (0.6)	1 (0.2)	1
Abdominal hemorrhage	0	1 (0.6)	0	1 (0.2)	0.32
Pulmonary embolism	2 (1.2)	0	0	2 (0.4)	0.22
Pneumothorax	0	0	0	0	1
Bronchospasm	0	0	1 (0.6)	1 (0.2)	1
Epistaxis	2 (1.2)	0	0	2 (0.4)	0.22
Bloodstream infection	0	1 (0.6)	0	1 (0.2)	0.32
Itching	0	0	0	0	1
Nausea	6 (3.5)	7 (4.4)	2 (1.2)	15 (3)	0.16
Vomiting	0	0	1 (0.6)	1 (0.2)	1
Anemia	17 (9.9)	10 (6.3)	10 (5.8)	37 (7.3)	0.30
ALT or AST elevation	20 (11.6)	17 (10.7)	7 (4)	44 (8.7)	0.02
Hypoglycemia	0	0	0	0	1
Bilirubin elevation	0	2 (1.3)	4 (2.3)	6 (1.2)	0.13

Leukopenia	4 (2.3)	3 (1.9)	5 (2.9)	12 (2.4)	0.93
Low Lymphocytes	19 (11)	14 (8.8)	23 (13.3)	56 (11.1)	0.45
Thrombocytopenia	9 (5.2)	11 (6.9)	18 (10.4)	38 (7.5)	0.21
Hypoacusia	0	0	0	0	1

*Data are presented as no. (%). ALT denotes alanine aminotransferase; AST, aspartate aminotransferase; QTc, corrected QT interval; SAE, serious adverse event.
†Fisher exact test.

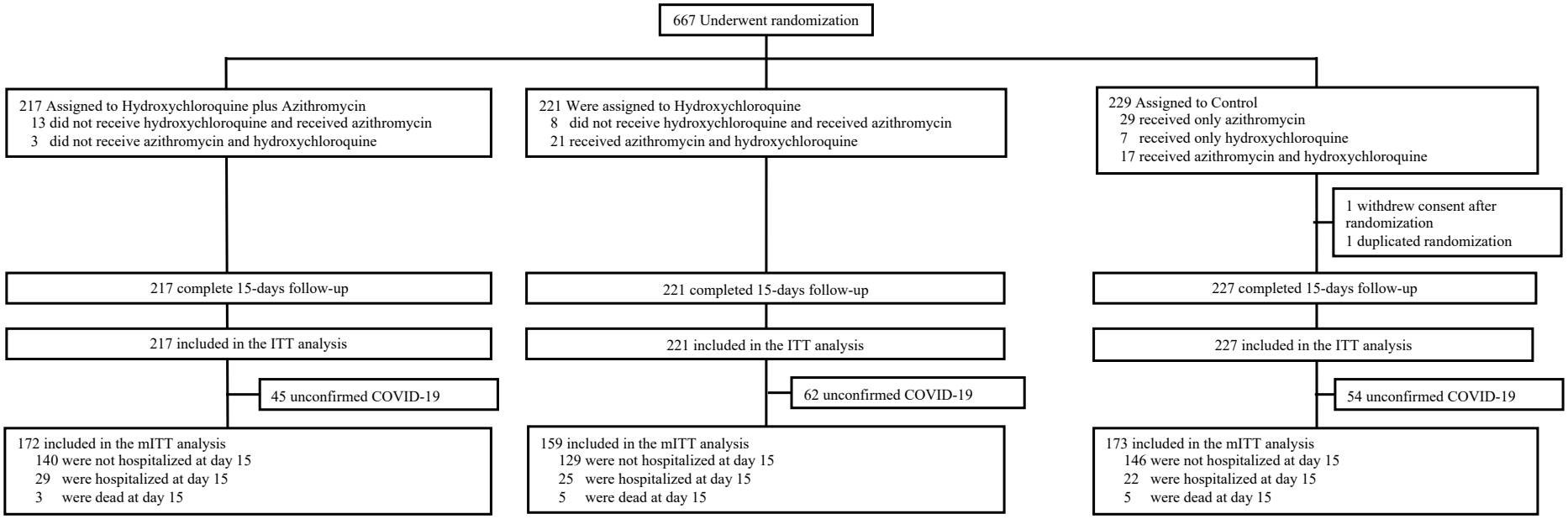

Figure S1. Study flowchart
ITT denotes intention-to-treat and mITT denotes modified intention-to-treat.

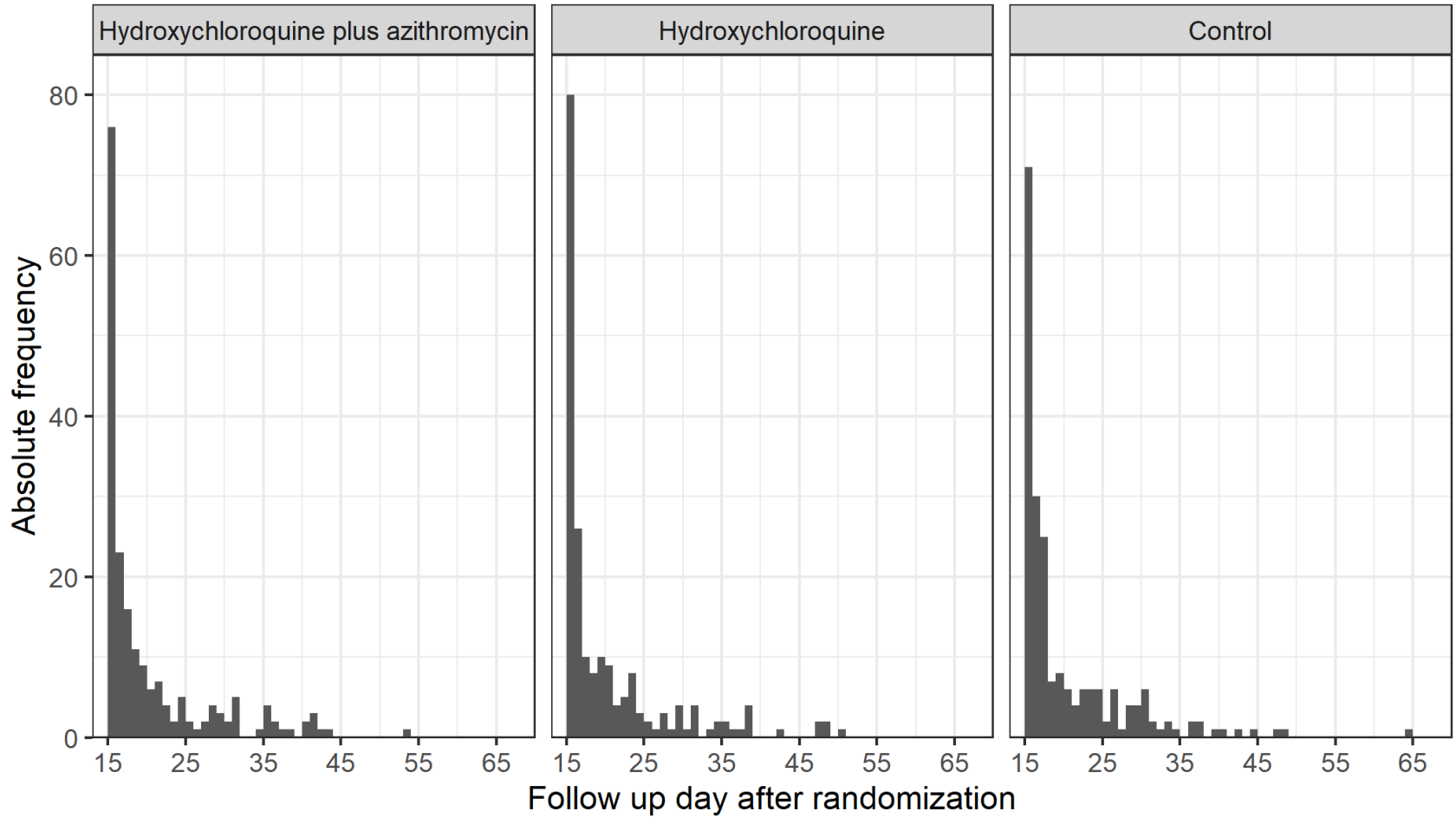

Figure S2. Day after randomization that 15-day follow-up call was performed

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