Evaluation of remdesivir and hydroxychloroquine on viral clearance in Covid-19: Results from a Randomized Trial

Andreas Barratt-Due[1,2,9,*], Inge Christoffer Olsen[3], Katerina Nezvalova-Henriksen[4,5], Trine Kåsine[1,9], Fridtjof Lund-Johansen[2,6], Hedda Hoel[7,9,10], Aleksander Rygh Holten[8,9], Anders Tveita[11], Alexander Mathiessen[12], Mette Haugli[13], Ragnhild Eiken[14], Anders Benjamin Kildal[15], Åse Berg[16], Asgeir Johannessen[9,17], Lars Heggelund[18,19], Tuva Børresdatter Dahl[1,10], Karoline Hansen Skåra[10], Pawel Mielnik[20], Lan Ai Kieu Le[21], Lars Thoresen[22], Gernot Ernst[23], Dag Arne Lihaug Hoff[24], Hilde Skudal[25], Bård Reiakvam Kittang[26], Roy Bjørkholt Olsen[27], Birgitte Tholin[28], Carl Magnus Ystrøm[29], Nina Vibeche Skei[30], Trung Tran[2], Susanne Dudman[9,39], Jan Terje Andersen[9,31], Raisa Hannula[32], Olav Dalgard[9,33], Ane-Kristine Finbråten[7,34], Kristian Tonby[9,35], Bjorn Blomberg[36,37], Saad Aballi[38], Cathrine Fladeby[39], Anne Steffensen[9], Fredrik Müller[9,39], Anne Ma Dyrhol-Riise[9,35], Marius Trøseid[9,40] and Pål Aukrust[9,10,40] ,*The NOR-Solidarity trial*[#]

[1]Division of Critical Care and Emergencies, Oslo University Hospital, 0424 Oslo, Norway
[2]Division of laboratory Medicine, Dept. of Immunology, Oslo University Hospital, 0424 Oslo, Norway
[3]Department of Research Support for Clinical Trials, Oslo University Hospital, 0424 Oslo, Norway
[4]Department of Haematology, Oslo University Hospital, 0424 Oslo, Norway
[5]Hospital Pharmacies, South-Eastern Norway Enterprise, 0050 Oslo, Norway
[6]ImmunoLingo Covergence Centre, University of Oslo, 0315 Oslo, Norway
[7]Medical Department, Lovisenberg Diaconal Hospital, 0424 Oslo, Norway
[8]Department of Acute Medicine, Oslo University Hospital, 0424 Oslo, Norway
[9]Institute of Clinical Medicine, University of Oslo, 0315 Oslo, Norway
[10]Research Institute of Internal Medicine, Oslo University Hospital, 0424 Oslo, Norway
[11]Medical Department, Bærum Hospital, Vestre Viken Hospital Trust, 3004 Drammen, Norway
[12]Division of Medicine, Diakonhjemmet Hospital, 0319 Oslo, Norway
[13]Infectious Disease Department, Sørlandet Hospital SSK, 4604 Kristiansand, Norway
[14]Innlandet Hospital Trust, 2629 Lillehammer, Norway
[15]Department of Anesthesiology and Intensive Care, University Hospital of North Norway, 9019 Tromsø, Norway
[16]Department of Infectious Diseases, Stavanger University Hospital, 4068 Stavanger, Norway
[17]Department of Infectious Diseases, Vestfold Hospital Trust, 3103 Tønsberg, Norway
[18]Medical Department, Drammen Hospital, Vestre Viken Hospital Trust, 3004 Drammen, Norway
[19]Department of Clinical Science, University of Bergen, Norway
[20]Department for Neurology, Rheumatology and Physical Medicine, Førde Central Hospital, 6812 Førde, Norway
[21]Division of Pulmonary Medicine, Haugesund Hospital, 5528 Haugesund, Norway
[22]Department of Medicine, Ringerike Hospital, Vestre Viken Hospital Trust, 3511 Ringerike, Norway
[23]Department of Anaesthesiology, Kongsberg Hospital, Vestre Viken Hospital Trust, 3004 Drammen, Norway
[24]Department of Medicine, Ålesund Hospital, Møre & Romsdal Hospital Trust, 6026 Ålesund, Norway

[25]Division of infectious Diseases, Telemark Hospital Trust, 3710 Skien, Norway
[26]Department of Medicine, Haraldsplass Deaconess Hospital, 5892 Bergen, Norway
[27]Department of Anaesthesiology, Sorlandet Hospital, Arendal, Norway
[28]Department of Internal Medicine, Molde Hospital, Møre & Romsdal Hospital Trust, 6412 Molde, Norway
[29]Department of Medicine, Innlandet Hospital Trust, Elverum, 2409 Elverum, Norway
[30]Department of Anesthesia and Intensive Care, Levanger Hospital, Nord-Trøndelag Hospital Trust, 7601 Levanger, Norway
[31]Department of Pharmacology, Oslo University Hospital, 0424 Oslo, Norway
[32]Department of Infectious Diseases, Trondheim University Hospital, 7006 Trondheim, Norway
[33]Department of Infectious Diseases, Akershus University Hospital, 1478 Lørenskog, Norway
[34]Unger-Vetlesen Institute, Lovisenberg Diaconal Hospital, 0456 Oslo, Norway
[35]Department of Infectious Diseases, Oslo University Hospital, 0424 Oslo, Norway
[36]Department of Medicine, Haukeland University Hospital, 5021 Bergen, Norway
[37]Department of Clinical Science, University of Bergen, 5021 Bergen, Norway
[38]Department of Infectious Diseases, Østfold Hospital Kalnes, 1714 Grålum, Norway
[39]Department of Microbiology, Oslo University Hospital, 0424 Oslo, Norway
[40]Section of Immunology and infectious Diseases, Oslo University Hospital, 0424 Oslo, Norway
[#]NOR-Solidarity trial (see appendix)

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[*]**Address correspondence**: Andreas Barratt-Due, Division of Emergencies and Critical Care, Oslo University Hospital Rikshospitalet, N-0027 Oslo, Norway. Phone: +47 98209974. E-mail: andreas.barrattdue@gmail.com

Abstract

Background

There is an urgent need for new treatment modalities in COVID-19 patients. The 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 as well as viral clearance in the oropharynx.

Design

NOR-Solidarity is an independent add-on randomized controlled trial to the WHO Solidarity trial, including biobanking and a clinical three-month follow-up (ClinicalTrials.gov: NCT04321616).

Settings

Twenty-three hospitals in Norway.

Patients

Eligible patients were adults admitted to the hospital with confirmed SARS-CoV-2 infection.

Intervention

Between March 28 and October 4, 2020, 185 patients were randomized and 181 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 WHO solidarity primary endpoint, study-specific outcomes were viral clearance in oropharyngeal specimens, the degree of respiratory failure and inflammatory parameters.

Results

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

Limitation

There was no placebo group.

Conclusion

We found no effect on viral clearance by either remdesivir or HCQ in hospitalized COVID-19 patients.

Primary Funding Source

National Clinical Therapy Research in the Specialist Health Services, Norway.

Introduction

In February 2020, a WHO expert group recommended that four drugs approved for other indications, hydroxychloroquine (HCQ), remdesivir, ritonavir-boosted lopinavir and interferon (IFN) β1a 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 the initiation of the WHO Solidarity trial (1). The HCQ and lopinavir arms of this trial were subsequently stopped due to reported lack of effect based on emerging external evidence from the RECOVERY trial, as well as internal evidence from interim analyses (2).

In October 2020, the WHO Solidarity trial consortium published interim results, reporting that all 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 the ACTT trial that reporting remdesivir significantly reduced time to recovery and discharge from hospital, in particular in patients not on mechanical ventilation (3).

Of major interest was whether remdesivir could impact the clinical course in patients with mild or moderate disease where viral replication is believed to drive disease progression, as opposed to severe form of the disease in which inflammation appears to play a predominant role. Remdesivir is a viral RNA polymerase inhibitor shown to have antiviral effects on SARS-CoV2 *in vitro* through interference with viral RNA production (4, 5). However, data on any anti-viral 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 to SoC in hospitalized COVID-19 patients. Herein we present the effect of remdesivir and HCQ compared to SoC on viral clearance as assessed by SARS-CoV-2 PCR in oropharyngeal specimens. We also examined whether remdesivir and HCQ had any effects on inflammatory biomarkers and the degree of respiratory failure.

Methods

Trial design

NOR-Solidarity is an independent add-on trial to WHO Solidarity trial; a large open label, adaptive randomized clinical trial, evaluating the effect of repurposed antiviral drugs on hospitalized COVID-19 patients. WHO Solidarity included 405 hospitals in 30 countries; 11,330 adults underwent randomization, 2750 were assigned to receive 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 confirmed SARS-2-CoV-2 infection by PCR, admitted to the hospital ward or the intensive care unit (ICU) with no anticipated transfer to a non-study hospital within 72 hours of inclusion. Informed consent by the study participant or legally authorized representative was provided prior to inclusion.

Key exclusion criteria were severe co-morbidity with life expectancy <3 months, AST/ALT > 5 times the upper limit of normal, QTc-time >470 ms, pregnancy, breast-feeding, acute co-morbidity occurrence 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 two 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 back-up if allocation according to the global list was not available. The randomization procedure ensured that a patient could only be allocated 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 arms: i) local SoC ii) SoC + oral HCQ 800 mg twice daily day 1, then 400 mg twice daily up to 9 days or iii) SoC + intravenous remdesivir 400 mg day 1, then 200 mg daily up to 9 days. All study treatments were stopped at discharge. During the course of 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 (September 4th 2020) (6).

Recruitment

NOR-Solidarity started recruiting patients on March 28th 2020, as the first study site within the WHO Solidarity Trial. Patients were initially randomized to HCQ or SoC. Randomization to remdesivir started on April 7th. HCQ was removed as a treatment arm after advice from the NOR-Solidarity steering committee on June 8th 2020 due to lack of evidence of its effectiveness, confirmed both in internal WHO interim analyses and an external report from the Recovery study (7, 8). Thus, from June 8th 2020, NOR-Solidarity allocated patients only to SoC and remdesivir. On October 4th 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 arm was continued in the WHO Solidarity trial, it was stopped in the NOR-Solidarity study, on October 5th due to 1) general low mortality in hospitalized patients in Norway, 2) the potential for untoward effects in ventilated patients, and 3) 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 NOR-Solidarity primary outcome was all-cause in-hospital mortality compared to SoC. Secondary outcomes were receipt of invasive mechanical ventilation, time to first receiving mechanical ventilation and duration, receipt and duration of treatment at intensive care unit (ICU) and occurrence of Suspected Unexpected Serious Adverse Reactions (SUSARs). As NOR-Solidarity was an add-on trial to the WHO Solidarity, most of these data have already been published as part of this report (1), but are now presented separately.

Further sub-study specific secondary outcomes included viral clearance as assessed by SARS-CoV-2 PCR in oropharyngeal specimens (measured at baseline, days 3-5, days 7-9 and thereafter every third day). Respiratory failure as assessed by pO_2/fiO_2-(P/F-ratio) and inflammatory laboratory parameters (i.e., C-reactive protein [CRP], procalcitonin [PCT], lactate dehydrogenase [LDH], ferritin and lymphocyte and neutrophil counts), were additionally pre-specified secondary endpoints and measured daily during hospitalization. Details are presented in the protocol and the statistical analysis plan (See Appendix file).

The exploratory objective of identifying potential determinants of individual treatment responses by relating viral clearance to demographics and clinical characteristics (i.e., age and time since symptom debut), baseline viral load, inflammatory markers (i.e., CRP and ferritin) and levels of anti-SARS-CoV-2 antibodies is described below.

Statistical methods

Following the WHO core protocol, no sample size was pre-specified.

Before locking the database, and deliberately without knowledge of allocation, a statistical analysis plan was written and approved, prespecifying and detailing all analyses (Appendix file). As this is

an add-on study, there are no adjustments for multiple testing. Interpretations of results are based on unadjusted confidence intervals. All treatment comparisons are with concurrent controls.

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 ($\log_e$RR) was estimated using the (O-E)/V estimator from the log-rank statistic with 95 % confidence intervals 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 observed in blinded reviews, stratification variables in the primary analyses were not used. Subjects who withdrew their consent or were alive but still in hospital at time of database lock were censored at last known time of contact. Discharged participants were assumed alive and censored at time of database lock unless otherwise confirmed. Subjects who had an end-of-study visit at 3 months were censored at this date.

Dichotomous endpoints were analyzed using logistic regression without adjustment for any baseline covariates. The estimated average marginal risk difference and corresponding 95 % confidence interval were estimated using the delta method. Missing data due to discharge or participant withdrawal was 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 first week treatment effect. We also computed the average marginal point estimate at day 10 as a separate measure of treatment 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. Sub-group analyses were performed by including the sub-group as an interaction term with the treatment term in the mixed model. High and low baseline sub-groups were defined by the overall median. The 90-days outcomes on antibodies against SARS-CoV-2 were analyzed using the t-distribution. Duration of mechanical ventilation and ICU stay is descriptively presented using cumulative probability plots.

All statistical analyses were performed with Stata version 16.1 and R version 4.0.3 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.

Ethics

The trial protocol was approved by the Regional Ethic 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 (Appendix file).

Role of the funding source

The National Clinical Therapy Research in the Specialist Health Services funded this research, but had no role in the design, analysis, management, interpretation of data, preparation and approval of manuscript or played any other conducting role.

Description of Methods for RT-PCR of SARS-CoV-2 quantification and Methods for quantification of antibodies against SARS-CoV-2 are described in Appendix.

Results

Participant flow

From March 28 to October 4, 185 patients from 23 different hospitals in Norway were entered into the trial, which according to the National Intensive Care and Pandemic Registry, accounted for 24% of all SARS-CoV-2 hospitalized patients in Norway in the study period (9). Four patients were excluded due to absence of post-randomization information. Of the 181 randomized patients, 87 were assigned to receive SoC and 97 patients assigned to receive treatment with either remdesivir (n=43) or HCQ (n=54) with a SoC group matched to each treatment arm (Figure 1). A total of 149 patients (remdesivir, n=34 and HCQ, n=41, SoC, n=74) completed the three months follow-up, whereas a total of 32 patients were lost to follow-up due to death (n=12), voluntary discontinuation (n=7), other reasons including emigration or progression of underlying cancer (n=7) or unknown (n=6) (Figure 1). Not all parameters were available in all patients and missing values on patient characteristics and baseline are reported in Appendix Table 1.

The baseline demographics and disease characteristics were generally balanced among the different treatment groups (Table 1). However, the percentage of patients with P/F ratio <40 kPa was higher in the remdesivir- and HCQ-group as compared with their respective SoC group, whereas the percentage that used ACE inhibitors was lower in the two treatment groups. The majority of the patients were men (65.7 %) and the mean age was 59.8±15.3 years. On average, patients were admitted to the hospital within 8±4.9 days of onset of symptoms. Forty-three percent had respiratory failure (i.e., P/F-ratio <40 kPa). At hospital admittance, SARS-CoV-2 antibodies to receptor binding domain (RBD) and Nucleocapsid antigen were present in 47 % and 39.4 % of the patients, respectively. Median (IQR) treatment duration was 5 (3-9) days for remdesivir and HCQ and 6 (3-9) day for SoC, and the patients received a median total dose of 700 mg (IQR 500-1050 mg) of remdesivir and 5400 mg (IQR 3500-8500 mg) of HCQ. The majority of the patients were discharged home (n=137), whereas 25 patients were discharged to convalescence stay or nursing home (Appendix Table 2).

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 observed between the remdesivir group and the HCQ group and their 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.

Similarly to the WHO Solidarity study, we found no effects of remdesivir or HCQ on the rate of ICU admission, or the use of mechanical ventilation during hospitalization (Table 2). Furthermore, we found no differences in time to receipt of mechanical ventilation (Table 2). Also, duration of ICU-stay and mechanical ventilation, reported as cumulative probability plots, showed no differences between the treatments (Appendix Figure 1).

Adverse events

Two patients in the HCQ-group developed prolonged QTc-time, and the treatment was withdrawn. The majority of other serious adverse events were related to respiratory failure and interpreted as attributable to disease progression (Appendix Table 3). One Suspected Unexpected Serious Adverse Reaction was reported in the remdesivir group (Appendix Table 3).

Secondary end points specific for the NOR-Solidarity trial

Effect of treatment on viral load in oropharynx

The most important secondary outcome in the NOR-Solidarity trial was viral load in 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 both the remdesivir and HCQ groups

and the SoC groups (Figure 2). The difference between the treatment groups regarding the decrease rate during the first week and at Day 10 were nominally in favour of SoC, with CIs excluding major effects on viral clearance for both active treatments. For sensitivity analyses including box-plots, see Appendix Figure 2.

Effect of treatment on the degree of respiratory failure

An improved respiratory function reflected by an increase in the P/F-ratio was observed in all groups of patients during the first week after randomization (Figure 3). 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 group (Figure 3). At day 10 the P/F-ratio was not affected by any of the intervention arms when compared with the SoC groups (Figure 3).

Effect of treatment on inflammatory markers

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 a significantly more rapid ferritin decrease rate during the first week after randomization (both remdesivir and HCQ), LDH (remdesivir) and PCT (remdesivir), and a significant lower CRP level in the remdesivir group, but higher in the HCQ group at day 10, there were no marked or consistent effects of the treatment arms on these inflammatory markers (Appendix Figure 3 and 4).

Effects of remdesivir and HCQ on viral load in relation to baseline characteristics

It could be hypothesized that the effect of remdesivir or HCQ on viral load would be dependent on symptom duration before hospitalization (≥7 days versus <7 days), the presence of SARS-CoV-2 antibodies or high or low viral load at hospital admission. Interestingly, in these subgroup analyses, remdesivir did not exert any increased oropharyngeal viral clearance as compared with SoC (Appendix Figure 5). Similar results were demonstrated for HCQ (Appendix Figure 6). In addition, in subgroup analyses evaluating age

(≥60 years versus <60 years) and degree of inflammation (ferritin and CRP; ≥ median versus <median levels) at baseline, we did not find any significant treatment effects on viral clearance by either remdesivir or HCQ versus their respective SoC (Appendix Figure 7 and 8).

Discussion

Recently published results of the WHO Solidarity study concluded that neither remdesivir nor HCQ had any 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, the degree of viral load and the 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 arms in NOR-Solidarity, the main difference between the trials was a substantially lower mortality in the NOR-Solidarity trial (6.6% versus 11.8 % after 28 days). However, the mortality in NOR-Solidarity was equivalent to 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 healthcare systems, which may explain the reduced mortality, in particular the favorably lower ICU-mortality (18.4%) compared to other countries (10). There were also some differences in the presence of co-morbidities (e.g., diabetes 25 % versus 17.2 % and chronic heart disease 21 % versus 15.6 %, WHO Solidarity and NOR-Solidarity, respectively) (1), which could 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 et al. found no effect on SARS-CoV-2 clearance in 155 hospitalized patients receiving remdesivir as compared with 78 patients receiving placebo (12). Moreover, Lyngbakken et al. showed no antiviral effects of HCQ in 27 hospitalized patients compared with

26 patients receiving SoC (13). It has been claimed that these antiviral drugs, and in particular remdesivir, could be of importance 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 <7 days or in patients with 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 COVID-19 patients with moderate disease, but the present data suggest that only a study of even earlier intervention (i.e., in an out-patient, primary care setting), if any, would be warranted to rule out any antiviral effects of remdesivir in COVID-19 patients. 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 following negative results in several large trials. First the Recovery trial and later the WHO Solidarity study demonstrated lack of any material benefit of this drug in the treatment of COVID-19 disease (1, 2). Despite concerns about cardiac toxicity related to the loading dose of HCQ (16), we did not observe any grade 4 adverse effects related to either HCQ, or remdesvir, although two patients in the HCQ-group developed prolonged QTc-time 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 from most of hospitals in Norway, ensuring enrollment of a large proportion of the patients that was hospitalized during the study period. As this was a pragmatic trial, in a real-world clinical setting, our results may be generalisable to similar patient populations. However, the study has also has many limitations. Despite being a randomized controlled trial with blinded analyses of all relevant data, it did not include a placebo group. The number of patients included was relatively low, with CIs wide enough to include moderate effects. Our conclusion and in particular 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 5-6 days, and most of the patients did not receive the full treatment length of the tested medication, although recent studies have found no statistical 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 disease was accompanied by a paucity of effect on oropharyngeal SARS-CoV-2 viral clearance. Our findings question the antiviral potential of these antiviral drugs in hospitalized COVID-19 patients.

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Contributors

ABD, ICO, PA, MT, AMDR, KNH, and TK were responsible for the management, coordination, research activity planning and execution of the trial. ABD, ICO, and PA had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. FM, CF, SD and AS were responsible and carried out virus analyses. FLJ, TT and JTA were responsible and carried out SARS-CoV-2 antibody analyses. TBD, KHS, ABD and PA coordinated the collection and storage of all biobank material. HH, ARH, AT, AM, M, RE, BK, ÅB, AJ, LH, PM, LAKL, LT, GE, DALH, HS, BRK, RBO, BT, CMY, NVS, RH, OD, AKF, KT, BB, SA and AMDR were locally responsible for conducting the trial at the various included hospitals. PA, ABD, ICO, and MT drafted the manuscript. AT, AMDR, KNH and TK critically revised the manuscript. All authors contributed to conducting the trial and all authors revised and approved the final version of the manuscript.

Declaration of interest

All authors declare no competing interest

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Figure legends

Figure 1. Patient flowchart

Flowchart of patients enrolled in NOR-Solidarity from March 28th to October 5th 2020; 181 patients were randomized and assigned to receive standard of care (SoC), remdesivir + SoC or hydroxychloroquine (HCQ) + SoC. A total of 149 patients completed the three months follow up. Each pairwise intention-to-treat analysis was between the remdesivir group, the HCQ-group and its respective SoC. There is partial overlap of the two control groups.

Figure 2. Efficacy of viral clearance by remdesivir and hydroxychloroquine (HCQ)

Viral measurement was done by quantitative PCR 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 remdesivir, hydroxychloroquine (HCQ) and their 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 (day 0, 3-5, 7-9 and 12-16) is indicated separately by study arm. Data are given as mean (95% CI).

Figure 3. Effect of remdesivir and hydroxychloroquine (HCQ) on the degree of respiratory failure assessed by P/F-ratio.

P/F-ratios were calculated based on estimated levels of partial pressure of oxygen in arterial blood (pO_2) and the fraction of inspired oxygen (FiO_2). In patients missing arterial oxygen tension, pO_2 was approximated from peripheral O_2-saturation according to the table stated in the analysis plan. Likewise, the fraction of inspired oxygen (FiO_2) in patients not supported by mechanical ventilation or non-invasive 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

475 P/F-ratio increase rates between remdesivir, HCQ and their respective SoC during the first week after
476 randomization, and in differences in P/F-ratio at day 10. The number of patients under observation at
477 each time point (day 0, 3-5, 7-9 and 12-16) is indicated separately by study arm. Data are given as mean
478 (95% CI).

479

Tables main manuscript:

Table 1: Patient characteristics and baseline values

	All patients	**Remdesivir versus its control**		**HCQ versus its control**	
		Remdesivir+SoC	SoC	HCQ+SoC	SoC
Demographics, mean (SD) or n (%)	*n=181*	*n=42*	*n=57*	*n=52*	*n=54*
Age, years	59.8 (15.3)	59.7 (16.5)	58.1 (15.7)	60.3 (13.3)	59.2 (16.4)
Female	62 (34.3%)	13 (31%)	14 (24.6%)	21 (40.4%)	20 (37%)
Body Mass Index (kg/m^2)	28 (5)	28 (5)	28 (4)	28 (5)	27 (4)
Symptoms prior to admission (days)	8 (4.9)	7.5 (6.1)	7.2 (3.5)	8.4 (4.3)	8.6 (5.3)
P/F-ratio at admittance (kPa)	41 (13)	38 (13)	43 (12)	41 (15)	43 (11)
P/F-ratio < 40kPa	77 (43%)	22 (52.4%)	22 (38.6%)	24 (48%)	15 (27.8%)
Respiratory rate (breaths/min)	21.8 (5.8)	21.9 (5.3)	22 (5.4)	21.6 (5.8)	21.5 (5.8)
Temperature (°C)	37.4 (0.9)	37.2 (0.9)	37.5 (1)	37.6 (0.9)	37.3 (0.8)
Admitted to ward	171 (94.5%)	39 (92.9%)	56 (98.2%)	47 (90.4%)	53 (98.1%)
Admitted to ICU	10 (5.5%)	3 (7.1%)	1 (1.8%)	5 (9.6%)	1 (1.9%)
Comorbidities, 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%)
Co-medication, 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 inhibitor	12 (6.7%)	2 (4.9%)	4 (7.1%)	1 (1.9%)	7 (13%)
AT-II blockers	30 (16.8%)	11 (26.8%)	7 (12.5%)	9 (17.3%)	7 (13%)
Hematology, median (IQR)					

Hemoglobin (g/L)	132 (123-141)	132 (124-143)	136 (129-141)	130 (120-141)	132 (126-140)
WBC (x10^9/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)
Neutrophils (x10^9/L) *, median (IQR)*	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)
Lymphocytes (x10^9/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)
Platelet counts (x10^9/L)	203 (159-271)	206 (162-268)	203 (166-269)	184 (151.5-270)	208 (167-276)
Inflammatory markers, median (IQR)					
C-Reactive Protein (mg/L)	70 (36.5-137.5)	70 (39.8-139.2)	82 (33-141.8)	76 (47-133)	65.5 (34-124)
Procalcitonin (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)
Ferritin (µg/L)	613 (319-1173)	695 (343-1262)	589 (318-1077)	626 (295-1298)	531.5 (321-991)
Other , median (IQR)					
LDH (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)
D-dimer (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)
AST (U/L)	39 (27.2-59)	49 (34.5-77)	34 (24 - 54.8)	39 (28-59)	32 (24-53)
ALT (U/L)	33 (20-58)	41 (22-69.2)	31 (20.5 - 54)	33 (22-53)	30 (18.8-52)
Creatinine/eGFR (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 (SD)					
Viral load (log_{10} counts/1000 cells)	2 (1.6)	1.6 (1.6)	2.3 (1.8)	2.3 (1.5)	2 (1.5)
Anti-SARS-CoV-2 Ab, 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%)

Values are given as mean (standard deviation), number (percent), and median (interquartile range) as indicated. SD = standard deviation; IQR = interquartile range; HCQ = hydroxychloroquine; BMI = body mass index; ACE = angiotensin converting enzyme; AT= angiotensin; WBC = total white blood cell counts; LDH = lactate dehydrogenase; AST = aspartate transaminase; ALT = alanine transaminase; RBD = receptor binding domain. Missing values are given in a corresponding table in the supplemental file.

Table 2: Mortality, admission to ICU and mechanical ventilation

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

CI = confidence interval; ICU=Intensive Care Unit. HCQ=hydroxychloroquine; SoC= Standard of Care; Relative risks and hazard ratios are based on time to event analyses (log-rank and cox regression); estimated marginal risk differences are based on logistic regression analyses for dichotomous endpoints.

Supplemental tables:

Appendix Table 1: Missing values on patient characteristics and baseline values presented in Table 1

	All patients	**Remdesivir versus its control**		**HCQ versus its control**	
		Remdesivir+SoC	SoC	HCQ+SoC	SoC
Demographics	*n=181*	*n=42*	*n=57*	*n=52*	*n=54*
Age, years	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Female	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Body Mass Index	17 (9.4%)	4 (9.5%)	8 (14%)	3 (5.8%)	4 (7.4%)
Symptoms prior to admission	1 (0.6%)	1 (2.4%)	0 (0%)	0 (0%)	0 (0%)
P/F-ratio at admittance	2 (1.1%)	0 (0%)	0 (0%)	2 (3.8%)	0 (0%)
P/F-ratio < 40kPa	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%)
Comorbidities					
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%)
Co-medication					
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 inhibitor	2 (1.1%)	1 (2.4%)	1 (1.8%)	0 (0%)	0 (0%)
AT-II blockers	2 (1.1%)	1 (2.4%)	1 (1.8%)	0 (0%)	0 (0%)
Hematology					

Hemoglobin	3 (1.7%)	1 (2.4%)	1 (1.8%)	1 (1.9%)	0 (0%)
WBC	1 (0.6%)	1 (2.4%)	0 (0%)	0 (0%)	0 (0%)
Neutrophils	10 (5.5%)	3 (7.1%)	4 (7%)	2 (3.8%)	3 (5.6%)
Lymphocytes	9 (5%)	2 (4.8%)	4 (7%)	2 (3.8%)	3 (5.6%)
Platelet counts	3 (1.7%)	1 (2.4%)	1 (1.8%)	1 (1.9%)	1 (1.9%)
Inflammatory markers					
C-Reactive Protein	2 (1.1%)	0 (0%)	1 (1.8%)	1 (1.9%)	0 (0%)
Procalcitonin	58 (32%)	9 (21.4%)	18 (31.6%)	21 (40.4%)	19 (35.2%)
Ferritin	9 (5%)	0 (0%)	3 (5.3%)	3 (5.8%)	4 (7.4%)
Other					
LDH	8 (4.4%)	1 (2.4%)	5 (8.8%)	1 (1.9%)	4 (7.4%)
D-dimer	19 (10.5%)	2 (4.8%)	8 (14%)	6 (11.5%)	7 (13%)
AST	11 (6.1%)	2 (4.8%)	5 (8.8%)	3 (5.8%)	4 (7.4%)
ALT	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 Ab					
Seroconverted	54 (29.8%)	9 (21.4%)	18 (31.6%)	17 (32.7%)	17 (31.5%)
Seroconverted	54 (29.8%)	9 (21.4%)	18 (31.6%)	17 (32.7%)	17 (31.5%)

The table is in correspondence with Table 1, *Patient characteristics and baseline values,* indicating all missing values, exact by number and percentages and include missing values for the whole study population as well as the intervention groups and their respective concurrent SoC-group.
HCQ=hydroxychloroquine; SoC= Standard of Care.

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	1 (0.6%)
NK	8 (9.2%)	4 (9.5%)	6 (11.5%)	18 (9.9%)

NA= not known. Data are given as absolute number and (percentage). HCQ=hydroxychloroquine; SoC= Standard of Care

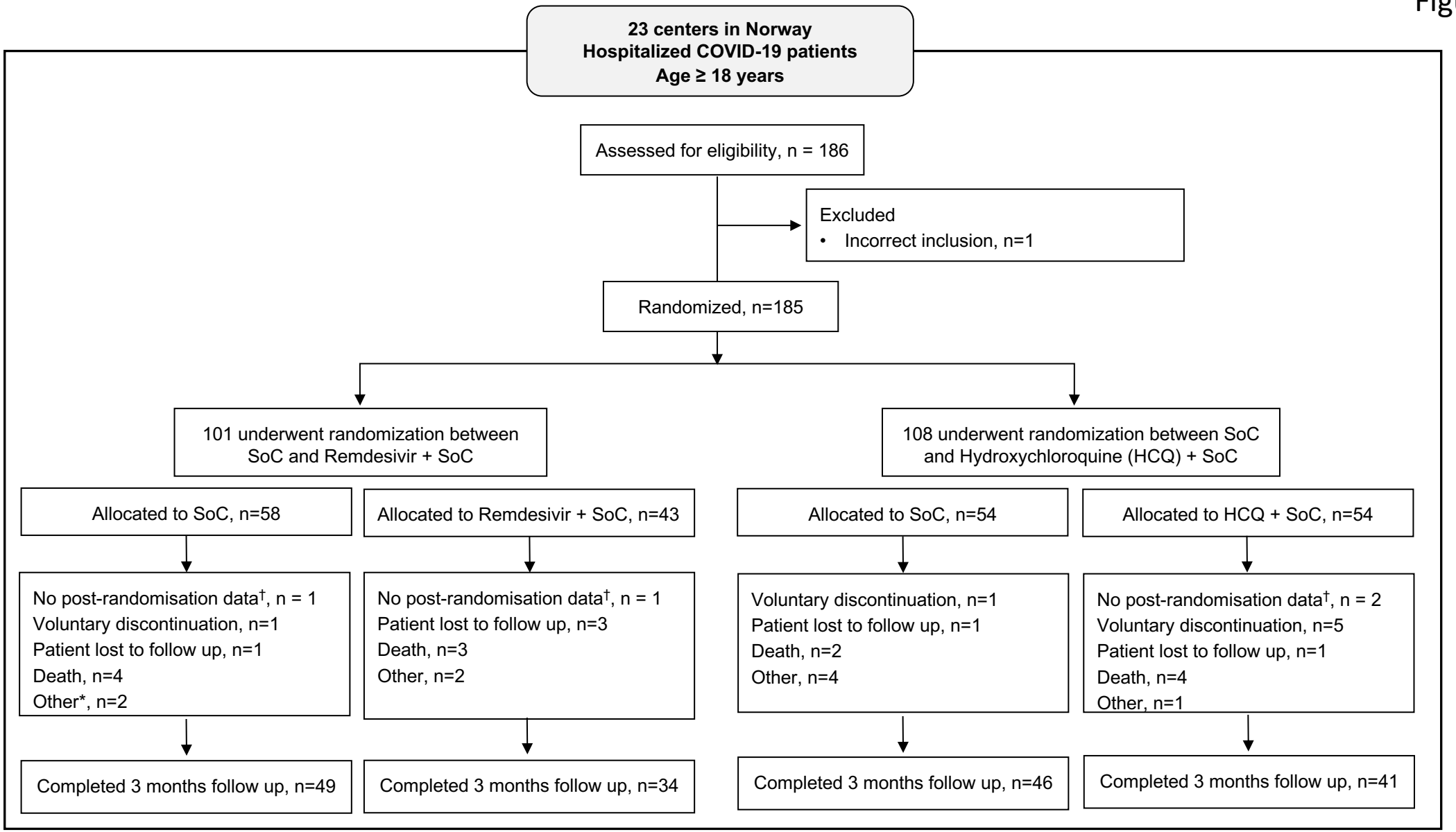
Appendix Table 3: Adverse events, safety data AND SUSAR

	SoC, n=87	Remdesivir+ SoC, n=42	HCQ + SoC, n=52
Total adverse events	33	34	26
Number of patients with adverse event	22 (25.3%)	20 (38.5%)	16 (38.1%)
Number of patients with > 1 adverse event	7 (8.0%)	6 (14.0%)	5 (9.3%)
Number of patients with AEs by system organ class			
- Blood and lymphatic system disorders	0	0	1 (1.9%)
- Cardiac disorders	1 (1.1%)	2 (4.8%)	0
- Gastrointestinal disorders	2 (2.3%)	3 (7.1%)	4 (7.7%)
- General disorders and adm. site conditions	3 (3.4%)	2 (4.8%)	0
- Hepatobiliary disorders	1 (1.1%)	0	0
- Infections and infestations	4 (4.6%)	0	1 (1.9%)
- Injury, poisoning and procedural complications	2 (2.3%)	0	0
- Investigations	3 (3.4%)	4 (9.5%)	6 (11.5%)
- Metabolism and nutrition disorders	0	0	1 (1.9%)
- Musculoskeletal and connective tissue disorders	0	0	2 (3.8%)
- Neoplasms benign, malignant and unspecified	1 (1.1%)	0	0
- Nervous system disorders	2 (2.3%)	2 (4.8%)	1 (1.9%)
- Renal and urinary disorders	1 (1.1%)	0	1 (1.9%)
- Respiratory, thoracic and mediastinal disorders	8 (9.2%)	6 (14.3%)	7 (13.5%)
- Skin and subcutaneous tissue disorders	0	2 (4.8%)	0
- Vascular disorders	1 (1.1%)	1 (2.4%)	1 (1.9%)
Number of serious adverse events*	20	13	12
Number of patients with serious adverse event	13 (14.9%)	8 (15.4%)	10 (23.8%)
Number of patients with SAEs by system organ class			
- Gastrointestinal disorders	1 (1.1%)	1 (2.4%)	0

- General disorders and adm. site conditions	2 (2.3%)	1 (2.4%)	0
- Hepatobiliary disorders	1 (1.1%)	0	0
- Infections and infestations	2 (2.3%)	0	1 (1.9%)
- Injury, poisoning and procedural complications	2 (2.3%)	0	0
- Investigations	1 (1.1%)	2 (4.8%)	2 (3.8%)
- Neoplasms benign, malignant and unspecified	1 (1.1%)	0	0
- Nervous system disorders	1 (1.1%)	1 (2.4%)	0
- Renal and urinary disorders	1 (1.1%)	0	1 (1.9%)
- Respiratory, thoracic and mediastinal disorders	6 (6.9%)	5 (11.9%)	7 (13.5%
Number of patients with prolonged QTc time	0	0	**2 (3.8%)**
Withdrawal of treatment due to adverse event	0	0	2 (3.8%)
Event with fatal outcome	0	0	0
Suspected Unexpected Serious Adverse Reaction			
Diarrhea hemorrhagic	0	1 (2.4%)	0

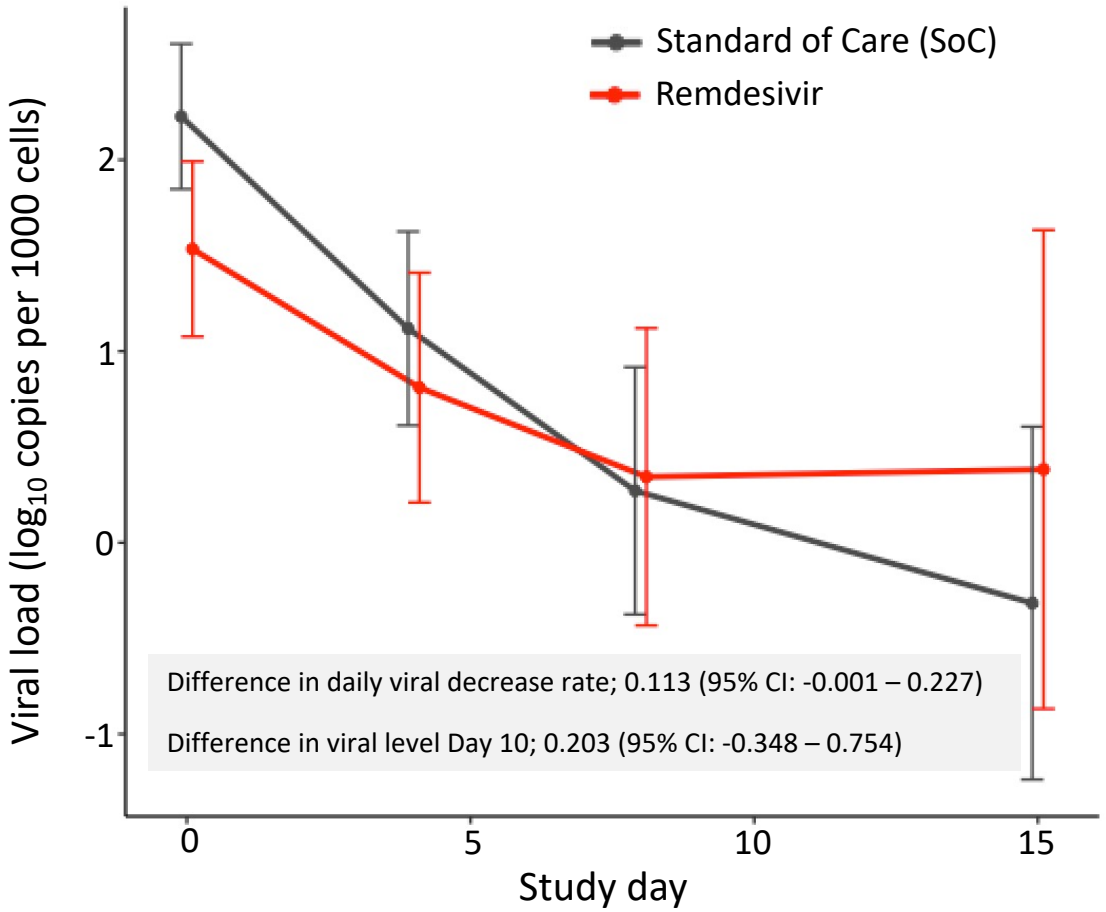
*Several events have may have occurred to one patient. AE=Adverse Event. SAE=Serious Adverse Event. SUSAR= Suspected Unexpected Serious Adverse Reaction. HCQ=hydroxychloroquine; SoC= Standard of Care. Values are number of patients (percent) or number of events. An adverse event was considered serious if, in the view of either the investigator or the sponsor, any of the outcome occurred; death, a life-threatening adverse event, 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.

Figure 1



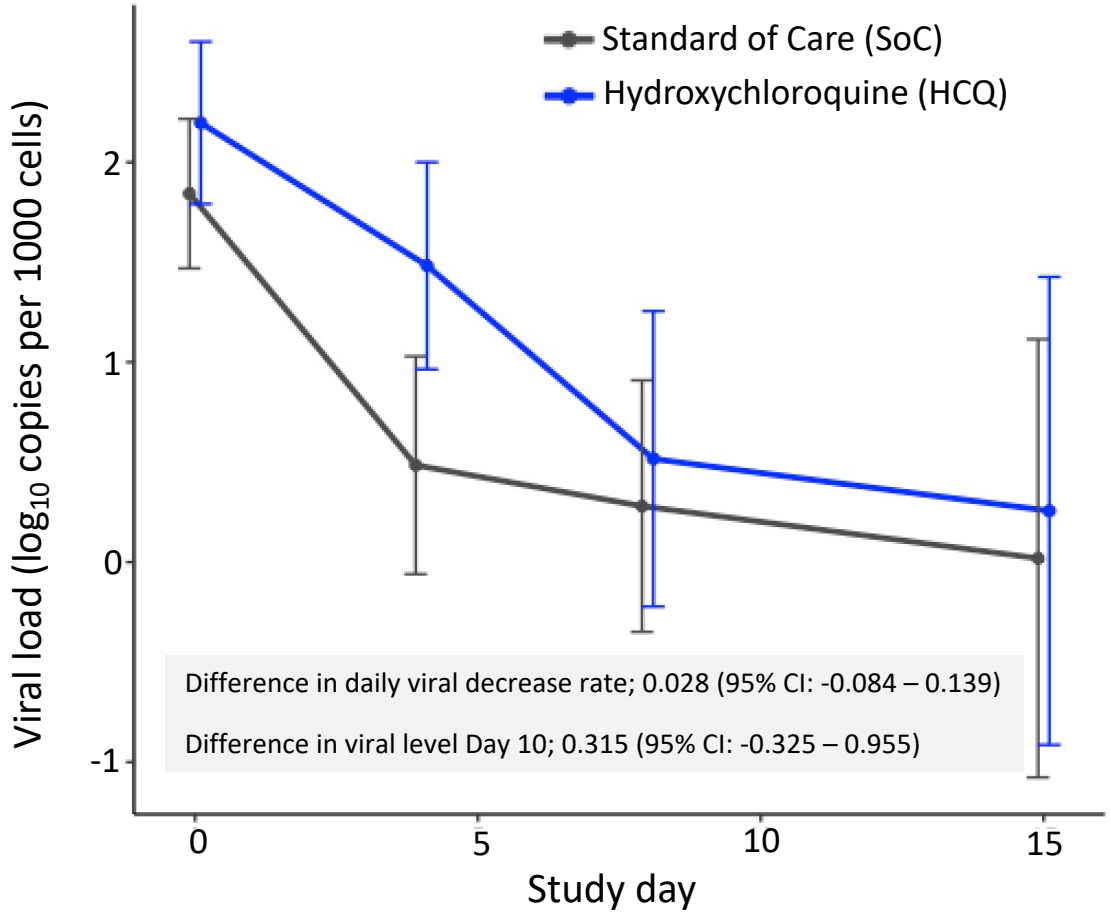
**Other: Emigration, progression of cancer diseases; † Excluded from the full analysis set*

Figure 2



Number under observation

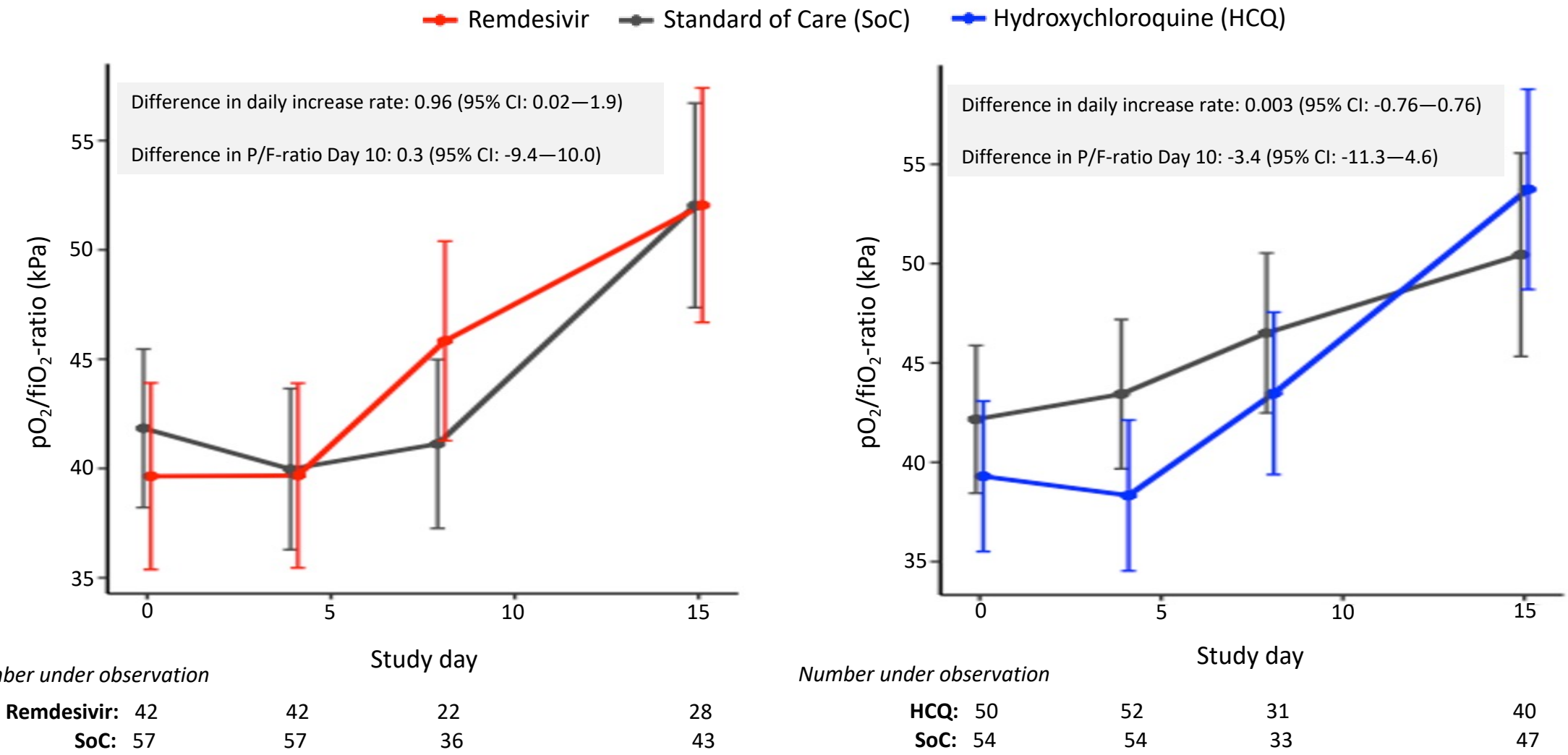
Remdesivir:	36	32	23	7
SoC:	53	41	23	13



Number under observation

HCQ:	36	35	18	6
SoC:	44	32	19	8

Figure 3


Remdesivir
Standard of Care (SoC)
Hydroxychloroquine (HCQ)
Difference in daily increase rate: 0.96 (95% CI: 0.02—1.9)
Difference in P/F-ratio Day 10: 0.3 (95% CI: -9.4—10.0)
Difference in daily increase rate: 0.003 (95% CI: -0.76—0.76)
Difference in P/F-ratio Day 10: -3.4 (95% CI: -11.3—4.6)
pO2/fiO2-ratio (kPa)
55
50
45
40
35
0
5
10
15
Study day
Number under observation
Remdesivir: 42 42 22 28
SoC: 57 57 36 43
Number under observation
HCQ: 50 52 31 40
SoC: 54 54 33 47