Evaluation of remdesivir and hydroxychloroquine on viral clearance in Covid-19 patients: Results from the NOR-Solidarity Randomised Trial

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Abstract

Background There is an urgent need for new treatment modalities in COVID-19 patients. Recently, the WHO Solidarity trial showed no effects of remdesivir or hydroxychloroquine (HCQ) on mortality. However, the antiviral effects of these drugs and the possible relation to clinical characteristics at admission is not known

Methods NOR-Solidarity is an independent add-on study to the WHO Solidarity trial, including biobanking, and a clinical three-month follow-up. Eligible patients were adults (≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection. Patients were randomly assigned to receive remdesivir, HCQ or standard of care (SoC). In-hospital mortality, admission to intensive care unit and initiation of mechanical ventilation were primary and secondary clinical endpoints shared with WHO Solidarity. Secondary endpoints were impact of remdesivir or HCQ on SARS-CoV-2 clearance in the oropharynx, as well as their effects on systemic inflammation and the degree of respiratory failure (ClinicalTrials.gov: NCT04321616).

Findings Between March 28 and October 4, 185 patients from 23 hospitals in Norway were randomized and 181 included in the full analysis set: remdesivir (n=42), HCQ (n=52) and SoC (n=87). No significant differences in mortality during hospitalisation, ICU admission or occurrence of mechanical ventilation between the treatment groups and SoC were observed. There was a marked decrease in SARS-CoV-2 load in oropharynx during the first week with similar decrease and 10-day levels between remdesivir, HCQ and their respective SoC. Remdesivir and HCQ did not exert any effect on the degree of respiratory failure or on inflammatory parameters in peripheral blood. Notably, the lack of anti-viral effect was not associated with symptom duration, level of viral load or presence of antibodies against SARS-CoV-2 at hospital admittance.

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

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Introduction

When COVID-19 was declared a pandemic in early 2020, there were no approved anti-viral treatments against the causative virus, SARS-CoV2. An unprecedented international effort of repurposing existing drugs with known safety profile and potential antiviral effect against SARS-CoV2 and/or immunomodulatory properties with potential beneficial effects in COVID-19 disease was initiated.

In February 2020, a WHO expert group recommended that four repurposed drugs, hydroxychloroquine (HCQ), remdesivir, ritonavir-boosted lopinavir and interferon (IFN) β1a alone or in combination should be evaluated in an international adaptive open label randomized clinical trial and compared with standard of care (SoC). This initiative expediently materialized through the launch of the WHO Solidarity trial.[1] The HCQ and lopinavir-arms were eventually stopped due to 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 of mechanical ventilation.[1] For remdesivir, these results contrasted those of the ACTT trial, reporting that remdesivir significantly reduced time to recovery and discharge from hospital, in particular in those that were not on mechanical ventilation.[3] Of note, remdesivir has received approval for COVID-19 treatment by the U.S. Food and Drug administration (FDA), but not from the European Medicines Agencies (EMA).

A crucial point of discussion is whether remdesivir could impact the clinical course of early stages of SARS-CoV-2 infection, or 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. Notably, 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

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anti-viral effects of remdesivir in SARS-CoV-2 infected humans are scarce with only one Chinese study reporting no effect on viral clearance in the upper and lower respiratory tract.[6]

The NOR-Solidarity trial is an independent add-on study to the WHO Solidarity trial, which has evaluated the effects of HCQ and remdesivir compared to SoC in hospitalised COVID-19 patients. We herein present the effect of remdesivir and HCQ compared to SoC on viral clearance as assessed by SARS-CoV-2 PCR in sequential oropharyngeal specimens. We also examined whether remdesivir and HCQ had any effects on circulating levels of biomarkers of inflammation, clinical variables (e.g., the degree of respiratory failure) as well as the concentration of SARS-CoV2 antibodies. An additional exploratory objective was to identify potential treatment effects in subpopulations, by relating viral clearance to the interaction between the treatment arms (remdesivir and HCQ) *and* patient demographics and clinical characteristics as well as viral load, levels of inflammatory markers and the presence of SARS-CoV-2 antibodies at baseline.

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Methods

Trial design

NOR-Solidarity is an independent add-on trial to WHO Solidarity; a large, multi-country, open label, adaptive randomized clinical trial, evaluating the effect of repurposed antiviral drugs on hospitalised COVID-19 patients. The NOR-SOLIDARITY trial includes 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 subject 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.

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

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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). [7]

Recruitment

NOR-Solidarity recruited patients from March 28th 2020, as the first study site within the WHO Solidarity Trial. Patients were initially randomized to HCQ or SoC. Randomisation 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. 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 hospitalised patients in Norway, 2) the potential for untoward effects in ventilated patients, and 3) potentially little, if any, effect of remdesivir for patients with mild disease. This decision was supported by the independent national data monitoring and safety committee.

Randomisation

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 steering group. The second was a local (national) list prepared as a back-up if allocation according to the global list was not available. The randomization procedure accommodated availability of each treatment such that a patient could not be

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allocated to an unavailable treatment. The allocation lists were not stratified or blocked, thus the randomisation can be regarded as simple. The trial was open label without a placebo control.

Outcomes

The WHO Solidarity primary outcome; all-cause in-hospital mortality compared to SoC, and secondary outcomes; duration of hospitalisation, receipt of invasive mechanical ventilation and the need for treatment at ICU, have been published [1]. Thus, these outcomes will be mentioned only briefly in this report.

Further sub-study specific secondary outcomes included viral clearance as assessed by SARS-CoV-2 PCR in oropharyngeal specimens, respiratory failure as assessed by pO_2/fiO_2-(P/F-ratio), SARS-CoV-2 antibodies at three months and inflammatory laboratory parameters (i.e., C-reactive protein [CRP], procalcitonin [PCT], lactate dehydrogenase [LDH], ferritin and lymphocyte and neutrophil counts). Details of the outcomes are presented in the protocol and the statistical analysis plan (See Suppl. Appendix).

The pre-specified objective specific to the NOR-Solidarity trial evaluating the effect of remdesivir and HCQ compared to their respective SoC on viral clearance as assessed by SARS-CoV-2 PCR in oropharyngeal specimens as described below.

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 also described below.

RNA extraction, RT-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, Penzberg, Germany), and eluted in 100 µL.

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Bacteriophage MS2 RNA (Merck, Sigma-Aldrich, Darmstadt, Germany) was added before extraction as an internal control. SARS-CoV-2 RNA real-time RT-PCR targeting the viral envelope (E)-gene was performed as was performed as described by Corman et al., using MS2 primers according to Dreier et. al., on the AriaDx PCR instrument (Agilent Technologies, Santa Clara, CA).[8,9] The quality and cellular quantification of oropharyngeal samples were analysed using the CELL Control r-gene kit (bioMérieux, Marcy-l'Étoile, France) 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 (EVAg, Marseille, France). Viral loads for respiratory samples were normalized according to the cellular quantification as $\log_{10}$ RNA copies per 1000 cells.

Measurements of antibodies against SARS-CoV-2

A multiplexed bead-based flow cytometric assay, referred to as microsphere affinity proteomics (MAP), was adapted for detection of SARS-CoV2 antibodies.[10] 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, Hurricane, UT) and neutravidin (Thermo Fisher, Waltham, MA). A DNA construct encoding the receptor-binding domain of Spike-1 protein (RBD) from SARS-CoV2 was provided by Florian Krammer, and the described protocol was used to produce recombinant protein in Expi293F cells.[11] Bacterially expressed full length nucleocapsid from SARS-CoV2 was purchased from Prospec Bio (www.prospecbio.com). Viral proteins solubilized in PBS 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 PBS containing 1 % Tween 20 (PBT), 1 % Bovine serum albumin, 10 μg/ml d-biotin and 10 μg/ml

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neutravidin (Thermo Fisher) and 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, labelled with R-Phycoerythrin-conjugated goat-anti-Human IgG-Fc (Jackson Immunoresearch West Grove, PA) for 20 minutes, washed again and analysed by flow cytometry (Attune Next, 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 cut-off for a positive antibody against RBP and Nucleocapsid, respectively. Reference panels containing samples from 287 individuals with PCR-confirmed SARS-CoV2 infection and 1343 pre-pandemic 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.

Routine laboratory analyses

CRP, ferritin, PCT, LDH, lymphocytes and neutrophils were analyses by the routine laboratory at the different hospitals included in the study.

Statistical methods

Sample size and power

According to the WHO core protocol, appropriate sample sizes could not be estimated at the start of the trial, as the "numbers entered will depend on how the epidemic develops." In Norway, very effective public infection control measures limited the development of the epidemic, as well as recruitment to NOR-Solidarity. Thus there are no pre-assessment calculations of sample size needed nor the assumed power to detect a clinically meaningful treatment effect.

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

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is an add-on study, there are no adjustments for multiple testing. Interpretations of results are based on unadjusted confidence intervals. Intervals excluding no difference are denoted as significant.

All-cause in-hospital mortality is summarized using counts and percentages and Kaplan-Meier estimates of the 28-day survival curves for each randomised treatment arm. We used the log-rank statistic to test the null hypothesis of no treatment effect. 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. Because of the low number of deaths observed in blinded reviews, stratification variables in the primary analyses were not used. Subjects who withdraw their consent or are alive but still in hospital at time of database lock were censored at last known time of contact. Subjects who were discharged are assumed alive and censored at time of database lock unless there exists information confirming otherwise. Subjects who have an end-of-study visit at 3 months were censored at this date.

Dichotomous endpoints were analysed 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. Continuous outcomes during the first 14 days were analysed using a mixed model with fixed and random intercept and slope. We used average marginal estimates of the first week slope and the day 10 level to estimate the treatment effect. 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 analysed using to the t-distribution.

A post-hoc decision was made to include nucleocapsid in the outcomes and to form sub-groups.

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

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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, oversight and analyses can be found in the protocol and statistical analysis plan (Suppl. Appendix).

The study was funded by the National Clinical Therapy Research in the Specialist Health Services (KLINBEFORSK), Norway. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Results

Participant flow

From March 28 to October 4, 185 patients from 23 different hospitals in Norway were included into the trial. Four patients were excluded due to no post-randomisation information. Of the 181 randomised patients, 87 were assigned to receive SoC and 97 patients assigned to receive treatment of either remdesivir (n=43) or HCQ (n=54) with a SoC group matched to each treatment arm (Fig. 1). A total of 149 patients (remdesivir, n=34 and HCQ, n=41) completed the three months follow-up, whereas altogether 32 patients were lost to follow-up due to death, voluntary discontinuation by the patient or other reasons like emigration or progression of cancer diseases (Fig. 1). Not all parameters were available in all patients (Suppl. Table S1).

The baseline demographics and disease characteristics were generally balanced between the different treatment groups (Table 1a-b). The majority of the patients were men (65·7 %) and the mean (±standard deviation) age was 59·8±15·3 years. On average, patients were admitted to the hospital within 8±4·9 days of symptom debut of COVID-19. Forty-three percent had respiratory failure defined as a P/F-ratio < 40 kPa. At admittance to the hospital, SARS-CoV-2 antibodies to RBD and Nucleocapsid antigen were present in 47 % and 39·4 % of the patients, respectively. Median (interquartile range (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 5400mg (IQR 3500-8500 mg) of HCQ.

Primary and secondary efficacy outcome shared with the WHO Solidarity trial

Mortality during hospitalisation among all included patients was 6·6 %; considerably lower than the overall mortality reported in the WHO Solidarity trial (11·8 %). Nonetheless, no differences in mortality,

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including in-hospital mortality, 28 days mortality or 60 days mortality, were observed between the remdesivir group and the HCQ group and their respective SoC group (Suppl. Table S2). Similar to the WHO Solidarity study, we found no effects of remdesivir or HCQ on the rate of ICU admission or the occurrence of mechanical ventilation during hospitalisation (Suppl. Table S2).

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 distress or failure and interpreted as attributable to disease progression (Table 2).

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. As depicted in Figure 2, there was a general marked decrease in SARS-CoV-2 oropharyngeal load during the first week after randomisation, with a similar decrease and levels after 10 days in both the remdesivir and HCQ arms and their respective SoC arms (Fig. 2).

Effect of treatment on the degree of respiratory failure

Lung is the primary target organ of the SARS-CoV-2, and respiratory failure is the most severe complication in COVID-19 patients. 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 randomisation (Suppl. Fig. S1). 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 respective SoC group (Suppl. Fig. S1). At day 10 the P/F-ratio was not affected by any of the intervention arms when compared with their respective SoC group (Suppl. Fig. S1).

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Effect of treatment on inflammatory markers

Hospitalised COVID-19 patients seem to be characterized by a state of hyperinflammation [12], and indeed, in the present study the patient group as a whole were at baseline characterized by markedly elevated plasma levels of CRP and ferritin whereas they had decreased lymphocyte counts and neutrophil counts albeit within normal limits (Table 1b). While CRP markedly decreased during follow-up, ferritin showed an incidental increase before a marked decrease during hospitalisation. In contrast, granulocyte and in particular lymphocyte counts increased during follow-up (Suppl. Fig. S2-3). However, except for a significantly more rapid ferritin decrease rate during the first week after randomisation (both remdesivir and HCQ), LDH (remdesivir) and PCT (remdesivir), no significant differences were observed at day 10 indicating that there were no marked or consistent effects of the treatment arms on these inflammatory markers (Suppl. Fig. S2-3).

Effects of treatment on SARS-CoV-2 antibodies after three months – an explorative endpoint

At admission, SARS-CoV-2 antibodies to RBD and Nucleocapsid antigens were present in 47 % and 39 %, respectively (Table 1b). As expected, rates of seropositivity increased with time, and antibodies against both proteins were present in 83 % of the patients after three months. However, we observed no differences in the levels of seropositivity between remdesvir or HCQ and their respective SoC (Suppl. Table S3).

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 were dependent on symptom duration before hospitalisation (≥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 (Fig. S3-4). Similar results were demonstrated for HCQ (Suppl. Fig. S4). 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

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did not find any significant treatment effects on viral clearance of either remdesivir or HCQ versus their respective SoC (Suppl. Fig. S5-6).

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Discussion

Recently published interim results of the WHO Solidarity study demonstrated 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 Norwegian subpopulation are consistent with the main findings of this report, with no effect of either remdesivir or HCQ on mortality, ICU admission or need of mechanical ventilation during hospitalisation. Moreover, 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.

Despite the early emergence of reports that both remdesivir and HCQ effectively exerted strong antiviral activities against SARS-CoV-2 in preclinical models,[13] our results show no antiviral effect of these drugs in hospitalised patients. Previously, Wang et al. found no effect on SARS-CoV-2 clearance in 155 hospitalised patients receiving remdesivir as compared with 78 patients receiving placebo.[6] More recently, Lyngbakken et al. showed no antiviral effects of HCQ in 27 hospitalised patients compared with 26 patients receiving SoC.[14] In the present study we extend these previous findings. It has been claimed that these antiviral drugs, and in particular remdesivir, could be of particular importance in the early stages of the infection, before clinical progression to a state of hyperinflammation.[15] 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, at baseline, 47 % and 39·4 % had detectable antibodies against the RBD and nucleocapsid of SARS-CoV-2, respectively. However, the presence of SARS-CoV-2 antibodies or high or low viral load at hospital admission did not influence the potential antiviral effects of remdesivir or HCQ. Similar findings were observed when evaluating the impact of age (≥60 years versus <60 years) on potential antiviral effects. Much focus has recently been directed at the use of remdesivir in hospitalised COVID-19 patients with

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moderate disease, but the present data may suggest that even earlier intervention (i.e., in an out-patient, primary care setting) might be warranted to rule out any antiviral effects of remdesivir in COVID-19 patients.

The overall mortality was lower compared to what was observed globally, but equivalent to data from the Norwegian national registry on in-hospital COVID-19-related mortality. Nevertheless, we found no effect on mortality, rate of ICU admission or need for mechanical ventilation, which was expected and consistent with the overall results of the WHO Solidarity study. Moreover, we also examined some additional relevant secondary end points. Firstly, the lungs are the primary target for SARS-CoV-2. Yet neither remdesivir nor HCQ had any beneficial effect on respiratory condition assessed by the P/F-ratio, which is a reliable marker of the degree of respiratory failure. Secondly, elevated levels of inflammatory markers are an important characteristic of hospitalised COVID-19 patients and in particular those with severe disease.[16,17] We found raised CRP and ferritin baseline levels accompanied by decreased lymphocyte counts which is also a well-recognized feature of COVID-19 disease.[18] However, neither remdesivir nor HCQ showed any consistent effects on inflammatory markers or lymphocyte/neutrophil counts during the first 10 days in these hospitalised COVID-19 patients as compared with SoC.

In the present study we observed that approximately 45 % of the patients had antibodies against SARS-CoV-2 at admission, and 83 % harbored detectable levels of SARS-CoV-2 antibodies after three months, which is line with some previous studies in symptomatic COVID-19 patients.[19-21] Notably, the occurrence of antibodies at baseline did not influence the antiviral effects of remdesivir and HCQ, and these drugs did not influence the levels of antibodies after three months.

The widespread use of HCQ in the first phase of the pandemic came to a quick halt following negative results in several large, randomized 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 related to cardiac toxicity related to the loading dose of HCQ [22], we did not observe any

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grade 4 adverse effects related to either remdesivir or HCQ, although two patients in the HCQ-group developed prolonged QTc-time, resulting in treatment withdrawal.

The study has some strengths and limitations. Strengths include a strong national coverage with participation by a majority of hospitals in Norway, ensuring enrollment of a large proportion of the patients that was hospitalized during the study period. This was also a pragmatic trial, in a real-world clinical setting, indicating a high level of generalisability to similar patient populations. With a comprehensive data collection, we were able to assess not only the main clinical outcomes, but also more granular effects of the treatments such as potential impact on viral load and the emergence of antibodies against SARS-CoV-2. However, the study also has some limitations. Firstly, the number of included patients was relatively low. Secondly, although this was a randomised controlled trial with blinded analyses of all relevant data, it did not include a placebo group. Thirdly, not all data were available from all patients at all time points. Fourthly, the patients were discharged from the hospital based on at the discretion of the treating physician and according to the medical recommendations in Norway. Accordingly, the median duration of hospitalisation was 5-6 days, and most of the patients did not fulfil the full treatment length of the tested medication. Importantly, however, recent studies have found no statistical difference between a 5-day course and a 10-day course of remdesivir. [23]

In conclusion, the lack of effects of remdesivir and HCQ on the clinical course of patient hospitalized for COVID-19 disease was accompanied by a paucity of effect on oropharyngeal SARS-CoV-2 viral clearance. Notably, the lack of antiviral effect was not significantly influenced by symptom duration and age, nor the degree of viral load, presence of antibodies against SARS-CoV-2, or degree of systemic inflammation at admission. 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

Patient flowchart describes 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 remdeseivir and hydroxycloroquine (HCQ)

Viral measurement was done by quantitative PCR of SARS-CoV-2 in oropharynx and 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 randomisation. Treatment effects are given as estimated differences in daily viral decrease rates between remdesivir, hydroxychloroquine (HCQ) and its respective SoC during the first week, and in differences in viral load at day 10. Data are given as mean (95% CI).

Figure 3. Efficacy of remdesivir on viral clearance in patients with short versus long symptom duration and with high versus low baseline viral load

Subgroup analyses evaluating the effect viral clearance of remdesivir compared to SoC in patients with short (<7 days) and long (≥7 days) symptom duration before hospitalization (upper panel), and in patients with high or low viral load (defined as above or below median level) at admission to hospital (lower panel). Treatment effects are given as estimated differences in average daily viral decrease rates during the first

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week after randomization, between remdesivir and SoC for all subanalyses. Data are given as mean (95% CI).

Figure 4. Efficacy of remdesivir on viral clearance in patients with the presence or absence of SARS-CoV-2 antibodies.

Patients with the presence of SARS-CoV-2 antibodies towards Receptor Binding Domain (RBD) or Nucleocapsid, at a level ≥ 5 or ≥10, respectively, were defined as seroconverted. The effect of remdesivir on viral clearance compared to SoC in the presence or absence of RBD (upper panel) and Nucleocapsid (lower panel) was evaluated in subgroup analyses. Treatment effects are given as estimated differences in average daily viral decrease rates during the first week after randomisation, between remdesivir and SoC for all subanalyses. Data are given as mean (95% CI).

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Tables

Table 1a: Admission characteristics

	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	59·8 (15·3)	59·7 (16·5)	58·1 (15·7)	60·3 (13·3)	59·2 (16·4)
Female, n (%)	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, n (%)	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, 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%)
Comorbidities					
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, n (%)	71 (39·4%)	16 (39%)	27 (47·4%)	18 (34·6%)	21 (38·9%)
Hypertension, n (%)	55 (30·6%)	15 (36·6%)	14 (24·6%)	17 (32·7%)	18 (33·3%)
Diabetes, n (%)	31 (17·2%)	9 (22%)	9 (15·8%)	7 (13·5%)	8 (14·8%)
Obesity (BMI > 30 kg/m^2), n (%)	44 (26·8%)	11 (28·9%)	9 (18·4%)	16 (32·7%)	11 (22%)
Co-medication					
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%)

Data are given as mean values with percentage or standard deviation in parenthesis. HCQ=Hydroxychloroquine; BMI=body mass index; ACE= angiotensin converting enzyme; AT=Angiotentsin.

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Table 1b: Biochemistry, anti-SARS-CoV-2 Ab and viral load at baseline

	All patients	Remdesivir versus its control		HCQ versus its control	
Laboratory values (median, IQR)		Remdesivir+ SoC	SoC	HCQ+SoC	SoC
Hematology	*n=181*	*n=42*	*n=57*	*n=52*	*n=54*
Hemoglobin (g/dL)	13·2 (12·3-14·1)	13·2 (12·4-14·3)	13·6 (12·9-14·1)	13 (12-14·1)	13·2 (12·6-14)
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)	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					
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					
LDH (U/L)	277 (214-360)	284 (234-400)	239 (195 - 352)	287 (235-361)	252 (200-325)
D-dimer (mg/L FEU)	0·68 (0·45-1·12)	0·76 (0·47-1·03)	0·5 (0·37 - 0·87)	0·9 (0·5-1·53)	0·77 (0·5-1·26)
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)					
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					
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%)

HCQ, Hydroxychloroquine; WBC, total white blood cell counts; LDH, lactate dehydrogenase; AST, aspartate transaminase; ALT, alanine transaminase; RBD, Receptor Binding Domain. Data are given as median and interquartile range.

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Table 2: Adverse events

	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 serious events	20	13	12
Number of patients with serious event	13 (14·9%)	8 (15·4%)	10 (23·8%)
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

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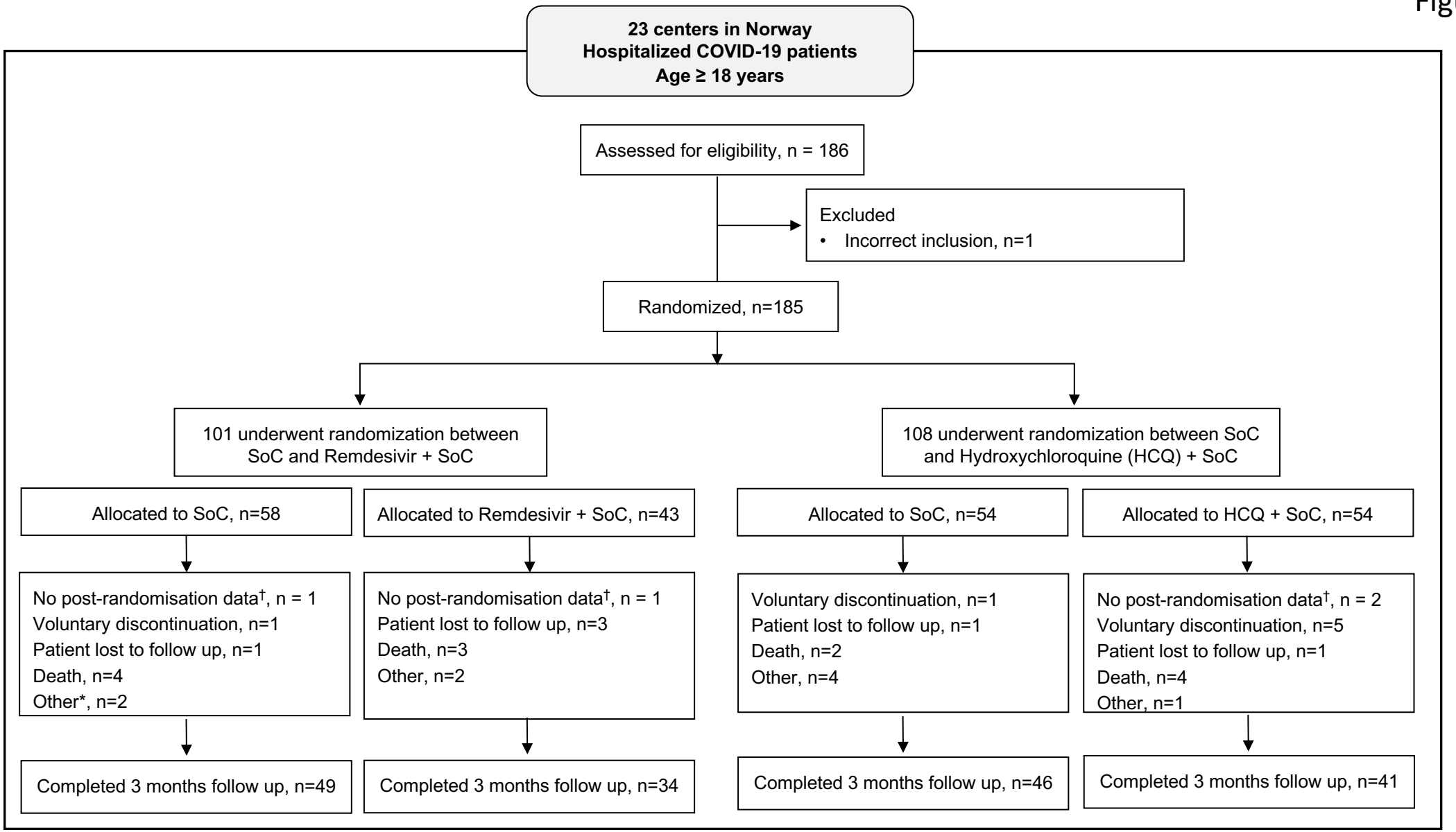
Figure 1



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

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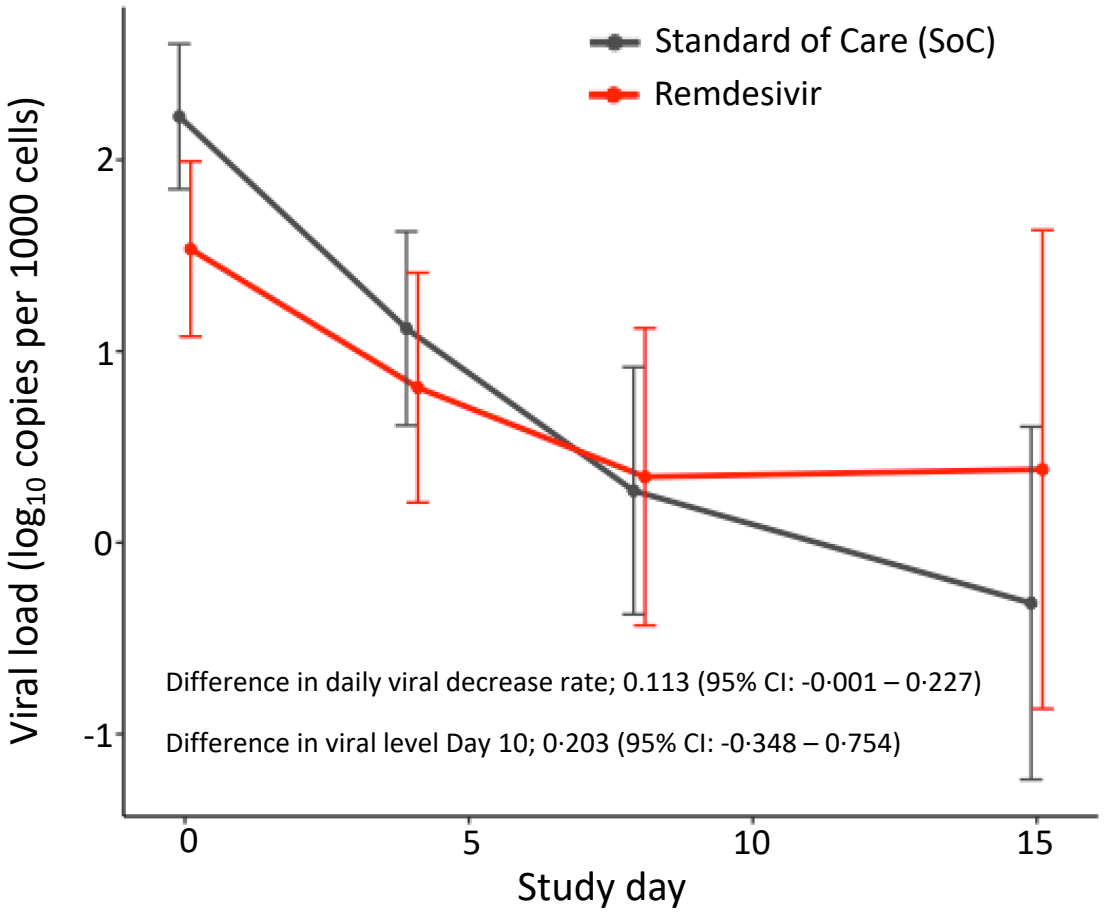
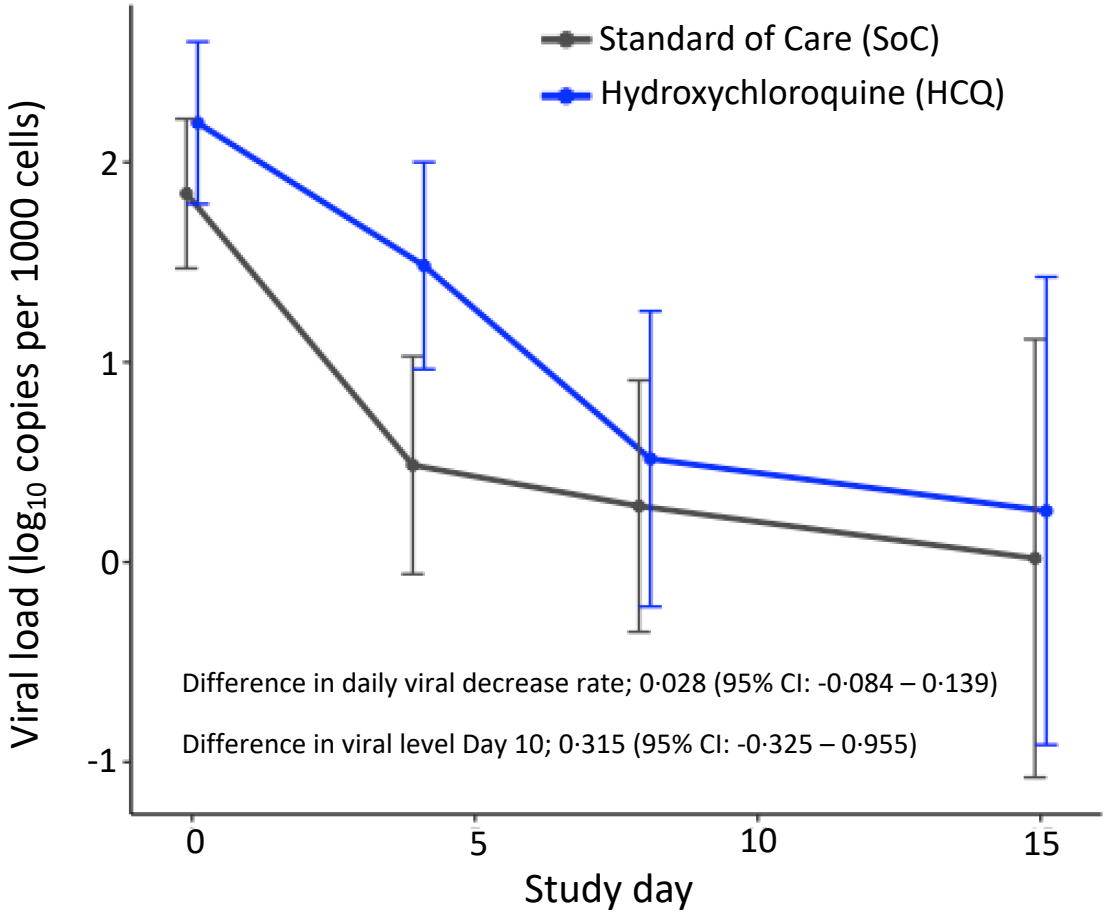
Figure 2





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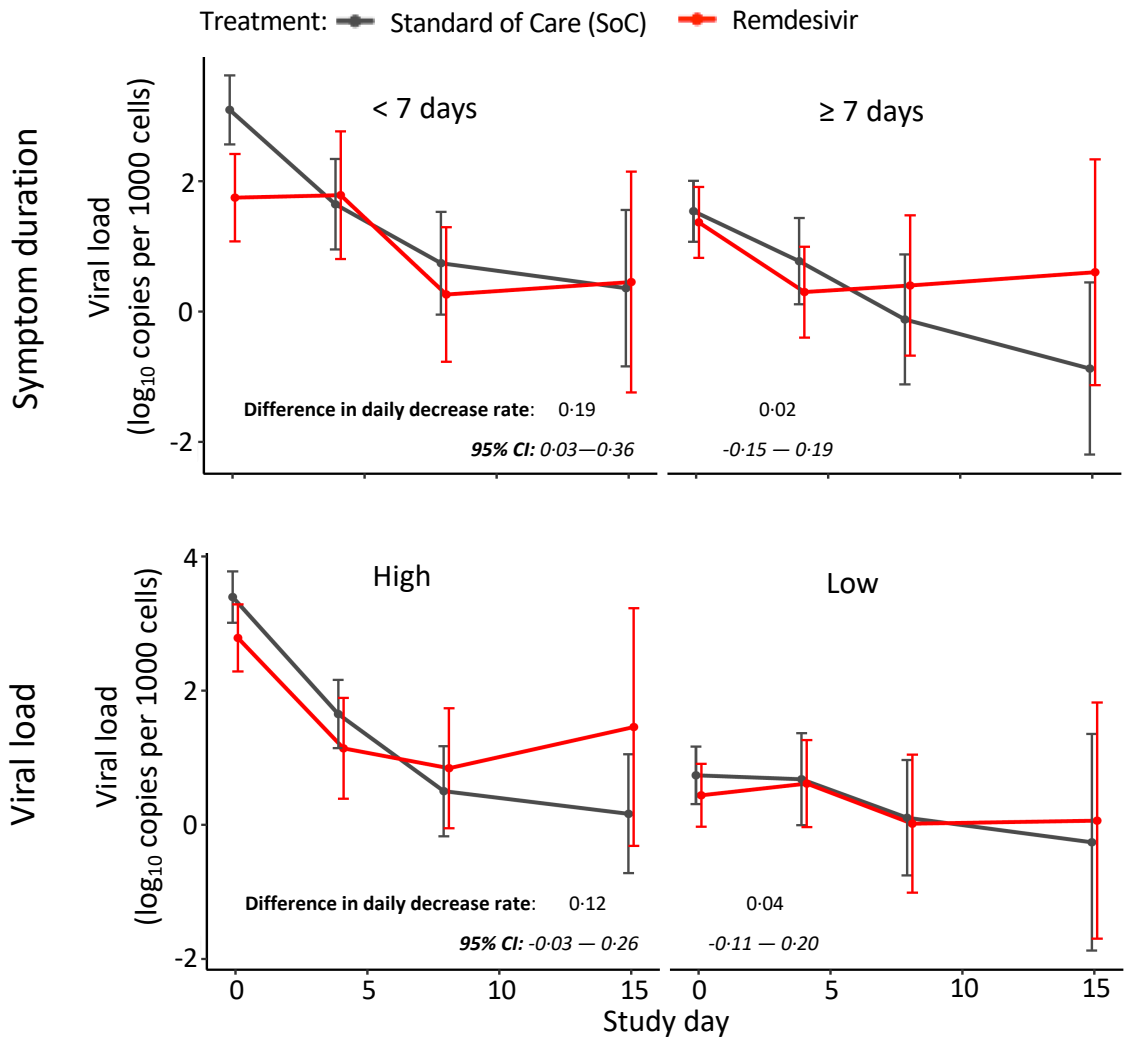

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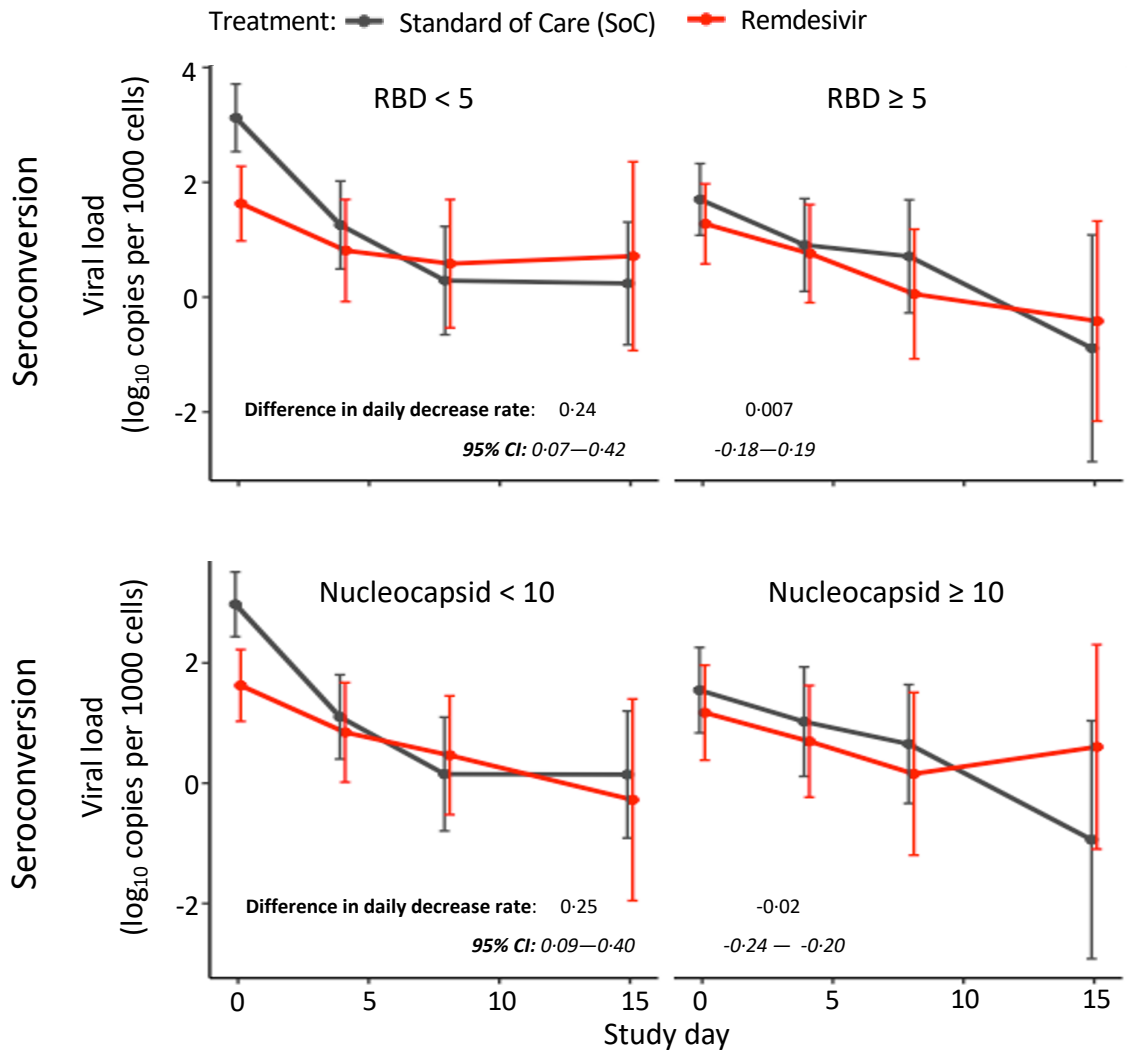

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