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# Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19

## A Randomized Trial

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**Background:** New treatment modalities are urgently needed for patients with COVID-19. The World Health Organization (WHO) Solidarity trial showed no effect of remdesivir or hydroxychloroquine (HCQ) on mortality, but the antiviral effects of these drugs are not known.

**Objective:** To evaluate the effects of remdesivir and HCQ on all-cause, in-hospital mortality; the degree of respiratory failure and inflammation; and viral clearance in the oropharynx.

**Design:** NOR-Solidarity is an independent, add-on, randomized controlled trial to the WHO Solidarity trial that included biobanking and 3 months of clinical follow-up (ClinicalTrials.gov: NCT04321616)

**Setting:** 23 hospitals in Norway.

**Patients:** Eligible patients were adults hospitalized with confirmed SARS-CoV-2 infection.

**Intervention:** Between 28 March and 4 October 2020, a total of 185 patients were randomly assigned and 181 were included in the full analysis set. Patients received remdesivir ($n = 42$), HCQ ($n = 52$), or standard of care (SoC) ($n = 87$).

**Measurements:** In addition to the primary end point of WHO Solidarity, study-specific outcomes were viral clearance in oropharyngeal specimens, the degree of respiratory failure, and inflammatory variables.

**Results:** No significant differences were seen between treatment groups in mortality during hospitalization. There was a marked decrease in SARS-CoV-2 load in the oropharynx during the first week overall, with similar decreases and 10-day viral loads among the remdesivir, HCQ, and SoC groups. Remdesivir and HCQ did not affect the degree of respiratory failure or inflammatory variables in plasma or serum. The lack of antiviral effect was not associated with symptom duration, level of viral load, degree of inflammation, or presence of antibodies against SARS-CoV-2 at hospital admittance.

**Limitation:** The trial had no placebo group.

**Conclusion:** Neither remdesivir nor HCQ affected viral clearance in hospitalized patients with COVID-19.

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* For members of the NOR-Solidarity trial, see Appendix 1 (available at Annals.org).

In February 2020, a World Health Organization (WHO) expert group recommended that 4 drugs approved for other indications–hydroxychloroquine (HCQ), remdesivir, ritonavir-boosted lopinavir, and interferon-$\beta$1a–should be evaluated in an international, adaptive, open-label, randomized clinical trial and compared with standard of care (SoC) in the treatment of hospitalized patients with SARS-CoV-2 infection. This initiative resulted in initiation of the WHO Solidarity trial (1). The HCQ and lopinavir groups of this trial were subsequently stopped because of reported lack of effect based on emerging external evidence from the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial, as well as internal evidence from interim analyses (2).

In October 2020, the WHO Solidarity trial consortium published interim results, reporting that all of the repurposed drugs evaluated showed little or no effect on in-hospital mortality and did not reduce the need for mechanical ventilation (1). For remdesivir, these results contrasted with those of ACTT (Adaptive COVID-19 Treatment Trial), which reported that remdesivir significantly reduced time to recovery and discharge from the hospital, in particular in patients not receiving mechanical ventilation (3).

Of major interest was whether remdesivir could affect the clinical course in patients with mild or moderate disease, where viral replication is believed to drive disease progression, as opposed to severe disease, in which inflammation seems to play a predominant role.

**See also:**

*Web-Only*
Supplement

Remdesivir is a viral RNA polymerase inhibitor shown to have antiviral effects on SARS-CoV-2 in vitro through interference with viral RNA production (4,5). However, data on any antiviral effects of remdesivir in SARS-CoV-2–infected humans are scarce.

The NOR-Solidarity trial is an independent add-on study to the WHO Solidarity trial that evaluated the effects of HCQ and remdesivir compared with SoC in hospitalized patients with COVID-19. Here, we present the effect of remdesivir and HCQ compared with SoC on viral clearance as assessed by SARS-CoV-2 polymerase chain reaction (PCR) in oropharyngeal specimens. We also examined whether remdesivir and HCQ had any effects on inflammatory biomarkers and degree of respiratory failure.

## METHODS

### Trial Design

NOR-Solidarity is an independent add-on trial to the WHO Solidarity trial, a large, open-label, adaptive, randomized clinical trial evaluating the effect of repurposed antiviral drugs on hospitalized patients with COVID-19. WHO Solidarity included 405 hospitals in 30 countries; 11 330 adults were randomly assigned, 2750 to remdesivir, 954 to HCQ, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to SoC. The NOR-Solidarity trial included biobanking and additional clinical and biochemistry data collection, as well as follow-up beyond the WHO Solidarity core protocol (ClinicalTrials.gov: NCT04321616).

### Participants

The participants in NOR-Solidarity were recruited from 23 Norwegian hospitals. Eligibility criteria were adult patients (≥18 years) with SARS-CoV-2 infection confirmed by PCR who were admitted to the hospital ward or intensive care unit (ICU) with no anticipated transfer to a nonstudy hospital within 72 hours of inclusion. Informed consent by the study participant or legally authorized representative was provided before inclusion.

Key exclusion criteria were severe comorbid conditions with life expectancy less than 3 months, level of aspartate aminotransferase or alanine aminotransferase more than 5 times the upper limit of normal, rate-corrected QT interval greater than 470 ms, pregnancy, breastfeeding, acute occurrence of a comorbid condition in a 7-day period before inclusion, known intolerance to study drugs, participation in a potentially confounding trial, or concomitant medications interfering with the study drugs.

### Randomization

Eligible patients were allocated in an equal ratio using computer randomization procedures. There were 2 separate allocation lists. The first was the global list, in which the allocation sequence was prepared by an independent statistician appointed by the international trial steering group. A secondary national list was additionally prepared as a backup if allocation according to the global list was not available. The randomization procedure ensured that a patient could be allocated only to an available treatment. The randomization lists were not stratified or blocked; thus, the randomization can be regarded as simple. The trial was open-label, without a placebo control.

### Interventions

The participants were randomly assigned to the following groups: 1) local SoC; 2) SoC plus 800 mg of oral HCQ twice daily on day 1, then 400 mg twice daily up to 9 days; or 3) SoC plus 200 mg of intravenous remdesivir on day 1, then 100 mg daily up to 9 days. All study treatments were discontinued at discharge. During the study, local SoC changed as a result of the RECOVERY trial and updated WHO guidelines recommending systemic steroids for severe and critical COVID-19 (4 September 2020) (6).

### Recruitment

NOR-Solidarity started recruiting patients on 28 March 2020, as the first study site within the WHO Solidarity trial. Patients were initially randomly assigned to HCQ or SoC. Randomization to remdesivir started on 7 April. Hydroxychloroquine was removed as a treatment group after advice from the NOR-Solidarity steering committee on 8 June 2020 because of lack of evidence of its effectiveness, confirmed in both internal WHO interim analyses and an external report from the RECOVERY study (7,8). Thus, from 8 June 2020 on, NOR-Solidarity allocated patients only to SoC and remdesivir. On 4 October 2020, the WHO Solidarity trial consortium published interim results reporting that HCQ and remdesivir, as well as the other repurposed drugs in the trial, had little or no effect on in-hospital mortality. Whereas the remdesivir group was continued in the WHO Solidarity trial, it was stopped in the NOR-Solidarity study on 5 October because of general low mortality in hospitalized patients in Norway; the potential for adverse effects in ventilated patients; and potentially little, if any, effect of remdesivir in patients with mild disease. This decision was supported by the independent national data monitoring and safety committee.

### Outcomes

The primary outcome of NOR-Solidarity was all-cause, in-hospital mortality with study treatment compared with SoC. Secondary outcomes were receipt of invasive mechanical ventilation, time to first receipt and duration of mechanical ventilation, receipt and duration of treatment at an ICU, and occurrence of suspected unexpected serious adverse reactions. Because NOR-Solidarity was an add-on trial to WHO Solidarity, most of these data have already been published as part of this report (1) but are now presented separately.

Further substudy-specific secondary outcomes included viral clearance as assessed by SARS-CoV-2 PCR in oropharyngeal specimens (measured at baseline, days 3 to 5, days 7 to 9, and thereafter every third day). Respiratory failure, as assessed by $P_{O_2}$–$F_{I_{O_2}}$ (P–F) ratio and inflammatory laboratory variables (that is, C-reactive protein [CRP], procalcitonin, lactate dehydrogenase, and ferritin levels and lymphocyte and neutrophil counts) measured daily during hospitalization, was an additional prespecified secondary end point. Details are presented in the protocol and statistical analysis plan (**Supplement**, available at Annals.org).

The exploratory objective of identifying potential determinants of individual treatment responses by relating viral clearance to demographic and clinical characteristics (that is, age and time since symptom onset), baseline viral load, inflammatory markers (that is, CRP and ferritin), and levels of anti–SARS-CoV-2 antibodies with affinity to either receptor-binding domain or nucleocapsid antigen.

## Statistical Analysis

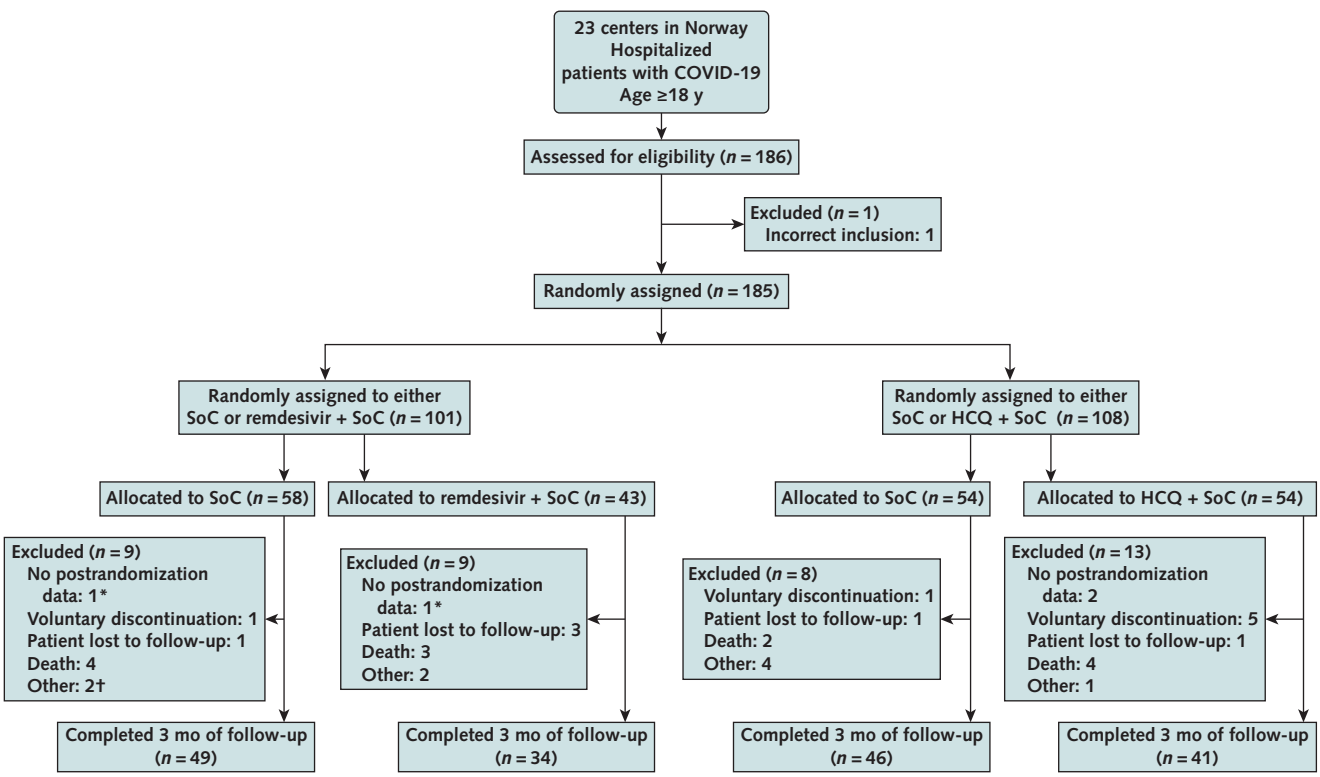
Following the WHO core protocol, no sample size was prespecified.

Before the database was locked, and deliberately without knowledge of allocation, a statistical analysis plan was written and approved, prespecifying and detailing all analyses (**Supplement**). Because this is an add-on study, there are no adjustments for multiple testing. Interpretations of results are based on unadjusted CIs. All treatment comparisons are with concurrent controls. Thus, some participants receiving SoC act as controls for both active treatment groups, whereas some act in one or the other.

We used the log-rank statistic to test the null hypothesis of no treatment effect on all-cause mortality. The natural logarithm of the average mortality rate ratio was estimated using the $(O - E)/V$ estimator (where O is observed events, E is expected events, and V is variance) from the log-rank statistic with 95% CIs estimated using a normal distribution with 1/V as variance. Hazard ratios, estimated using Cox proportional hazards models, were reported as advised by the journal's editors and reviewers. Because of the low number of deaths in blinded reviews, stratification variables in the primary analyses were not used. Participants who withdrew consent or were alive but still in the hospital at the time of database locking were censored at last known time of contact. Discharged participants were assumed to be alive and were censored at the time of database locking unless otherwise confirmed. Those who had an end-of-study visit at 3 months were censored at this date.

Dichotomous end points were analyzed using logistic regression without adjustment for any baseline covariates. The estimated average marginal risk difference and corresponding 95% CI were estimated using the delta method. Missing data due to discharge or participant withdrawal were imputed with best outcome. Continuous outcomes during the first 14 days were analyzed using a mixed model with fixed intercept and separate slopes before and after day 7, and random intercept and slope. The difference in slope before day 7 was used to estimate the treatment effect in the first week. We also computed the average marginal point estimate at day 10 as a separate measure of treatment

***Figure 1.*** Study flow diagram.




Flow chart of patients enrolled in NOR-Solidarity from 28 March to 5 October 2020; a total of 181 patients were randomly assigned to receive SoC, remdesivir + SoC, or HCQ + SoC. A total of 149 patients completed the 3 mo of follow-up. Each pairwise intention-to-treat analysis was between the remdesivir or HCQ group and its respective SoC. Some participants receiving SoC act as controls for both active treatment groups, whereas some act in one or the other, giving a partial overlap of the 2 control groups. HCQ = hydroxychloroquine; SoC = standard of care.

* Excluded from the full analysis set.

† Other: emigration, progression of cancer diseases.

***Table 1.*** Patient Characteristics and Baseline Values*

| Characteristic | All Patients (*n* = 181) | Remdesivir vs. Its Control | | HCQ vs. Its Control | |
|---|---|---|---|---|---|
| | | Remdesivir + SoC (*n* = 42) | SoC (*n* = 57) | HCQ + SoC (*n* = 52) | SoC (*n* = 54) |
| **Demographics** | | | | | |
| Mean age (SD), *y* | 59.8 (15.3) | 59.7 (16.5) | 58.1 (15.7) | 60.3 (13.3) | 59.2 (16.4) |
| Female sex, *n (%)* | 62 (34.3) | 13 (31) | 14 (24.6) | 21 (40.4) | 20 (37) |
| Mean BMI (SD), $kg/m^2$ | 28 (5) | 28 (5) | 28 (4) | 28 (5) | 27 (4) |
| Mean symptom duration before admission (SD), *d* | 8 (4.9) | 7.5 (6.1) | 7.2 (3.5) | 8.4 (4.3) | 8.6 (5.3) |
| Mean P–F ratio at admission (SD), *kPa* | 41 (13) | 38 (13) | 43 (12) | 41 (15) | 43 (11) |
| P–F ratio <40 kPa, *n (%)* | 77 (43) | 22 (52.4) | 22 (38.6) | 24 (48) | 15 (27.8) |
| Mean respiratory rate (SD), *breaths/min* | 21.8 (5.8) | 21.9 (5.3) | 22 (5.4) | 21.6 (5.8) | 21.5 (5.8) |
| Mean temperature (SD), °*C* | 37.4 (0.9) | 37.2 (0.9) | 37.5 (1) | 37.6 (0.9) | 37.3 (0.8) |
| Admitted to ward, *n (%)* | 171 (94.5) | 39 (92.9) | 56 (98.2) | 47 (90.4) | 53 (98.1) |
| Admitted to ICU, *n (%)* | 10 (5.5) | 3 (7.1) | 1 (1.8) | 5 (9.6) | 1 (1.9) |
| **Comorbid conditions, *n (%)*** | | | | | |
| Chronic cardiac disease | 28 (15.6) | 6 (14.6) | 12 (21.1) | 6 (11.5) | 9 (16.7) |
| Chronic pulmonary disease | 10 (5.6) | 4 (9.8) | 3 (5.3) | 2 (3.8) | 1 (1.9) |
| Ever smoking | 71 (39.4) | 16 (39) | 27 (47.4) | 18 (34.6) | 21 (38.9) |
| Hypertension | 55 (30.6) | 15 (36.6) | 14 (24.6) | 17 (32.7) | 18 (33.3) |
| Diabetes | 31 (17.2) | 9 (22) | 9 (15.8) | 7 (13.5) | 8 (14.8) |
| Obesity (BMI >30 $kg/m^2$) | 44 (26.8) | 11 (28.9) | 9 (18.4) | 16 (32.7) | 11 (22) |
| **Comedication, *n (%)*** | | | | | |
| Steroids | 8 (4.5) | 1 (2.4) | 2 (3.6) | 2 (3.8) | 4 (7.4) |
| Other immunomodulatory drugs | 8 (4.5) | 1 (2.4) | 1 (1.8) | 2 (3.8) | 4 (7.4) |
| ACE inhibitors | 12 (6.7) | 2 (4.9) | 4 (7.1) | 1 (1.9) | 7 (13) |
| Angiotensin II receptor blockers | 30 (16.8) | 11 (26.8) | 7 (12.5) | 9 (17.3) | 7 (13) |
| **Hematology** | | | | | |
| Median hemoglobin level (IQR), *g/L* | 132 (123–141) | 132 (124–143) | 136 (129–141) | 130 (120–141) | 132 (126–140) |
| Median leukocyte count (IQR), × $10^9$ *cells/L* | 6.2 (4.7–8.7) | 6 (4.9–8.7) | 6.3 (4.8–8) | 6.6 (4.4–9.2) | 6 (4.8–8.5) |
| Median neutrophil count (IQR), × $10^9$ *cells/L* | 4.3 (3.0–6.6) | 4.3 (2.7–6.8) | 4.5 (2.9–6.6) | 4.9 (3–6.8) | 4.1 (2.8–6.3) |
| Median lymphocyte count (IQR), × $10^9$ *cells/L* | 1.1 (0.8–1.4) | 1.1 (0.9–1.5) | 1 (0.8–1.5) | 1 (0.7–1.3) | 1.1 (0.9–1.4) |
| Median platelet count (IQR), × $10^9$ *cells/L* | 203 (159–271) | 206 (162–268) | 203 (166–269) | 184 (151.5–270) | 208 (167–276) |
| **Inflammatory markers** | | | | | |
| Median C-reactive protein level (IQR), *mg/L* | 70 (36.5–137.5) | 70 (39.8–139.2) | 82 (33–141.8) | 76 (47–133) | 65.5 (34–124) |
| Median procalcitonin level (IQR), *μg/L* | 0.12 (0.1–0.21) | 0.13 (0.1–0.2) | 0.11 (0.1–0.3) | 0.13 (0.1–0.26) | 0.1 (0.1–0.2) |
| Median ferritin level (IQR), *μg/L* | 613 (319–1173) | 695 (343–1262) | 589 (318–1077) | 626 (295–1298) | 531.5 (321–991) |
| **Other** | | | | | |
| Median LDH level (IQR), *μkat/L* | 4.6 (3.6–6.0) | 4.7 (3.9–6.7) | 4.0 (3.3–5.9) | 4.8 (3.9–6.0) | 4.2 (3.3–5.4) |
| Median D-dimer level (IQR), *nmol/L* | 3.7 (2.5–6.1) | 4.2 (2.6–5.6) | 2.7 (2.0–4.8) | 4.9 (2.7–8.4) | 4.2 (2.7–6.9) |
| Median AST level (IQR), *U/L* | 39 (27.2–59) | 49 (34.5–77) | 34 (24–54.8) | 39 (28–59) | 32 (24–53) |
| Median ALT level (IQR), *U/L* | 33 (20–58) | 41 (22–69.2) | 31 (20.5–54) | 33 (22–53) | 30 (18.8–52) |
| Median creatinine/eGFR (IQR), *mL/min/1.73* $m^2$ | 89.7 (74.2–105.5) | 90.6 (77.2–106.2) | 89.7 (79.8–105.6) | 86.3 (67.5–101.2) | 91.8 (82.7–104.7) |
| **Viral load (oropharynx)** | | | | | |
| Mean viral load (SD), $log_{10}$ *count/1000 cells* | 2 (1.6) | 1.6 (1.6) | 2.3 (1.8) | 2.3 (1.5) | 2 (1.5) |

*Continued on following page*

*Table1*–Continued

| Characteristic | All Patients (*n* = 181) | Remdesivir vs. Its Control | | HCQ vs. Its Control | |
|---|---|---|---|---|---|
| | | Remdesivir + SoC (*n* = 42) | SoC (*n* = 57) | HCQ + SoC (*n* = 52) | SoC (*n* = 54) |
| **Anti-SARS-CoV-2 antibodies, *n* (%)** | | | | | |
| Seroconverted (RBD ≥5) | 60 (47.2) | 14 (42.4) | 18 (46.2) | 15 (42.9) | 20 (54.1) |
| Seroconverted (nucleocapsid ≥10) | 50 (39.4) | 11 (33.3) | 14 (35.9) | 15 (42.9) | 17 (45.9) |

ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; ICU = intensive care unit; IQR = interquartile range; LDH = lactate dehydrogenase; P–F = $Po_2$–$Flo_2$; RBD = receptor-binding domain; SoC = standard of care.
* Missing values are given in Appendix Table 1 (available at Annals.org).

difference. As sensitivity analyses, we added simpler between-group analyses using*t* tests and Wilcoxon tests on the change from baseline to day 7 and day 10. Subgroup analyses were done by including the subgroup as an interaction term with the treatment term in the mixed model. High and low baseline subgroups were defined by the overall median. The 90-day outcomes on antibodies against SARS-CoV-2 were analyzed using the*t* distribution. Durations of mechanical ventilation and ICU stay are descriptively presented using cumulative probability plots.

Methods for reverse transcriptase PCR of SARS-CoV-2 quantification and for measurement of antibodies against SARS-CoV-2 are described inAppendix 2 (available at Annals.org).

All statistical analyses were done with Stata, version 16.1 (StataCorp), and R, version 4.0.3 (R Foundation), and all code is available in a public repository (https://doi.org/10.17605/OSF.IO/V8GZ6), together with the protocol and statistical analysis plan (**Supplement**).

### Ethics

The trial protocol was approved by the regional ethics committee (118684) and by the Norwegian Medicines Agency (20/04950-23) and was overseen by an independent data and safety monitoring board. Informed consent was obtained from each patient or from the patient's legally authorized representative if the patient was not able to provide consent. Further details regarding design, overview, and analyses can be found in the protocol and statistical analysis plan (**Supplement**).

### Role of the Funding Source

The National Clinical Therapy Research in the Specialist Health Services funded this research but had no role in design, analysis, management, interpretation of data, or preparation or approval of the manuscript, nor did it play any other conducting role.

## RESULTS

### Participant Flow

From 28 March to 4 October 2020, a total of 185 patients from 23 hospitals in Norway were enrolled in the trial; according to the National Intensive Care and Pandemic Registry, this accounts for 24% of all patients hospitalized with SARS-CoV-2 in Norway during the study period (9). Four patients were excluded because of the absence of postrandomization information. Of the 181 patients who were randomly assigned, 87 were assigned to receive SoC and 97 to receive treatment with either remdesivir (*n* = 43) or HCQ (*n* = 54), with an SoC group matched to each treatment group (**Figure 1**). A total of 149 patients (remdesivir, *n* = 34; HCQ, *n* = 41; and SoC, *n* = 74) completed the 3 months of follow-up, whereas 32 patients were lost to follow-up because of death (*n* = 12); voluntary discontinuation (*n* = 7); other reasons, including emigration or progression of underlying cancer (*n* = 7); or unknown reasons (*n* = 6) (**Figure 1**). Not all variables were available in all patients, and missing data on patient characteristics and baseline values are reported in **Appendix Table 1** (available at Annals.org).

The baseline demographic and disease characteristics were generally balanced among the treatment groups (**Table 1**). However, the percentage of patients with a P–F ratio less than 40 kPa was higher in the remdesivir and HCQ groups than in their respective SoC groups, whereas the percentage that used angiotensin-converting enzyme inhibitors was lower in the 2 treatment groups. Most of the patients were men (65.7%), and the mean age was 59.8 years. On average, patients were hospitalized within 8 days of symptom onset. Forty-three percent had respiratory failure (that is, P–F ratio <40 kPa). At hospital admittance, SARS-CoV-2 antibodies to receptor-binding domain were present in 47% of patients and antibodies to nucleocapsid antigen in 39.4% of patients. Median treatment duration was 5 days (interquartile range [IQR], 3 to 9 days) for remdesivir and HCQ and 6 days (IQR, 3 to 9 days) for SoC, and the patients received a median total dose of 700 mg (IQR, 500 to 1050 mg) of remdesivir and 5400 mg (IQR, 3500 to 8500 mg) of HCQ. Most of the patients were discharged home (*n* = 137), whereas 25 were discharged to a convalescence stay or nursing home (**Appendix Table 2**, available at Annals.org).

### Primary and Secondary Efficacy Outcome Shared With the WHO Solidarity Trial

All-cause, in-hospital mortality was 6.6%, considerably lower than the overall mortality in the WHO Solidarity trial (11.8%). Nonetheless, no differences in mortality, including in-hospital mortality and mortality at 28 days or 60 days, were seen between the remdesivir or HCQ group and its respective SoC group (**Table 2**). Note, however, that the sample size was low, and a corresponding trial would have required a true treatment difference of 21% to reach 80% power.

Like the WHO Solidarity study, we found no effects of remdesivir or HCQ on the rate of ICU admission, use of mechanical ventilation during hospitalization, or time to receipt

*Table 2.* Mortality, Admission to ICU, and Mechanical Ventilation

| Variable | Treatment + SoC (95% CI), % | SoC (95% CI), % | Relative Risk (95% CI)* | Hazard Ratio (95% CI)* | Estimated Marginal Risk Difference (95% CI), *percentage points*† |
|---|---|---|---|---|---|
| **Remdesivir vs. its SoC** | | | | | |
| Mortality during hospitalization | 7.1 (1.8 to 17.5) | 7.0 (2.2 to 15.6) | 1.0 (0.2 to 4.6) | 1.0 (0.4 to 2.9) | |
| 28-d mortality | 2.4 (0.1 to 10.1) | 5.3 (1.3 to 13.1) | – | – | −2.9 (−10.3 to 4.5) |
| 60-d mortality | 7.1 (1.8 to 17.5) | 5.3 (1.3 to 13.1) | – | – | 1.9 (−7.8 to 11.6) |
| Admission to ICU during hospitalization | 19.0 (9.2 to 32.6) | 19.3 (10.5 to 30.8) | – | – | −0.3 (−15.9 to 15.4) |
| Mechanical ventilation during hospitalization | 9.5 (3.1 to 20.8) | 7.0 (2.2 to 15.6) | – | – | 2.5 (−8.6 to 13.6) |
| Time to receipt of mechani cal ventilation | – | – | 1.4 (0.4 to 5.8) | 1.3 (0.5 to 3.4) | – |
| **HCQ vs. its SoC** | | | | | |
| Mortality during hospitalization | 7.5 (2.4 to 16.7) | 3.6 (0.6 to 10.6) | 2.2 (0.4 to 10.8) | 3.1 (0.3 to 34.4) | |
| 28-d mortality | 7.5 (2.4 to 16.7) | 1.8 (0.1 to 7.6) | – | – | 5.8 (−2.2 to 13.7) |
| 60-d mortality | 7.5 (2.4 to 16.7) | 1.8 (0.1 to 7.6) | – | – | 5.8 (−2.2 to 13.7) |
| Admission to ICU during hospitalization | 22.6 (12.8 to 35) | 16.1 (8.1 to 27.1) | – | – | 6.6 (−8.2 to 21.4) |
| Mechanical ventilation during hospitalization | 15.1 (7.2 to 26.3) | 10.7 (4.4 to 20.5) | – | – | 4.4 (−8.2 to 17.0) |
| Time to receipt of mechanical ventilation | – | – | 2.1 (0.7 to 6.2) | 3.0 (0.6 to 16.3) | – |

HCQ = hydroxychloroquine; ICU = intensive care unit; SoC = standard of care.
* Based on time-to-event analyses (log-rank and Cox regression).
† Based on logistic regression analyses for dichotomous end points.

of mechanical ventilation (Table 2). Duration of ICU stay and mechanical ventilation, reported as cumulative probability plots, also showed no differences between the treatments (Appendix Figure 1, available at Annals.org).

Two patients in the HCQ group developed a prolonged rate-corrected QT interval, and the treatment was withdrawn. Most other serious adverse events were related to respiratory failure and interpreted as attributable to disease progression (Appendix Table 3, available at Annals.org). One suspected unexpected serious adverse reaction was reported in the remdesivir group (Appendix Table 3).

### Secondary End Points Specific to the NOR-Solidarity Trial

The most important secondary outcome in the NOR-Solidarity trial was viral load in the oropharynx. There was a general marked decrease in SARS-CoV-2 oropharyngeal load during the first week after randomization, with a similar decrease and levels after 10 days in the remdesivir, HCQ, and SoC groups (Figure 2). The differences between the treatment groups regarding the decrease rate during the first week and at day 10 were nominally in favor of SoC, with CIs excluding major effects on viral clearance for both active treatments. For sensitivity analyses, including box plots, see Appendix Figure 2 (available at Annals.org).

All groups of patients had improved respiratory function, reflected by an increase in P–F ratio, during the first week after randomization. However, the rate of improvement during the first 7 days was significantly (but only modestly) improved by remdesivir but not by HCQ compared with their SoC groups. At day 10, P–F ratio was not affected in any of the intervention groups compared with the SoC groups (Figure 3).

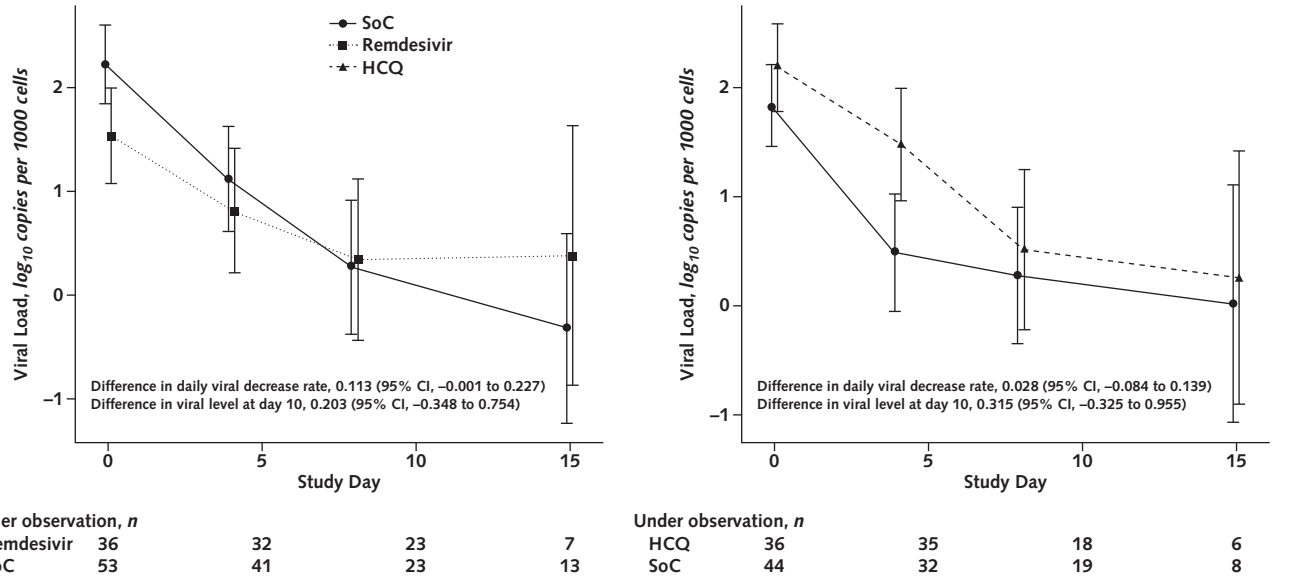
The patient group as a whole was at baseline characterized by markedly elevated plasma levels of CRP and ferritin, whereas they had decreased lymphocyte counts (Table 1). However, except for significantly more rapid decreases in levels of ferritin (both remdesivir and HCQ), lactate dehydrogenase (remdesivir), and procalcitonin (remdesivir) during the first week after randomization, and a significant lower CRP level in the remdesivir group (but higher in the HCQ group at day 10), the treatments had no marked or consistent effects on these inflammatory markers (Appendix Figures 3 and 4, available at Annals.org).

It could be hypothesized that the effect of remdesivir or HCQ on viral load would be dependent on symptom duration before hospitalization (≥7 vs. <7 days), the presence of SARS-CoV-2 antibodies, or high or low viral load at hospital admission. Of note, in these subgroup analyses, remdesivir did not exert any increased oropharyngeal viral clearance compared with SoC (Appendix Figure 5, available at Annals.org). Results were similar for HCQ (Appendix Figure 6, available at Annals.org). In addition, in subgroup analyses evaluating age (≥60 vs. <60 years) and degree of inflammation (ferritin and CRP; levels greater than or equal to median vs. lower than median) at baseline, we did not find any significant treatment effects on viral clearance by either remdesivir or HCQ versus its respective SoC (Appendix Figures 7 and 8, available at Annals.org).

## DISCUSSION

Recently published results of the WHO Solidarity study indicated that neither remdesivir nor HCQ had any

***Figure 2.*** Efficacy of viral clearance by remdesivir and HCQ.




Viral measurement was done by quantitative polymerase chain reaction testing of SARS-CoV-2 in the oropharynx. Viral load is given as the log value in 1000 cells. Viral clearance is expressed as an average decrease rate during the first week after randomization. Treatment effects are given as estimated differences in daily viral decrease rates between the remdesivir or HCQ group and its respective SoC during the first week, and in differences in viral load at day 10. The number of patients under observation at each time point (days 0, 3–5, 7–9, and 12–16) is indicated separately by study group. Data are given as means and 95% CIs. HCQ = hydroxychloroquine; SoC = standard of care.

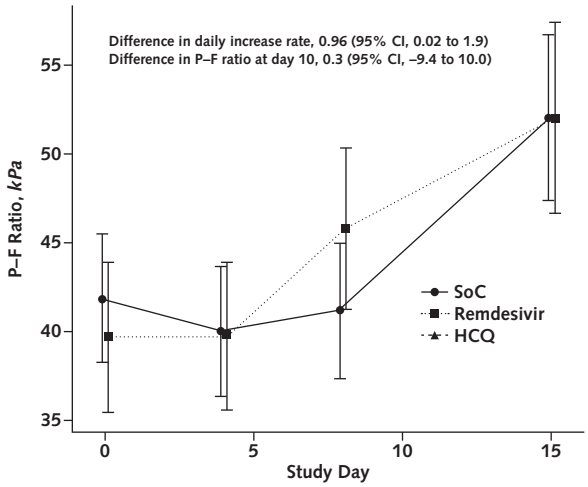
effect on mortality, the need for mechanical ventilation, or duration of hospital stay (1). The analyses of the NOR-Solidarity trial are consistent with the main findings of that report. In addition, we found no significant effects of either remdesivir or HCQ on the rate of SARS-CoV-2 clearance in oropharyngeal samples. This lack of antiviral effect was also corroborated when examining the influence of relevant baseline characteristics, such as age, symptom duration, degree of viral load, and presence of antibodies against SARS-CoV-2.

In addition to a large difference in sample size and only remdesivir and HCQ used as active treatment groups in NOR-Solidarity, the main difference between the trials was substantially lower mortality in the NOR-Solidarity trial (6.6% vs. 11.8% after 28 days). However, mortality in NOR-Solidarity was equal to that in data from the National Intensive Care and Pandemic Registry (9). In Norway, lockdown policies were effectively introduced during the initial phase of the pandemic, reducing pressure on hospital and health care systems, which may explain the lower mortality—in particular, the favorably lower ICU mortality (18.4%)—than in other countries (10). Some differences in the presence of comorbid conditions (for example, diabetes [25% vs. 17.2%] and chronic heart disease [21% vs. 15.6%], from WHO Solidarity vs. NOR-Solidarity, respectively) (1) could also have contributed to lower mortality in the NOR-Solidarity population. Nevertheless, we found no effect on mortality, rate of ICU admission, or need for mechanical ventilation, which was consistent with the overall results of the WHO Solidarity study.

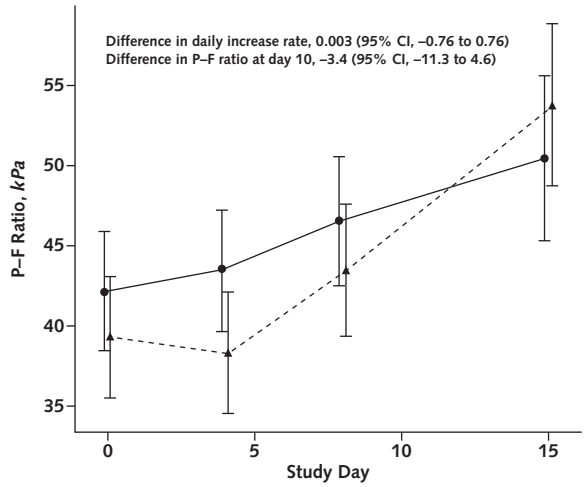
Despite the early emergence of reports that both remdesivir and HCQ effectively exerted strong antiviral activities against SARS-CoV-2 in preclinical models (11), our results show no antiviral effects of these drugs in hospitalized patients. Previously, Wang and colleagues (12) found no effect on SARS-CoV-2 clearance in 155 hospitalized patients receiving remdesivir compared with 78 patients receiving placebo. Moreover, Lyngbakken and colleagues (13) showed no antiviral effects of HCQ in 27 hospitalized patients compared with 26 patients receiving SoC. It has been claimed that these antiviral drugs, and in particular remdesivir, could be important in the early stages of COVID-19, before clinical progression to a state of hyperinflammation (14). However, we found no significant antiviral effects of remdesivir or HCQ, even in patients with symptom duration less than 7 days or baseline CRP and ferritin levels below median levels in the patient cohort. Moreover, the presence of SARS-CoV-2 antibodies or high or low viral load at hospital admission did not influence the potential antiviral effects of these drugs. Much focus has been directed at the use of remdesivir in hospitalized patients with moderate COVID-19, but the present data suggest that only a study of even earlier intervention (that is, in an outpatient, primary care setting), if any, would be warranted to rule out any antiviral effects of remdesivir in patients with COVID-19. Our data underscore the gap between preclinical and clinical studies on remdesivir (15).

The widespread use of HCQ in the first phase of the pandemic came to a quick halt after negative results in several large trials. First the RECOVERY trial and later the WHO Solidarity study demonstrated lack of any material

***Figure 3.*** Effect of remdesivir and HCQ on the degree of respiratory failure assessed by P–F ratio.




| Under observation, *n* | | | | |
|---|---|---|---|---|
| Remdesivir | 42 | 42 | 22 | 28 |
| SoC | 57 | 57 | 36 | 43 |




| Under observation, *n* | | | | |
|---|---|---|---|---|
| HCQ | 50 | 52 | 31 | 40 |
| SoC | 54 | 54 | 33 | 47 |

P–F ratios were calculated on the basis of estimated levels of Po2 and FIo2. In patients missing arterial oxygen tension, Po2 was approximated from peripheral O2 saturation according to the table stated in the analysis plan. Likewise, FIo2 in patients not supported by mechanical ventilation, noninvasive mechanical ventilation, or high-flow oxygen therapy was approximated from supplementation of oxygen as described in the analysis plan. Treatment effects are given as estimated differences in daily P–F ratio increase rates between the remdesivir or HCQ group and its respective SoC during the first week after randomization, and in differences in P–F ratio at day 10. The number of patients under observation at each time point (days 0, 3–5, 7–9, and 12–16) is indicated separately by study group. Data are given as means and 95% CIs. HCQ = hydroxychloroquine; P–F = Po2–FIo2; SoC = standard of care.

benefit of this drug in the treatment of COVID-19 (1, 2). Despite concerns about cardiac toxicity related to the loading dose of HCQ (16), we observed no grade 4 adverse effects related to either HCQ or remdesivir, although 2 patients in the HCQ group developed a prolonged rate-corrected QT interval resulting in treatment withdrawal. However, the number of patients included in this trial was too small to adequately address safety issues.

The study has both strengths and limitations. Strengths include participation of most hospitals in Norway, ensuring enrollment of a large proportion of the patients who were hospitalized during the study period. Because this was a pragmatic trial in a real-world clinical setting, our results may be generalizable to similar patient populations. However, the study also has many limitations. Despite being a randomized controlled trial with blinded analyses of all relevant data, it did not include a placebo group. Relatively few patients were included, and CIs were wide enough to include moderate effects. Our conclusion, and particularly our subgroup analyses, should therefore be interpreted with caution. Not all data were available from all patients at all time points. Finally, patients were discharged from the hospital at the discretion of the treating physician. Accordingly, the median duration of hospitalization was 5 to 6 days, and most of the patients did not receive the full treatment length of the tested medication, although recent studies have found no statistically significant difference between a 5-day course and a 10-day course of remdesivir (17).

In conclusion, the overall lack of effect of remdesivir and HCQ on the clinical course of patients hospitalized for COVID-19 was accompanied by a paucity of effect on SARS-CoV-2 viral clearance in the oropharynx. Our findings question the antiviral potential of these drugs in hospitalized patients with COVID-19.

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**Data Sharing Statement:** The following data will be made available with publication: deidentified participant data (contact Andreas Barratt-Due; e-mail, andreas.barrattdue@gmail.com). The following supporting documents will be made available with publication: study protocol (Supplement, available at Annals.org). These data will be made available to researchers whose proposed use of the data has been approved. Data will be available for individual patient data meta-analysis, comparable analysis, or further subanalysis. Data will be available after approval of a proposal and after a signed access agreement or data sharing agreement in order to maintain data integrity.

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## References

1. **Pan H, Peto R, Henao-Restrepo AM, et al; WHO Solidarity Trial Consortium.** Repurposed antiviral drugs for Covid-19 – interim WHO Solidarity trial results. N Engl J Med. 2021;384:497-511. [PMID: 33264556] doi:10.1056/NEJMoa2023184

2. **Horby P, Mafham M, Linsell L, et al; RECOVERY Collaborative Group.** Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med. 2020;383:2030-2040. [PMID: 33031652] doi:10.1056/NEJMoa2022926

3. **Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members.** Remdesivir for the treatment of Covid-19 – final report. N Engl J Med. 2020;383:1813-1826. [PMID: 32445440] doi:10.1056/NEJMoa2007764

4. **Gordon PA, Winer JB, Hoogendijk JE, et al.** Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. Cochrane Database Syst Rev. 2012:CD003643. [PMID: 22895935] doi:10.1002/14651858.CD003643.pub4

5. **Wang M, Cao R, Zhang L, et al.** Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro [Letter]. Cell Res. 2020;30:269-271. [PMID: 32020029] doi:10.1038/s41422-020-0282-0

6. **Rochwerg B, Siemieniuk RA, Agoritsas T, et al.** A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379. [PMID: 32887691] doi:10.1136/bmj.m3379

7. **Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine.** No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19. Nuffield Department of Population Health. 5 June 2020. Accessed at www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19 on 5 June 2020.

8. **World Health Organization.** WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. 4 July 2020. Accessed at www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19 on 4 July 2020.

9. National Intensive Care and Pandemic Registry. Accessed at www.kvalitetsregistre.no/register/skade-og-intensiv/norsk-intensiv-og-pandemiregister on 4 May 2021.

10. **Laake JH, Buanes EA, Småstuen MC, et al.** Characteristics, management and survival of ICU patients with coronavirus disease-19 in Norway, March-June 2020. A prospective observational study. Acta Anaesthesiol Scand. 2021;65:618-628. [PMID: 33501998] doi:10.1111/aas.13785

11. **Bimonte S, Crispo A, Amore A, et al.** Potential antiviral drugs for SARS-cov-2 treatment: preclinical findings and ongoing clinical research. In Vivo. 2020;34:1597-1602. [PMID: 32503817] doi:10.21873/invivo.11949

12. **Wang Y, Zhang D, Du G, et al.** Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395:1569-1578. [PMID: 32423584] doi:10.1016/S0140-6736(20)31022-9

13. **Lyngbakken MN, Berdal JE, Eskesen A, et al.** A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. Nat Commun. 2020;11:5284. [PMID: 33082342] doi:10.1038/s41467-020-19056-6

14. **Dolin R, Hirsch MS.** Remdesivir – an important first step [Editorial]. N Engl J Med. 2020;383:1886-1887. [PMID: 32459913] doi:10.1056/NEJMe2018715

15. **Maciorowski D, Idrissi SZE, Gupta Y, et al.** A review of the preclinical and clinical efficacy of remdesivir, hydroxychloroquine, and lopinavir-ritonavir treatments against COVID-19. SLAS Discov. 2020;25:1108-1122. [PMID: 32942923] doi:10.1177/2472555220958385

16. **White NJ, Watson JA, Hoglund RM, et al.** COVID-19 prevention and treatment: a critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. PLoS Med. 2020;17:e1003252. [PMID: 32881895] doi:10.1371/journal.pmed.1003252

17. **Spinner CD, Gottlieb RL, Criner GJ, et al; GS-US-540-5774 Investigators.** Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 2020;324:1048-1057. [PMID: 32821939] doi:10.1001/jama.2020.16349

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## Appendix 2: Materials and Methods

### RNA Extraction, Reverse Transcriptase PCR, and SARS-CoV-2 Quantification

Total nucleic acids were extracted from 200-µL oropharyngeal samples (MagNA Pure 96 system, MagNA Pure 96 DNA and Viral NA Small Volume Kit; Roche), and eluted in 100 µL. Bacteriophage MS2 RNA (Merck, Sigma-Aldrich) was added before extraction as an internal control. SARS-CoV-2 RNA real-time reverse transcriptase PCR targeting the viral envelope gene was done as described by Corman and colleagues (18), using MS2 primers according to Dreier and colleagues (19), on the AriaDx PCR instrument (Agilent Technologies). The

quality and cellular quantification of oropharyngeal samples were analyzed using the CELL Control r-gene kit (bioMérieux) according to the manufacturers' instructions. Viral load was calculated using standard dilution series of purified RNA from the Frankfurt1 strain, provided by the European Virus Archive Global. Viral loads for respiratory samples were normalized according to the cellular quantification as $\log_{10}$ RNA copies per 1000 cells.

### Measurement of Antibodies Against SARS-CoV-2

A multiplexed, bead-based, flow cytometric assay, called microsphere affinity proteomics, was adapted for detection of SARS-CoV-2 antibodies (20). Thus, amine-functionalized polymer beads were color-coded with fluorescent dyes, as described earlier, and reacted successively with amine-reactive biotin (Sulfo-NHS-LC-Biotin, Proteochem) and NeutrAvidin (Thermo Fisher). A DNA construct encoding the receptor-binding domain of spike-1 protein from SARS-CoV-2 was provided by Florian Krammer, and the described protocol was used to produce recombinant protein in Expi293F cells (Thermo Fisher) (21). Bacterially expressed full-length nucleocapsid from SARS-CoV-2 was purchased from Prospec Bio (www.prospecbio.com). Viral proteins solubilized in phosphate-buffered saline were biotinylated chemically using a 4:1 molar ratio of Sulfo-NHS-LC-Biotin to protein. Free biotin was removed using G50 Sephadex spin columns. Biotinylated proteins were bound to NeutrAvidin-coupled microspheres with fluorescent barcodes. Beads with NeutrAvidin only were used as reference for background binding. Sera were diluted 1:1000 in phosphate-buffered saline containing 1% Tween 20, 1% bovine serum albumin, 10 μg/mL d-biotin, and 10 μg/mL NeutrAvidin (Thermo Fisher) and were incubated with a mixture of antigen-coupled and NeutrAvidin-only beads for 1 hour at 22 , C under constant agitation. The beads were washed twice in PBT, labeled with R-phycoerythrin–conjugated goat anti-human IgG-Fc (Jackson Immunoresearch) for 20 minutes, washed again, and analyzed by flow cytometry (Attune NxT, Thermo Fisher). Specific binding was measured as the ratio of R-phycoerythrin fluorescence intensity of antigen-coupled beads and NeutrAvidin-only beads, with a ratio of 5 and 10 defining the cutoff for a positive antibody against RBP and nucleocapsid, respectively. Reference panels containing samples from 287 individuals with PCR-confirmed SARS-CoV-2 infection and 1343 prepandemic samples were used to set the cutoff. With a cutoff set to obtain a specificity of 100%, the sensitivity was 84%, and 92% when including borderline values.

### Web References


18. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020; 25. [PMID: 31992387] doi:10.2807/1560-7917.ES.2020.25.3.2000045

19. Dreier J, Störmer M, Kleesiek K. Use of bacteriophage MS2 as an internal control in viral reverse transcription-PCR assays. J Clin Microbiol. 2005;43:4551-7. [PMID: 16145106]

20. Holter JC, Pischke SE, de Boer E, et al. Systemic complement activation is associated with respiratory failure in COVID-19 hospitalized patients. Proc Natl Acad Sci U S A. 2020;117:25018-25025. [PMID: 32943538] doi:10.1073/pnas.2010540117

21. Amanat F, Stadlbauer D, Strohmeier S, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. Nat Med. 2020;26:1033-1036. [PMID: 32398876] doi:10.1038/s41591-020-0913-5

*Appendix Table 1.* Missing Data on Patient Characteristics and Baseline Values*

| Characteristic | All Patients (*n* = 181) | Remdesivir vs. Its Control | | HCQ vs. Its Control | |
|---|---|---|---|---|---|
| | | Remdesivir + SoC (*n* = 42) | SoC (*n* = 57) | HCQ + SoC (*n* = 52) | SoC (*n* = 54) |
| **Demographics** | | | | | |
| Age | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Female sex | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| BMI | 17 (9.4) | 4 (9.5) | 8 (14) | 3 (5.8) | 4 (7.4) |
| Symptom duration before admission | 1 (0.6) | 1 (2.4) | 0 (0) | 0 (0) | 0 (0) |
| P–F ratio at admission | 2 (1.1) | 0 (0) | 0 (0) | 2 (3.8) | 0 (0) |
| P–F ratio <40 kPa | 2 (1.1) | 0 (0) | 0 (0) | 2 (3.8) | 0 (0) |
| Respiratory rate | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Temperature | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Admitted to ward | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Admitted to ICU | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Comorbid conditions** | | | | | |
| Chronic cardiac disease | 1 (0.06) | 1 (2.4) | 0 (0) | 0 (0) | 0 (0) |
| Chronic pulmonary disease | 1 (0.06) | 1 (2.4) | 0 (0) | 0 (0) | 0 (0) |
| Ever smoking | 1 (0.06) | 1 (2.4) | 0 (0) | 0 (0) | 0 (0) |
| Hypertension | 1 (0.06) | 1 (2.4) | 0 (0) | 0 (0) | 0 (0) |
| Diabetes | 1 (0.06) | 1 (2.4) | 0 (0) | 0 (0) | 0 (0) |
| Obesity (BMI >30 kg/m$^2$) | 17 (9.4) | 4 (9.5) | 8 (14) | 3 (5.8) | 4 (7.4) |
| **Comedication** | | | | | |
| Steroids | 2 (1.1) | 1 (2.4) | 1 (1.8) | 0 (0) | 0 (0) |
| Other immunomodulatory drugs | 2 (1.1) | 1 (2.4) | 1 (1.8) | 0 (0) | 0 (0) |
| ACE inhibitors | 2 (1.1) | 1 (2.4) | 1 (1.8) | 0 (0) | 0 (0) |
| Angiotensin II receptor blockers | 2 (1.1) | 1 (2.4) | 1 (1.8) | 0 (0) | 0 (0) |
| **Hematology** | | | | | |
| Hemoglobin level | 3 (1.7) | 1 (2.4) | 1 (1.8) | 1 (1.9) | 0 (0) |
| Leukocyte count | 1 (0.6) | 1 (2.4) | 0 (0) | 0 (0) | 0 (0) |
| Neutrophil count | 10 (5.5) | 3 (7.1) | 4 (7) | 2 (3.8) | 3 (5.6) |
| Lymphocyte count | 9 (5) | 2 (4.8) | 4 (7) | 2 (3.8) | 3 (5.6) |
| Platelet count | 3 (1.7) | 1 (2.4) | 1 (1.8) | 1 (1.9) | 1 (1.9) |
| **Inflammatory markers** | | | | | |
| C-reactive protein level | 2 (1.1) | 0 (0) | 1 (1.8) | 1 (1.9) | 0 (0) |
| Procalcitonin level | 58 (32) | 9 (21.4) | 18 (31.6) | 21 (40.4) | 19 (35.2) |
| Ferritin level | 9 (5) | 0 (0) | 3 (5.3) | 3 (5.8) | 4 (7.4) |
| **Other** | | | | | |
| LDH level | 8 (4.4) | 1 (2.4) | 5 (8.8) | 1 (1.9) | 4 (7.4) |
| D-dimer level | 19 (10.5) | 2 (4.8) | 8 (14) | 6 (11.5) | 7 (13) |
| AST level | 11 (6.1) | 2 (4.8) | 5 (8.8) | 3 (5.8) | 4 (7.4) |
| ALT level | 8 (4.4) | 2 (4.8) | 2 (3.5) | 3 (5.8) | 2 (3.7) |
| Creatinine/eGFR | 1 (0.6) | 0 (0) | 0 (0) | 1 (1.9) | 0 (0) |
| **Viral load (oropharynx)** | | | | | |
| Viral load | 48 (26.5) | 10 (23.8) | 12 (21.1) | 17 (32.7) | 11 (20.4) |
| **Anti–SARS-CoV-2 antibodies** | | | | | |
| Seroconverted (RBD ≥5) | 54 (29.8) | 9 (21.4) | 18 (31.6) | 17 (32.7) | 17 (31.5) |
| Seroconverted (nucleocapsid ≥10) | 54 (29.8) | 9 (21.4) | 18 (31.6) | 17 (32.7) | 17 (31.5) |

ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; ICU = intensive care unit; IQR = interquartile range; LDH = lactate dehydrogenase; P–F = $Po_2$–$FIo_2$; RBD = receptor-binding domain; SoC = standard of care.

* Values are numbers (percentages). This table corresponds with Table 1, indicating all missing values for the whole study population as well as the intervention groups and their respective, concurrent SoC groups.

*Appendix Table 2.* Patient Discharge Status*

| Discharged to | SoC (*n* = 87) | Remdesivir + SoC (*n* = 42) | HCQ + SoC (*n* = 52) | Total (*n* = 181) |
|---|---|---|---|---|
| Home | 64 (73.6) | 28 (66.7) | 37 (71.2) | 129 (71.3) |
| Home, requiring municipal assistance | 3 (3.4) | 2 (4.8) | 3 (5.8) | 8 (4.4) |
| Recreation stay | 3 (3.4) | 3 (7.1) | 2 (3.8) | 8 (4.4) |
| Municipal rehabilitation/nursing home | 8 (9.2) | 5 (11.9) | 4 (7.7) | 17 (9.4) |
| Local hospital | 1 (1.1) | 0 (0) | 0 (0) | 1 (0.6) |
| NK | 8 (9.2) | 4 (9.5) | 6 (11.5) | 18 (9.9) |

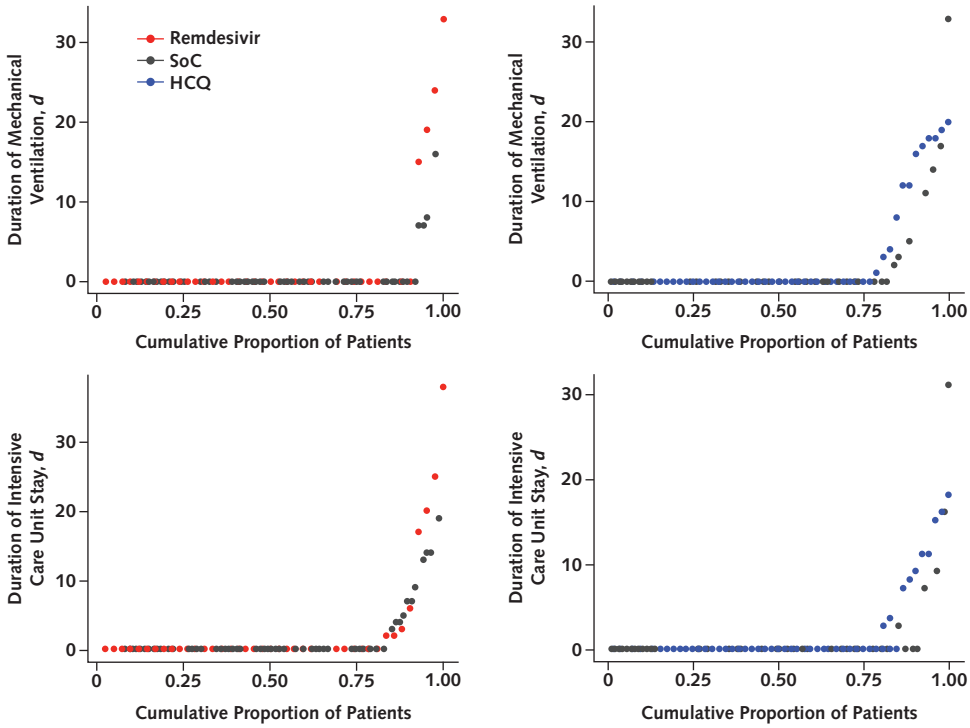
HCQ = hydroxychloroquine; NK = not known; SoC = standard of care.
* Data are absolute numbers (percentages).

*Appendix Table 3.* AEs, Safety Data, and SUSARs*

| Variable | SoC (*n* = 87) | Remdesivir + SoC (*n* = 42) | HCQ + SoC (*n* = 52) |
|---|---|---|---|
| **Total AEs, *n*** | 33 | 34 | 26 |
| Patients with AE | 22 (25.3) | 20 (38.5) | 16 (38.1) |
| Patients with >1 AE | 7 (8.0) | 6 (14.0) | 5 (9.3) |
| Patients with AEs, by system organ class | | | |
| Blood and lymphatic system disorders | 0 (0) | 0 (0) | 1 (1.9) |
| Cardiac disorders | 1 (1.1) | 2 (4.8) | 0 (0) |
| Gastrointestinal disorders | 2 (2.3) | 3 (7.1) | 4 (7.7) |
| General disorders and administration site conditions | 3 (3.4) | 2 (4.8) | 0 (0) |
| Hepatobiliary disorders | 1 (1.1) | 0 (0) | 0 (0) |
| Infections and infestations | 4 (4.6) | 0 (0) | 1 (1.9) |
| Injury, poisoning, and procedural complications | 2 (2.3) | 0 (0) | 0 (0) |
| Investigations | 3 (3.4) | 4 (9.5) | 6 (11.5) |
| Metabolic and nutritional disorders | 0 (0) | 0 (0) | 1 (1.9) |
| Musculoskeletal and connective tissue disorders | 0 (0) | 0 (0) | 2 (3.8) |
| Neoplasms: benign, malignant, and unspecified | 1 (1.1) | 0 (0) | 0 (0) |
| Nervous system disorders | 2 (2.3) | 2 (4.8) | 1 (1.9) |
| Renal and urinary disorders | 1 (1.1) | 0 (0) | 1 (1.9) |
| Respiratory, thoracic, and mediastinal disorders | 8 (9.2) | 6 (14.3) | 7 (13.5) |
| Skin and subcutaneous tissue disorders | 0 (0) | 2 (4.8) | 0 (0) |
| Vascular disorders | 1 (1.1) | 1 (2.4) | 1 (1.9) |
| | | | |
| **Serious AEs, *n*†** | 20 | 13 | 12 |
| Patients with serious AE | 13 (14.9) | 8 (15.4) | 10 (23.8) |
| Patients with serious AEs, by system organ class | | | |
| Gastrointestinal disorders | 1 (1.1) | 1 (2.4) | 0 (0) |
| General disorders and administration site conditions | 2 (2.3) | 1 (2.4) | 0 (0) |
| Hepatobiliary disorders | 1 (1.1) | 0 (0) | 0 (0) |
| Infections and infestations | 2 (2.3) | 0 (0) | 1 (1.9) |
| Injury, poisoning, and procedural complications | 2 (2.3) | 0 (0) | 0 (0) |
| Investigations | 1 (1.1) | 2 (4.8) | 2 (3.8) |
| Neoplasms: benign, malignant, and unspecified | 1 (1.1) | 0 (0) | 0 (0) |
| Nervous system disorders | 1 (1.1) | 1 (2.4) | 0 (0) |
| Renal and urinary disorders | 1 (1.1) | 0 (0) | 1 (1.9) |
| Respiratory, thoracic, and mediastinal disorders | 6 (6.9) | 5 (11.9) | 7 (13.5 |
| Patients with prolonged rate-corrected QT interval | 0 (0) | 0 (0) | 2 (3.8) |
| Withdrawal of treatment due to AE | 0 (0) | 0 (0) | 2 (3.8) |
| Event with fatal outcome | 0 (0) | 0 (0) | 0 (0) |
| | | | |
| **SUSAR** | | | |
| Hemorrhagic diarrhea | 0 (0) | 1 (2.4) | 0 (0) |

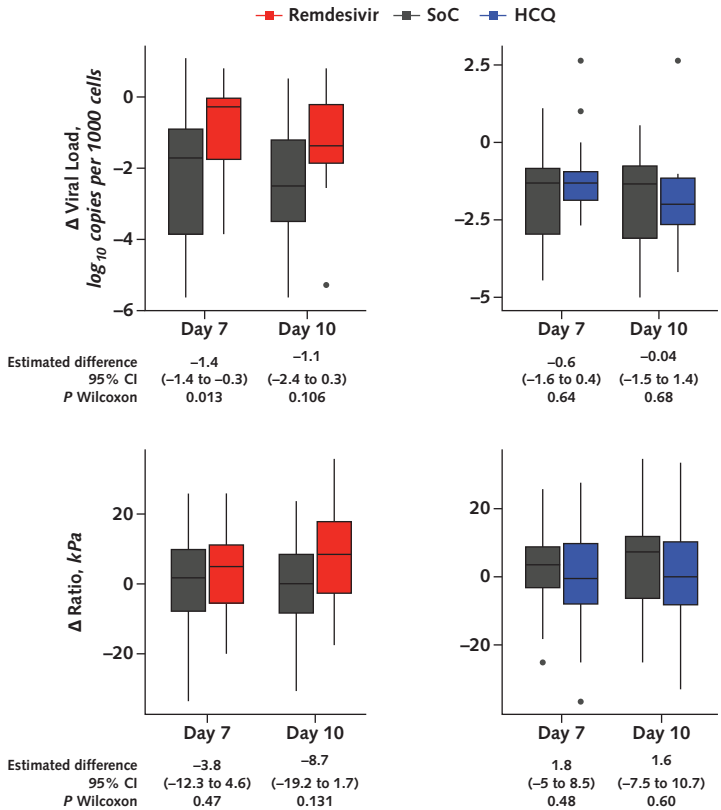
AE = adverse event; HCQ = hydroxychloroquine; SoC = standard of care; SUSAR = suspected unexpected serious adverse reaction.
* Values are numbers of patients (percentages) unless otherwise specified. An AE was considered serious if, in the view of either the investigator or the sponsor, any of the following outcomes occurred: death, a life-threatening AE, prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect or important medical events.
† Several events have may have occurred to 1 patient.

***Appendix Figure 1.*** Cumulative probability plots for duration of mechanical ventilation and intensive care unit stay.




HCQ = hydroxychloroquine; SoC = standard of care.

*Appendix Figure 2.* Box plots of change from baseline to days 7 and 10 in viral load and P–F ratio.




**Estimated Treatment Differences From Sensitivity Analyses**

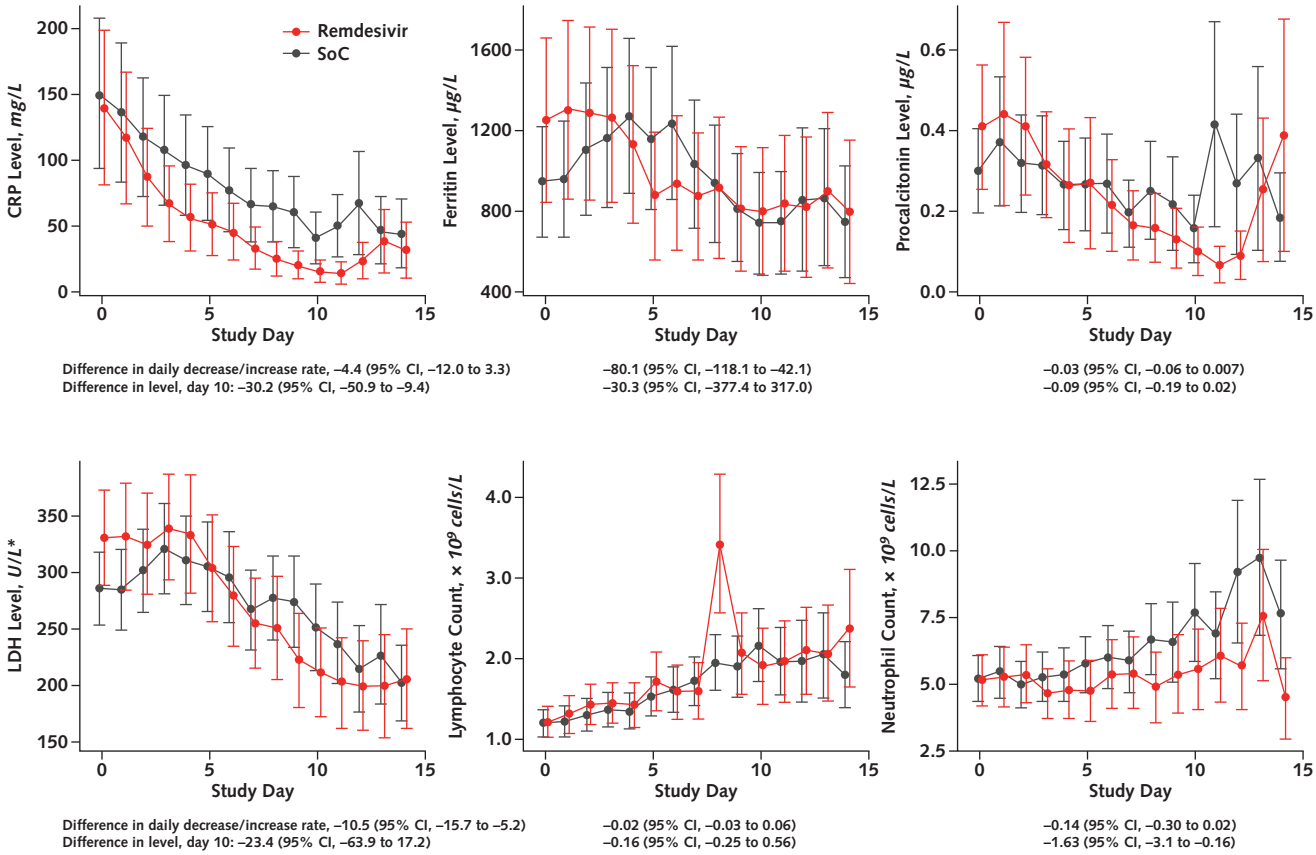
| End Point | Treatment | Time Point | Estimated Difference | 95% CI Lower Bound | 95% CI Upper Bound | *t* Test *P* Value | Wilcoxon *P* Value |
|---|---|---|---|---|---|---|---|
| Viral load* | HCQ | Day 7 | −0.6 | −1.6 | 0.4 | 0.24 | 0.64 |
| | | Day 10 | −0.04 | −1.5 | 1.4 | 0.96 | 0.68 |
| | Remdesivir | Day 7 | −1.4 | −2.4 | −0.3 | 0.011 | 0.013 |
| | | Day 10 | −1.1 | −2.4 | 0.3 | 0.107 | 0.106 |
| P–F ratio† | HCQ | Day 7 | 1.8 | −5.0 | 8.5 | 0.60 | 0.48 |
| | | Day 10 | 1.6 | −7.5 | 10.7 | 0.73 | 0.60 |
| | Remdesivir | Day 7 | −3.8 | −12.3 | 4.6 | 0.36 | 0.47 |
| | | Day 10 | −8.7 | −19.2 | 1.7 | 0.097 | 0.131 |

Horizontal lines denote the medians, and boxes denote the 25th and 75th percentiles. The whiskers extend to the largest value but no further than 1.5 times the interquartile range. Points outside the whiskers are considered outliers. We have used values between days 5 and 9 for the day 7 change, and between days 7 and 13 for the day 10 change. HCQ = hydroxychloroquine; P–F = Po2–Flo2.

* Positive values favor active treatment (HCQ or remdesivir).

† Negative values favor active treatment (HCQ or remdesivir).

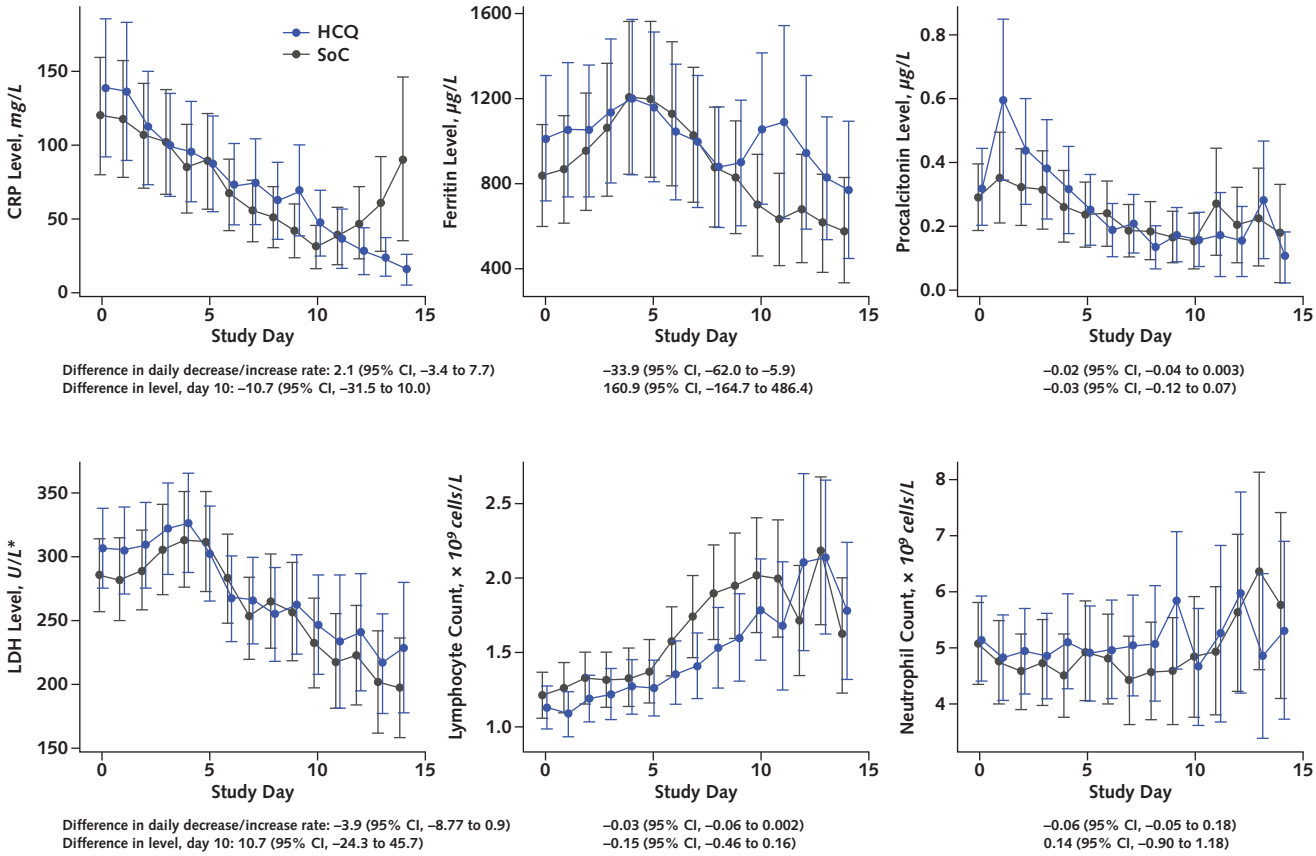
***Appendix Figure 3.*** Effect of remdesivir on inflammatory markers, lymphocytes, and neutrophils.




EDTA plasma samples were taken at randomization, between days 3 and 5, between days 7 and 9, and weekly thereafter. CRP, ferritin, procalcitonin, LDH, lymphocytes, and neutrophils were analyzed by the routine laboratory at the hospitals included in the study. Treatment effects are given as estimated differences in daily decrease rates (slopes) of the variables between remdesivir and its SoC during the first week, and in differences in point estimates at day 10. Results are presented as estimated treatment differences with 95% CIs. CRP = C-reactive protein; LDH = lactate dehydrogenase; SoC = standard of care.

* To convert to SI units (µkat/L), multiply by 0.0167.

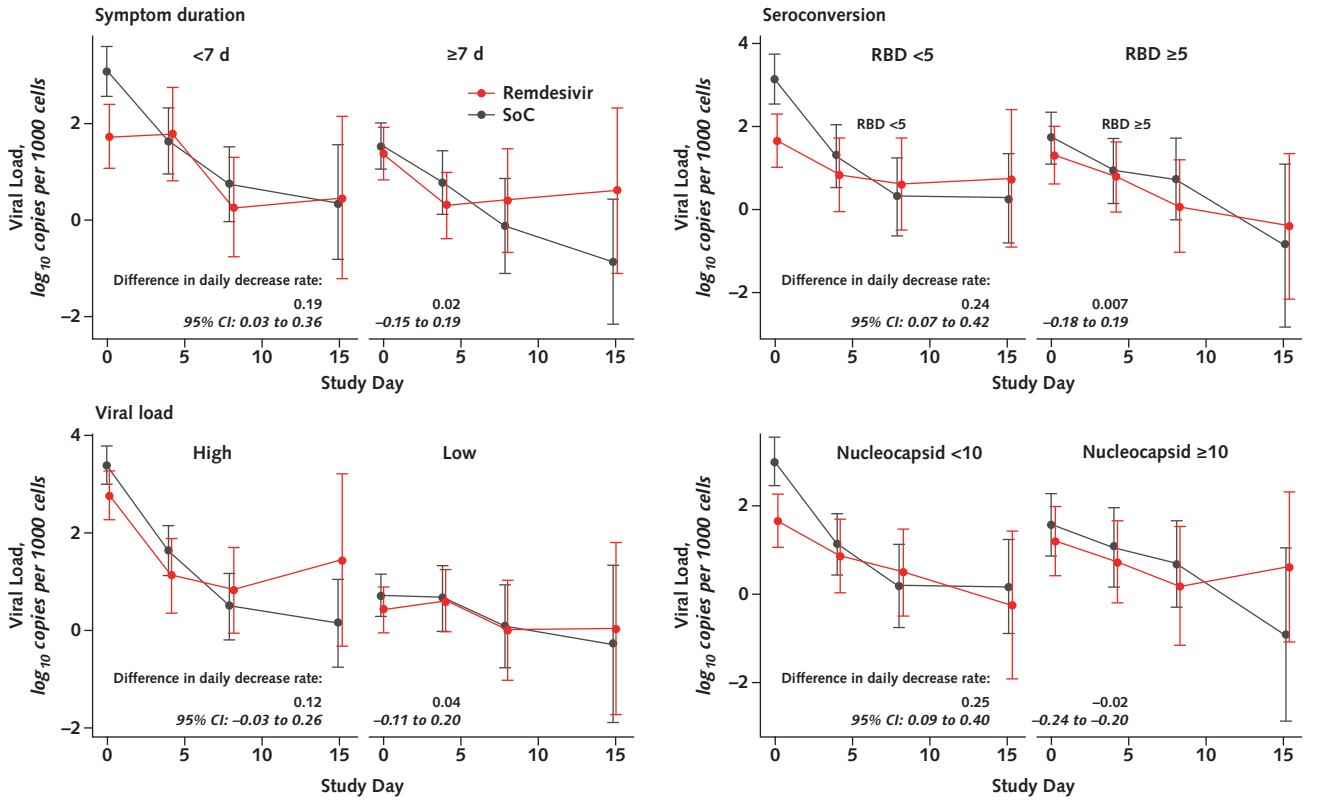
***Appendix Figure 4.*** Effect of HCQ on inflammatory markers, lymphocytes, and neutrophils.




EDTA plasma samples were taken at randomization, between days 3 and 5, between days 7 and 9, and weekly thereafter. CRP, ferritin, procalcitonin, LDH, lymphocytes, and neutrophils were analyzed by the routine laboratory at the hospitals included in the study. Treatment effects are given as estimated differences in daily decrease rates (slopes) of the variables between HCQ and its SoC during the first week, and in differences in point estimates at day 10. Results are presented as estimated treatment differences with 95% CIs. CRP = C-reactive protein; HCQ = hydroxychloroquine; LDH = lactate dehydrogenase; SoC = standard of care.

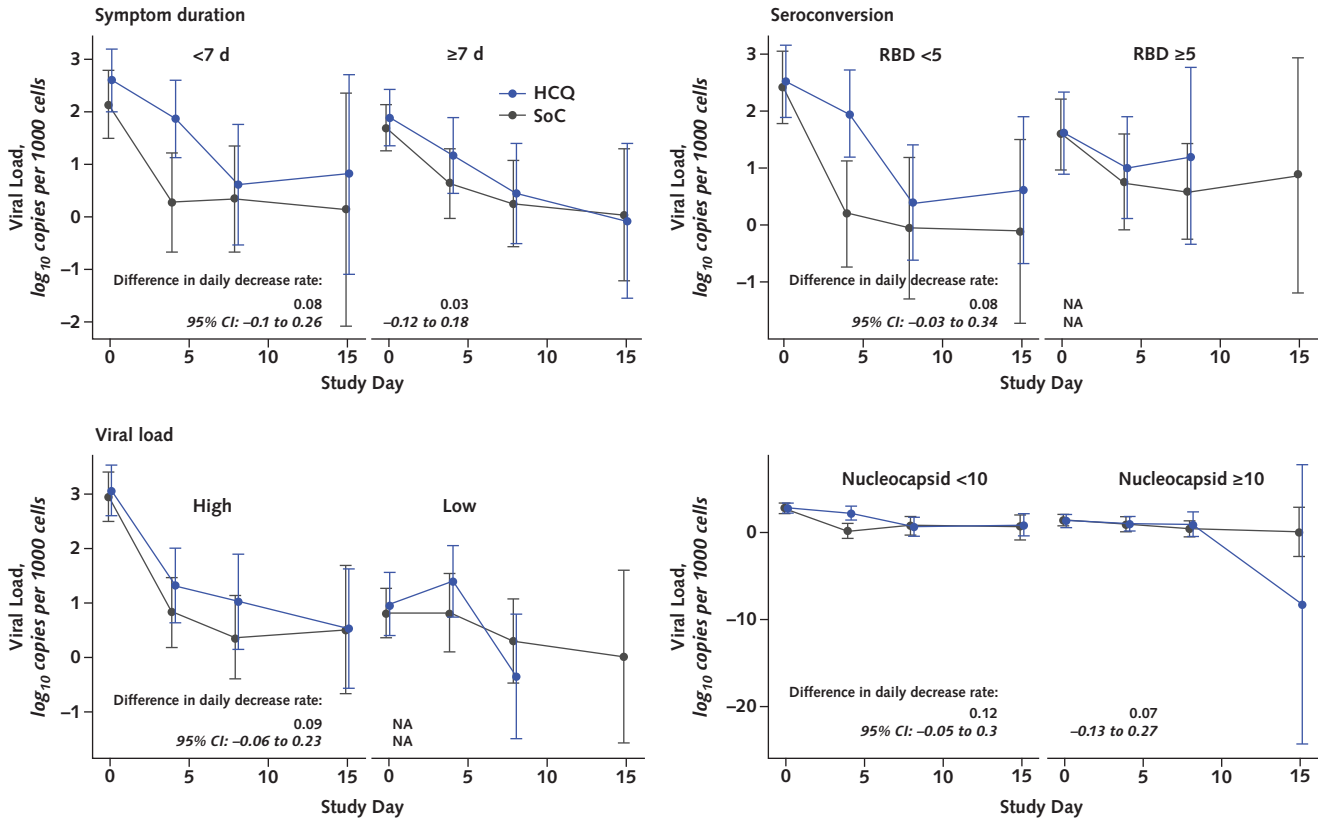
* To convert to SI units (µkat/L), multiply by 0.0167.

***Appendix Figure 5.*** Efficacy of remdesivir on viral clearance in patients with short versus long symptom duration, with high versus low baseline viral load, and with the presence or absence of SARS-CoV-2 antibodies.



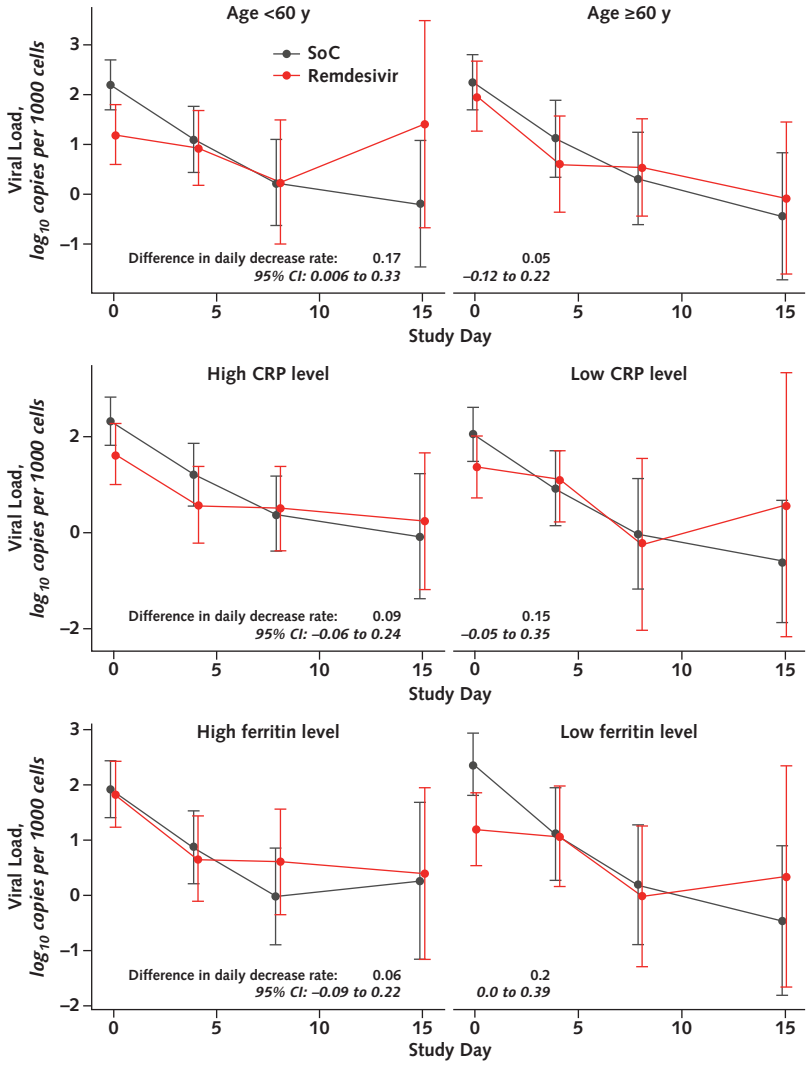

Subgroup analyses evaluating the effect on viral clearance of remdesivir compared with SoC in patients with short (<7 d) and long (≥7 d) symptom duration before hospitalization (*upper left*), in patients with high or low viral load (defined as above or below median level, respectively) at admission to hospital (*lower left*), and in the presence or absence of SARS-CoV-2 antibodies to RBD (cutoff ≥5) (*upper right*) and nucleocapsid (cutoff ≥10) (*lower right*). Treatment effects are given as estimated differences in average daily viral decrease rates (slopes) during the first week, between remdesivir and SoC, for all subanalyses. Results are presented as estimated treatment differences with 95% CIs. RBD = receptor-binding domain; SoC = standard of care.

***Appendix Figure 6.*** Efficacy of HCQ on viral clearance in patients with short versus long symptom duration, with high versus low baseline viral load, and with the presence or absence of SARS-CoV-2 antibodies.



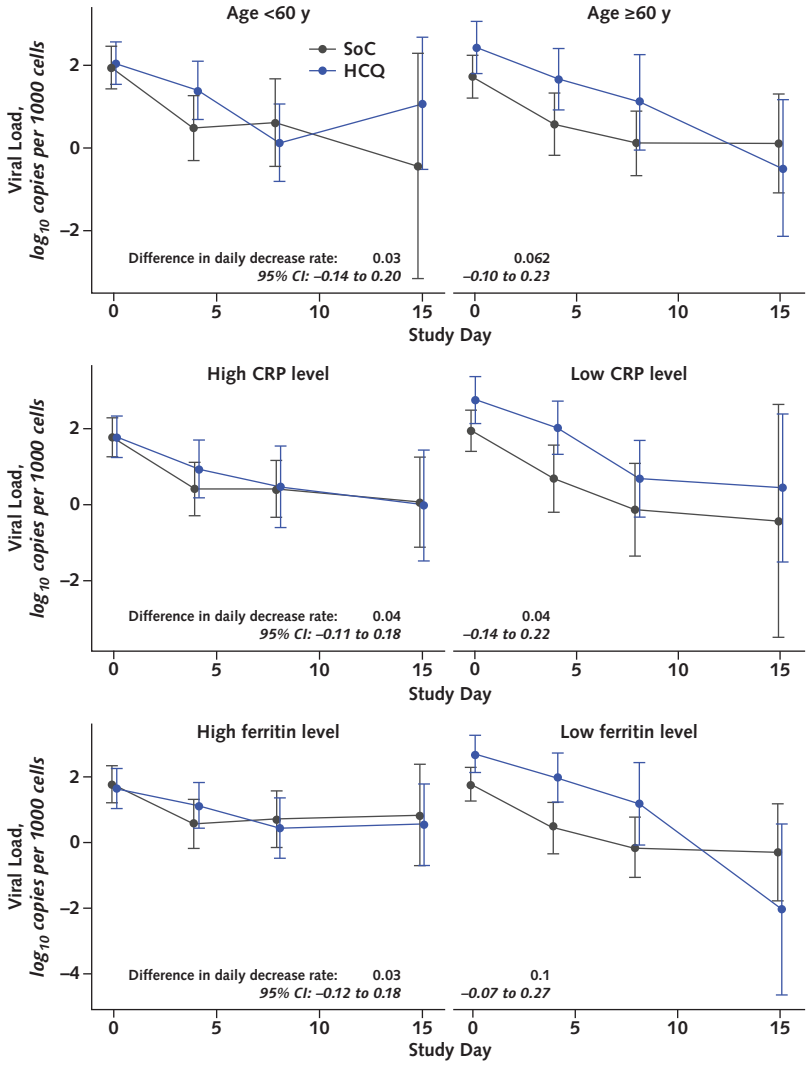

Subgroup analyses evaluating the effect on viral clearance of HCQ compared with SoC in patients with short (<7 d) and long (≥7 d) symptom duration before hospitalization (*upper left*), in patients with high or low viral load (defined as above or below median level, respectively) at admission to hospital (*lower left*), and in the presence or absence of SARS-CoV-2 antibodies to RBD (cutoff ≥5) (*upper right*) and nucleocapsid (cutoff ≥10) (*lower right*). Treatment effects are given as estimated differences in average daily viral decrease rates (slopes) during the first week, between HCQ and SoC, for all subanalyses. Results are presented as estimated treatment differences with 95% CIs. HCQ = hydroxychloroquine; RBD = receptor-binding domain; SoC = standard of care.

***Appendix Figure 7.*** Effect of remdesivir on inflammatory markers, lymphocytes, and neutrophils.




In subgroup analyses evaluating the effect of viral clearance related to age (≥60 vs. <60 y) and degree of inflammation (ferritin and CRP; levels greater than or equal to median vs. lower than median) at baseline. Treatment effects are given as estimated differences in average daily viral decrease rates (slopes) during the first week, between remdesivir and SoC, for all subanalyses. Results are presented as estimated treatment differences with 95% CIs. CRP = C-reactive protein; SoC = standard of care.

***Appendix Figure 8.*** Effect of HCQ on inflammatory markers, lymphocytes, and neutrophils.




In subgroup analyses evaluating the effect of viral clearance related to age (≥60 vs. <60 y) and degree of inflammation (ferritin and CRP; levels greater than or equal to median vs. lower than median) at baseline. Treatment effects are given as estimated differences in average daily viral decrease rates (slopes) during the first week, between hydroxychloroquine and SoC, for all subanalyses. Results are presented as estimated treatment differences with 95% CIs. CRP = C-reactive protein; HCQ = hydroxychloroquine; SoC = standard of care.