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Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial

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Abstract

Purpose: To study the efficacy of lopinavir-ritonavir and hydroxychloroquine in critically ill patients with coronavirus disease 2019 (COVID-19).

Methods: Critically ill adults with COVID-19 were randomized to receive lopinavir-ritonavir, hydroxychloroquine, combination therapy of lopinavir-ritonavir and hydroxychloroquine or no antiviral therapy (control). The primary endpoint was an ordinal scale of organ support-free days. Analyses used a Bayesian cumulative logistic model and expressed treatment effects as an adjusted odds ratio (OR) where an OR > 1 is favorable.

Results: We randomized 694 patients to receive lopinavir-ritonavir ($n = 255$), hydroxychloroquine ($n = 50$), combination therapy ($n = 27$) or control ($n = 362$). The median organ support-free days among patients in lopinavir-ritonavir, hydroxychloroquine, and combination therapy groups was 4 (– 1 to 15), 0 (– 1 to 9) and –1 (– 1 to 7), respectively,

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compared to 6 (– 1 to 16) in the control group with in-hospital mortality of 88/249 (35%), 17/49 (35%), 13/26 (50%), respectively, compared to 106/353 (30%) in the control group. The three interventions decreased organ support-free days compared to control (OR [95% credible interval]: 0.73 [0.55, 0.99], 0.57 [0.35, 0.83] 0.41 [0.24, 0.72]), yielding posterior probabilities that reached the threshold futility ($\geq 99.0\%$), and high probabilities of harm (98.0%, 99.9% and $> 99.9\%$, respectively). The three interventions reduced hospital survival compared with control (OR [95% CrI]: 0.65 [0.45, 0.95], 0.56 [0.30, 0.89], and 0.36 [0.17, 0.73]), yielding high probabilities of harm (98.5% and 99.4% and 99.8%, respectively).

Conclusion: Among critically ill patients with COVID-19, lopinavir-ritonavir, hydroxychloroquine, or combination therapy worsened outcomes compared to no antiviral therapy.

Keywords: Adaptive platform trial, Intensive care, Pneumonia, Pandemic, COVID-19, Lopinavir-ritonavir, Hydroxychloroquine

Introduction

In less than 18 months, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected more than 175 million people across the globe and caused more than 3.8 million deaths [1]. Given the emerging nature of the virus, several repurposed agents were considered as potential antiviral agents for COVID-19 [2]. Lopinavir-ritonavir and hydroxychloroquine were proposed based on data from severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) [3–8]. In vitro, lopinavir and hydroxychloroquine inhibit SARS-CoV-2 replication [9–11]. A pharmacokinetic analysis predicted that therapeutic doses of lopinavir, ritonavir and hydroxychloroquine would achieve concentrations in both plasma and lungs that are inhibitory of SARS-CoV-2 [12]. In a ferret infection model for SARS-CoV-2 infection, lopinavir-ritonavir or hydroxychloroquine resulted in improved clinical scores compared to the control group, although the virus titers were not different [13]. The two agents became widely used [14–16]. Several national guidelines for treatment of COVID-19 listed lopinavir-ritonavir and hydroxychloroquine (or chloroquine) as therapeutic options [17], and in March 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization for hydroxychloroquine, which was revoked later in June 2020 [18]. Subsequently, clinical trials were published, including the RECOVERY and Solidarity trials, demonstrating lack of benefit of lopinavir-ritonavir and hydroxychloroquine in hospitalized patients with COVID-19, although the proportions of critically ill patients were small [19–23]. In addition, most trials tested individual interventions, therefore, the effect of the combination of lopinavir-ritonavir and hydroxychloroquine and the interaction with other agents used for the treatment of COVID-19 such as corticosteroids and interleukin-6 (IL-6) receptor antagonists are unknown.

Take-home message

The Randomised, Embedded, Multifactorial Adaptive Platform (REMAP-CAP) trial is the largest randomized clinical trial in critically ill patients with COVID-19 to report the effects of lopinavir-ritonavir, hydroxychloroquine and combination therapy of lopinavir-ritonavir and hydroxychloroquine compared with no antiviral therapy. We found that, among critically ill patients with COVID-19, lopinavir-ritonavir, hydroxychloroquine and combination therapy reduced organ support-free days and survival compared to no COVID-19 antiviral therapy.

The objective of this trial was to evaluate the effects of lopinavir-ritonavir, hydroxychloroquine, and combination therapy of lopinavir-ritonavir and hydroxychloroquine compared to no COVID-19 antiviral therapy on organ support-free days in critically ill patients with COVID-19.

Methods

Study design

The Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP, NCT02735707) is an ongoing international adaptive platform trial designed to determine the best treatment strategies for patients with severe pneumonia in both pandemic and non-pandemic settings [24]. In the pandemic stratum, patients requiring organ support in an intensive care unit were enrolled as Severe State, and hospitalized patients not receiving organ support in the intensive care unit (ICU) were enrolled as Moderate State. Within the COVID-19 Antiviral Therapy Domain, patients were randomized to receive lopinavir-ritonavir, hydroxychloroquine, combination therapy of lopinavir-ritonavir and hydroxychloroquine or control (no antiviral agents against COVID-19). The pandemic stratum included other domains each with multiple interventions, and patients could be randomized to interventions in multiple domains (Statistical Analysis Committee Primary Analysis Report, Supplementary Appendix).

This report describes the results of the patients in the Severe State in the COVID-19 Antiviral Therapy Domain (Table S1). Some sites also enrolled patients in the Moderate State. These patients ($n=32$) are not included in the current analysis, though descriptive data are reported in the Supplementary Appendix.

The trial's protocol documents (REMAP-CAP Core Protocol, REMAP-CAP Pandemic Appendix to the Core Protocol, COVID-19 Antiviral Therapy Domain-Specific Appendix) and statistical analysis plan (REMAP-CAP Statistical Analysis Appendix, COVID-19 Antiviral Domain Statistical Analysis Plan) were posted online (<http://www.remapcap.org>) before analysis and are available in the Supplementary Appendix. The trial is managed by a blinded International Trial Steering Committee and is overseen by an unblinded Data and Safety Monitoring Board (DSMB).

The trial was approved by the relevant ethics committees in all regions. Written or verbal informed consent, in accordance with regional legislation, was obtained from all patients or their surrogates.

Patients

Patients were eligible for the COVID-19 Antiviral Therapy Domain- Severe State if they were ≥ 18 years old, admitted with suspected or confirmed COVID-19, and were receiving respiratory or cardiovascular organ failure support in an intensive care unit (ICU). Organ support included the provision of invasive mechanical ventilation, non-invasive mechanical ventilation, high-flow nasal cannulae with a flow rate of at least 30 L per minute and a fractional inspired oxygen concentration of 0.4 or higher, or the infusion of vasopressor or inotropes for shock. In addition to patients enrolled in the COVID-19 Antiviral Therapy Domain, the primary model included patients enrolled in other domains in Severe State, for covariate adjustment. Patients were excluded from the platform if (1) death was deemed to be imminent during the next 24 h AND one or more of the patient, substitute decision-maker, or attending physician are not committed to full active treatment, (2) expected to be discharged from hospital the same day or the following day, (3) more than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection, or (4) previous participation in this REMAP-CAP within the last 90 days. Additionally, patients were excluded from the COVID-19 Antiviral Therapy Domain in the presence of any of the following exclusion criteria (1) known hypersensitivity to lopinavir-ritonavir and hydroxychloroquine, (2) receiving lopinavir-ritonavir or hydroxychloroquine as a usual medication prior to this hospitalization, (3) known human immunodeficiency (HIV) infection (an exclusion criterion from receiving lopinavir-ritonavir), (4) severe

liver failure (an exclusion criterion from lopinavir-ritonavir), (5) known or suspected pregnancy, (6) receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 h prior to the assessment of eligibility (an exclusion criterion from lopinavir-ritonavir), (7) high clinical risk of sustained ventricular dysrhythmia (an exclusion criterion from hydroxychloroquine). Detailed platform and COVID-19 Antiviral Therapy Domain-specific inclusion and exclusion criteria are listed in Table S2 in the Supplementary Appendix.

Randomization and masking

Using a concealed online randomization system, patients were randomized to receive lopinavir-ritonavir, hydroxychloroquine, combination therapy of lopinavir-ritonavir and hydroxychloroquine or control (no antiviral agents against COVID-19). Based on local equipoise and drug availability, investigators at each participating site selected a priori two or more interventions, one of which had to be control, to which patients could be randomized. The REMAP-CAP platform uses response-adaptive randomization; however, the allocation in the COVID-19 Antiviral Therapy Domain did not deviate from the starting equal ratio before enrollment was halted. Although the interventions were given as open-label drugs, neither the clinical staff nor the ITSC were provided any information about aggregate patient outcomes.

Interventions

Lopinavir-ritonavir was administered for 5 days minimum, up to a maximum of 14 days or until ICU discharge whichever occurred first. Lopinavir-ritonavir was administered at a dose of 400 mg of lopinavir and 100 mg of ritonavir (Kaletra, AbbVie) every 12 h. For patients with a gastric tube who were unable to swallow tablets, lopinavir-ritonavir (at the same dose) was administered as a 5-ml suspension every 12 h or alternatively as two dissolved tablets or four crushed tablets (double dose), noting that systemic absorption is reduced by approximately 50% for crushed tablets [25]. Hydroxychloroquine was administered as two loading doses of 800 mg, 6-h apart, followed 6 h later by 400 mg 12 hourly for 12 doses. This dose regimen was supported by pharmacokinetic modelling and by guidance regarding safety from clinicians with experience with the use of hydroxychloroquine for the treatment of severe malaria [26]. If a patient was unable to swallow, crushed hydroxychloroquine tablets were administered via an enteral tube. The study protocol provided guidance for monitoring for drug interactions and QTc prolongation (Supplementary Appendix). Other aspects of care were provided as per each site's standard of care.

Outcomes

The primary outcome was a composite ordinal scale of the number of respiratory and cardiovascular organ support-free days (OSFD) and in-hospital mortality with death assigned the worst outcome (-1). Among survivors, respiratory and cardiovascular organ support-free days are calculated up to day 21, such that a higher number represents faster recovery. The definitions of respiratory and cardiovascular organ support were the same as in the inclusion criteria. This outcome was used in a recent FDA-approved registration trial, with a 1.5-day difference considered to be the minimal clinically important difference [27]. Each component of the composite, organ support free-days in survivors and in-hospital mortality, are reported separately. Secondary a priori outcomes were 90-day survival, respiratory support-free days, cardiovascular support-free days, time to ICU and hospital discharge, a composite outcome of progression to invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death among those not ventilated at baseline, the World Health Organisation ordinal scale assessed at 14 days and SARS-CoV-2 RNA clearance from respiratory specimens (COVID-19 Antiviral Therapy Domain-Specific Appendix and COVID-19 Antiviral Domain SAP, Supplementary Appendix) [28]. The WHO scale is a clinical progression scale that reflects patient trajectory and resource use over the course of clinical illness and ranges from 0 (no disease) to 8 (death). Safety a priori outcomes included serious adverse events and serious ventricular arrhythmia or sudden unexpected death while not receiving continuous cardiac monitoring (COVID-19 Antiviral Therapy Domain-Specific Appendix and COVID-19 Antiviral Domain SAP, Supplementary Appendix).

Statistical analysis

REMAP-CAP uses a Bayesian design with no prespecified sample size; enrollment in any intervention continues until a pre-defined statistical trigger is met at an adaptive analysis. Detailed statistical analysis plan is provided in the Supplementary Appendix (COVID-19 Antiviral Domain SAP). The primary model was run by an unblinded Statistical Analysis Committee, who conduct all protocol-specified trial update analyses independently of the ITSC, reporting results directly to the DSMB (Supplementary appendix).

The primary analysis was intention-to-treat, with a Bayesian cumulative logistic model with neutral prior distributions for treatment effects. The model estimated the proportional odds ratio for the ordinal primary outcome of organ support-free days. The primary analysis was adjusted for location (site, nested within country),

age (categorized into six groups), sex, and time period (2-week calendar epochs). The primary analysis was conducted on the REMAP-CAP Severe State cohort, including any patient randomized to at least one domain as of November 19, 2020 (Supplementary Appendix, Table S3). This approach allowed maximal incorporation of all information, providing a robust estimation of the coefficients of all covariates, as per the REMAP-CAP design [24]. Lopinavir-ritonavir and hydroxychloroquine were modeled hierarchically to allow for borrowing among the interventions' effect estimates. This meant that the effects of lopinavir-ritonavir and hydroxychloroquine shared a mean representing a common "antiviral effect". Distinct intervention-specific effects were estimated but the effects of lopinavir-ritonavir and hydroxychloroquine were shrunk toward the overall estimate of antiviral effect based on the heterogeneity of effects in the data. The combination therapy effect was estimated as the sum of the lopinavir-ritonavir and hydroxychloroquine and effects with an interaction effect between lopinavir-ritonavir and hydroxychloroquine.

The analysis of the primary outcome was repeated in models restricted to patients in the Unblinded cohort, which included severe COVID-19 patients randomized to the COVID-19 Antiviral Therapy Domain or other previously reported interventions and domains (Corticosteroid Domain and reported arms of the Immune Modulation Therapy Domain). We conducted additional analyses restricting to patients who were randomized concurrently with the lopinavir-ritonavir group or with hydroxychloroquine and combination therapy groups. Other analyses were conducted excluding those who tested negative for SARS-CoV-2, those in the COVID-19 Antiviral Therapy Domain cohort with no adjustment for assignment to interventions in other domains, and on the per-protocol cohort (Supplementary Appendix, Table S3). Additional secondary and sensitivity analyses of the primary outcome are described in the Supplementary Appendix.

Similar primary, secondary, and sensitivity analyses were conducted to estimate the effect on hospital survival. Interactions of antiviral interventions with corticosteroid therapy and with IL-6 receptor antagonists (tocilizumab, sarilumab) were modeled. The effect of antiviral interventions on secondary outcomes was assessed using the Unblinded cohort (defined above).

The Bayesian analysis models result in posterior distributions for parameters of interest including proportional odds ratios. Results from models of ordinal and dichotomous endpoints are reported as posterior median odds ratios (OR) and 95% credible intervals. Results from models of time-to-event endpoints are reported as posterior median hazard ratios (HR) and 95% CrIs. For consistency

of interpretation, all models are parameterized so that an OR/HR greater than 1 indicates patient benefit relative to the control group, and an OR/HR less than 1 indicates patient harm relative to the control group. The model allows the calculation of the posterior probability that each COVID-19 Antiviral Therapy Domain intervention (including the control group) was optimal, superior to control (OR/HR > 1), harmful (OR/HR < 1) or futile (OR/HR < 1.2). In this manuscript, we present the posterior probabilities of futility for the primary models and harm for all models; the posterior probabilities of being optimal or superior are available in the Statistical Analysis Committee Primary Analysis Report and ITSC Secondary Analysis Report in the Supplementary Appendix. An intervention was deemed harmful if the posterior probability of harm compared to control was greater than 90% (REMAP-CAP Pandemic Appendix to the Core Protocol-Supplementary Appendix). There was no imputation of missing primary (or secondary) outcomes.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The unblinded Statistical Analysis Committee had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Patients

Enrollment into the REMAP-CAP pandemic stratum started on March 9, 2020, and into the four arms of the COVID-19 Antiviral Therapy Domain on April 8, 2020, with patients enrolled from 99 sites across 8 countries (Table S1, Supplementary Appendix). Enrollment into the hydroxychloroquine and combination therapy arms was halted temporarily on May 23, 2020, based on published concerns regarding the safety and efficacy of hydroxychloroquine, but resumed later in a few sites, although only three patients (two in the hydroxychloroquine arm and one in the combination therapy arm) were enrolled after May 23, 2020, from one site. The hydroxychloroquine and combination therapy arms were closed completely on July 13, 2020. Enrollment into the lopinavir-ritonavir arm was halted on November 19, 2020, after reaching the prespecified futility threshold. Enrollment into the Corticosteroid Therapy Domain was halted on June 17-2020, while the COVID-19 Antiviral Therapy Domain was actively enrolling into the lopinavir-ritonavir and control groups, and enrollment into no immune modulation intervention in the Immune Modulation Domain was halted on November 19, 2020, simultaneously with lopinavir-ritonavir based on the results of the

adaptive analysis. The reports of corticosteroids and IL-6 receptor antagonists (tocilizumab and sarilumab) have been published [29, 30].

During the study period, 2046 patients with suspected or confirmed COVID-19 were enrolled in one or more REMAP-CAP domains (Fig. 1, Table S1, Supplementary Appendix), with 726 patients randomized within the COVID-19 Antiviral Therapy Domain (268 assigned to lopinavir-ritonavir, 52 to hydroxychloroquine, 29 to combination therapy of lopinavir-ritonavir and hydroxychloroquine and 377 to control). Within this domain, there were 32 patients for whom consent was withdrawn or not obtained and 17 patients with unavailable follow-up data on the primary outcome. As a result, 694 were included in this report, of whom 677 were analyzed for the primary outcome. Of the included patients, 502/694 (72.3%) were enrolled from the United Kingdom, 100/694 (14.4%) from Saudi Arabia, 42/694 (6.1%) from Canada, and remaining from other countries (Table S1).

The baseline characteristics were balanced across patients randomized concurrently with lopinavir-ritonavir (Table 1) and across patients randomized concurrently with hydroxychloroquine and combination therapy (Table S4). Of enrolled patients, 689/693 (99.4%) were receiving respiratory support (high-flow nasal cannula, noninvasive or invasive ventilation or ECMO) and 137/693 (19.8%) were receiving vasopressor support.

Intervention fidelity

Information on lopinavir-ritonavir and hydroxychloroquine dosing during the study period were available for 665/694 (95.8%) of patients (Tables S5 and S6, Supplementary Appendix). Among those assigned to the lopinavir-ritonavir, 220/247 (89.1%) received the allocated intervention for 7 days (5–12), among those assigned to hydroxychloroquine 46/49 (93.9%) received the allocated intervention for 7 days (5–12), among patients assigned to combination therapy 20/24 (83.3) received the allocated intervention for 11.5 days (5.8–14) and among those assigned to control group 360/362 (99.4%) received the allocated intervention (Tables S5 and S6, Supplementary Appendix). Concomitant therapy with corticosteroids, IL-6 receptor antagonists (Tocilizumab and Sarilumab), and remdesivir across patients randomized concurrently with lopinavir-ritonavir (Table S5, Supplementary Appendix) and across patients randomized concurrently with hydroxychloroquine and combination therapy (Table S6, Supplementary Appendix) were generally balanced.

Primary outcome

The median (IQR) organ support-free days among patients in lopinavir-ritonavir, hydroxychloroquine, and combination therapy groups were 4 (– 1 to 15), 0

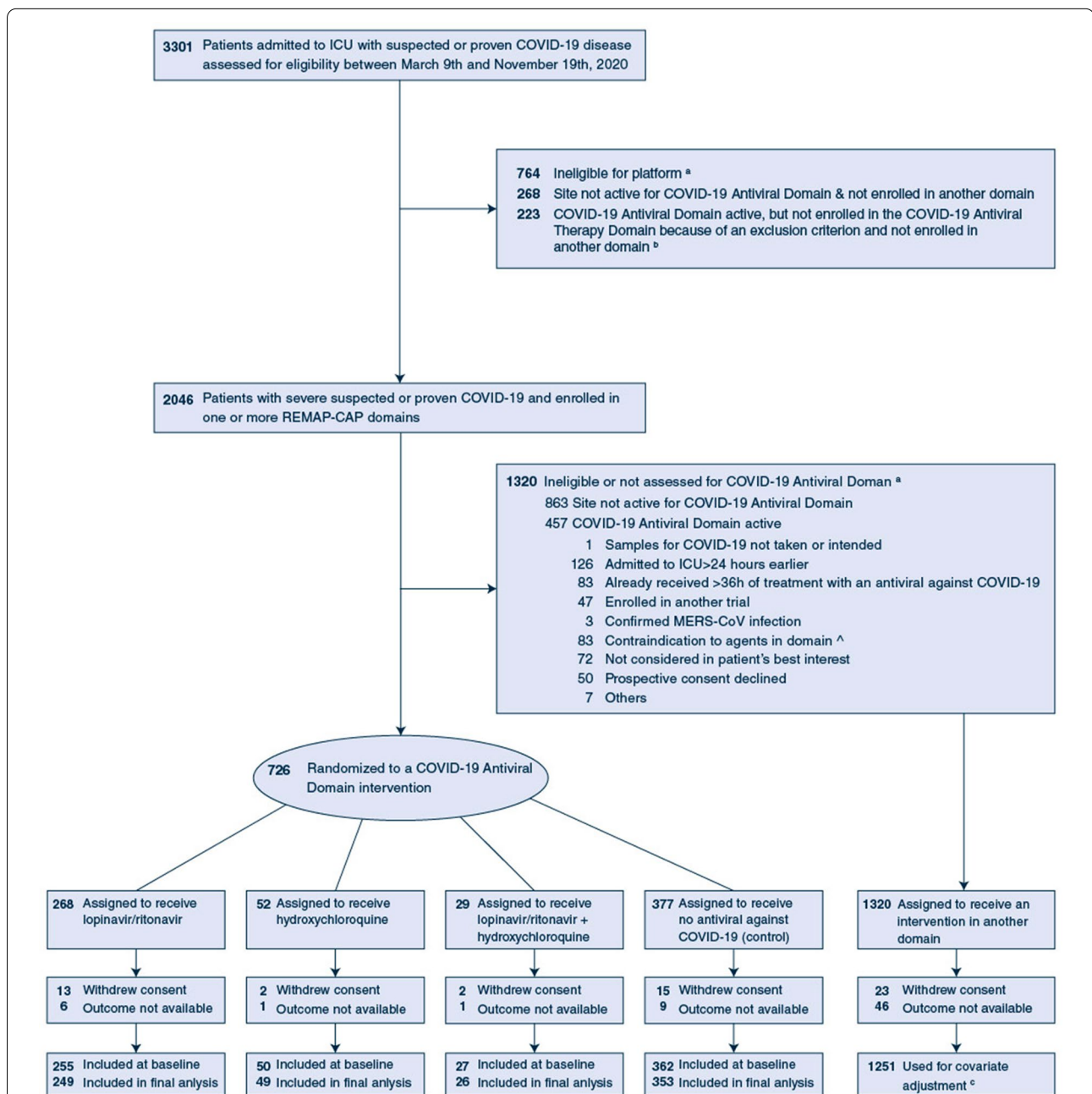


Fig. 1 Screening, randomization, and follow-up of patients in the REMAP-CAP COVID-19 Antiviral Therapy Domain randomized controlled trial.

^aPatients could meet more than one ineligibility criterion (Table S2, Supplementary Appendix). ^bDetails of platform exclusions are provided in the Supplementary Results (Supplementary Appendix). ^cThe primary analysis of organ support-free days (OSFD) and hospital survival were conducted on the REMAP-CAP intention-to-treat cohort which included all patients enrolled in the trial who met COVID-19 severe state criteria and were randomized within at least one domain, adjusting for patient factors and for assignment to interventions in other domains (Table S3, Supplementary Appendix). [^]Contraindications include hypersensitivity, receiving the study drug as usual medication prior to hospitalization, human immune deficiency (HIV) infection (contraindication of lopinavir-ritonavir), severe liver failure (contraindication of lopinavir-ritonavir), receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 h prior to assessment (contraindication of lopinavir-ritonavir) and high clinical risk of sustained ventricular dysrhythmia (contraindication of hydroxychloroquine) (Table S2, Supplementary Appendix)

Table 1 Patient characteristics at baseline

	Lopinavir-ritonavir (N = 255)	Hydroxychloroquine (N = 50)	Combination therapy (N = 27)	Control (N = 362)
Age—mean (SD), years	61 (13)	56.3 (13)	60.3 (8.9)	60.8 (12.9)
Male sex—n/N (%)	182/254 (71.7)	35/50 (70)	19/27 (70.4)	252/362 (69.6)
Body mass index—mean (SD), kg/m ²	31.8 (8.8)	31 (6.3)	30 (6.7)	31.9 (8)
Race/ethnicity ^{a,b}				
White—n/N (%)	84/111 (75.7)	18/31 (58.1)	6/8 (75)	112/150 (74.7)
Asian—n/N (%)	19/111 (17.1)	5/31 (16.1)	1/8 (12.5)	24/150 (16)
Black—n/N (%)	2/111 (1.8)	4/31 (12.9)	1/8 (12.5)	6/150 (4)
Other ^b —n/N (%)	6/111 (5.4)	4/31 (12.9)	0/8 (0)	8/150 (5.3)
Confirmed SARS-CoV2 infection ^c —n/N (%)	213/255 (83.5)	43/50 (86)	22/27 (81.5)	300/362 (82.9)
Pre-existing conditions—n/N (%)				
Diabetes mellitus	90/253 (35.6)	15/50 (30)	10/26 (38.5)	123/361 (34.1)
Respiratory disease	62/253 (24.5)	9/47 (19.1)	6/26 (23.1)	91/358 (25.4)
Kidney disease	31/232 (13.4)	3/44 (6.8)	4/24 (16.7)	37/327 (11.3)
Severe cardiovascular disease	40/249 (16.1)	2/48 (4.2)	3/26 (11.5)	37/353 (10.5)
Immunosuppressive disease	5/253 (2)	2/50 (4)	1/26 (3.8)	18/361 (5)
Chronic immunosuppressive therapy	14/253 (5.5)	0/47 (0)	1/26 (3.8)	16/356 (4.5)
Time to enrollment—median (IQR)				
From hospital admission—days	1.1 (0.8–2.7)	1 (0.6–1.7)	1.1 (0.8–1.5)	1.1 (0.8–2.2)
From ICU admission—hours	13 (6.7–18.9)	12.6 (5–20.4)	14.1 (4.3–18.6)	13.7 (6.4–19.4)
Acute respiratory support—n/N (%)				
None/supplemental oxygen only	0/254 (0)	0/50 (0)	0/27 (0)	4/362 (1.1)
High-flow nasal cannula	72/254 (28.3)	8/50 (16)	3/27 (11.1)	100/362 (27.6)
Non-invasive ventilation only	110/254 (43.3)	16/50 (32)	11/27 (40.7)	144/362 (39.8)
Invasive mechanical ventilation	72/254 (28.3)	26/50 (52)	13/27 (48.1)	114/362 (31.5)
ECMO	0/254 (0)	0/50 (0)	0/27 (0)	0/362 (0)
Vasopressor support—n/N (%)	47/254 (18.5)	13/50 (26)	5/27 (18.5)	72/362 (19.9)
APACHE II score ^d —median (IQR)	13.0 (8–18)	12.5 (7.8–20.2)	14 (10.2–20.8)	13 (8–19)
Glasgow Coma Scale ^e —mean (SD)	13.9 (3.1)	13.9 (3.1)	13 (4.4)	13.8 (3.2)
Acute physiology and laboratory values ^f				
PaO ₂ /FiO ₂ —median (IQR) mmHg	122 (89–174)	109 (85–149)	116 (91–151)	118 (88–169)
kPa	16.1 (11.7–22.9) (n = 214)	14.3 (11.2–19.6) (n = 46)	15.3 (12–19.9) (n = 24)	15.5 (11.6–22.2) (n = 317)
Creatinine—median (IQR), mg/dL	0.9 (0.7–1.2)	0.9 (0.7–1.3)	1 (0.7–1.5)	0.9 (0.7–1.2)
μmol/L	82 (65–110) (n = 253)	84 (61–114) (n = 50)	89 (61–132) (n = 26)	79 (64–108) (n = 361)
Lactate—median (IQR), mmol/L	1.3 (1–1.9) (n = 216)	1.1 (1–1.5) (n = 41)	1.1 (0.9–1.5) (n = 20)	1.3 (1–1.8) (n = 312)
Platelets—median (IQR), × 10 ⁹ /L	243 (181–308) (n = 252)	200 (166–271) (n = 50)	236 (194–374) (n = 26)	247 (189–311) (n = 359)
Bilirubin—median (IQR), mg/dL	0.6 (0.4–0.8) 10 (7–14) (n = 229)	0.6 (0.5–0.9) 11 (8–15) (n = 49)	0.7 (0.6–1) 12 (10–17) (n = 23)	0.6 (0.4–0.8) 10 (7–14) (n = 346)

SD standard deviation, APACHE Acute Physiology and Chronic Health Evaluation, IQR interquartile range, ECMO extracorporeal membrane oxygenation

^a Unless otherwise indicated. Percentages may not sum to 100 because of rounding

^b Data collection not approved in Canada and continental Europe. 'Other' includes 'declined' and 'multiple'

^c Infection confirmed by respiratory tract PCR test

^d Range: 0–71, with higher scores indicating greater severity of illness

^e Range: 3–15, with higher scores indicating greater consciousness, using values closest to randomization but prior to use of sedative agents

^f Value closest to randomization within prior 8 h. For creatinine, lactate, platelets and bilirubin, if pre-randomization value missing, the closest value within 2 h post-randomization was used. Laboratory values were only added to the case report form on August 6, 2020

(− 1 to 9) − 1 (− 1 to 7), respectively, compared to 6 (− 1 to 16) days in the control group (Table 2, Fig. 1). Compared with control, the corresponding median adjusted ORs (95% CrI) were 0.73 (0.55–0.99) for lopinavir-ritonavir, 0.57 (0.35–0.83) for hydroxychloroquine and 0.41 (0.24–0.72) for combination therapy, yielding posterior probabilities that reached the criteria for futility (all 99.9% or greater), yielding high posterior probabilities of harm (98%, 99.9% and > 99.9%, respectively, Table 2). In-hospital mortality among patients in lopinavir-ritonavir, hydroxychloroquine, combination therapy was 88/249 (35.3%), 17/49 (34.7%), 13/26 (50%), respectively, compared to 106/353 (30%) in the control group (Table 2, Fig. 2). In the primary analysis of hospital survival, the three interventions decreased survival compared to control, with the corresponding median adjusted ORs (95% CrI) of 0.65 (0.45–0.95), 0.56 (0.36–0.89), 0.36 (0.17–0.73), respectively, yielding

high probabilities of harm (98.5% and 99.4% and 99.8%, respectively, Table 2). Estimates from secondary and sensitivity analyses of the organ support-free days and hospital survival, including analyses restricting to concurrent controls of lopinavir-ritonavir and concurrent controls of hydroxychloroquine/combination therapy groups were consistent with the primary analyses (Figure S1, Tables S7 and S8 in Supplementary appendix).

Secondary outcomes

Lopinavir-ritonavir, hydroxychloroquine, and combination therapy resulted in a longer time to both ICU and hospital discharge compared with control and reduced survival over 90 days. All secondary outcome analyses yielded high posterior probabilities of harm (Table 3). The distribution of SARS-CoV-2 RNA clearance among patients randomized to receive lopinavir-ritonavir, hydroxychloroquine, combination therapy, and control was not visually different (Figure S2, Supplementary

Table 2 Primary and secondary analyses of organ support-free days (OSFDs) and hospital survival

Outcome/analysis	Lopinavir-ritonavir (N = 255)	Hydroxychloroquine (N = 50)	Combination therapy (N = 27)	Control (N = 362)
Primary outcome, organ support-free days (OSFDs)				
Median (IQR)	4 (− 1, 15)	0 (− 1, 9)	− 1 (− 1, 7)	6 (− 1, 16)
Adjusted OR—median (95% CrI)	0.73 (0.55, 0.99)	0.57 (0.35, 0.83)	0.41 (0.24, 0.72)	1
Probability of futility, %	99.9	> 99.9	> 99.9	–
Probability of harm compared to control, %	98	99.9	> 99.9	–
Subcomponents of OSFDs				
In-hospital deaths, n (%)	88/249 (35.3%)	17/49 (34.7%)	13/26 (50%)	106/353 (30%)
OSFDs in survivors, median (IQR)	14 (7, 17)	4 (0, 13)	8 (0, 13)	14 (3, 18)
Primary analysis of hospital survival				
Adjusted OR—median (95% CrI)	0.65 (0.45–0.95)	0.56 (0.30–0.89)	0.36 (0.17–0.73)	1
Probability of harm compared to control, %	98.5	99.4	99.8	–
Secondary analysis of primary outcome				
Adjusted OR—median (95% CrI)	0.76 (0.57, 1.02)	0.59 (0.35, 0.88)	0.45 (0.25, 0.78)	1
Probability of futility, %	99.9	> 99.9	> 99.9	–
Probability of harm compared to control, %	96.3	99.6	99.8	–
Secondary analysis of hospital survival				
Adjusted OR—median (95% CrI)	0.66 (0.46, 0.96)	0.58 (0.32, 0.91)	0.38 (0.18, 0.76)	1
Probability of harm compared to control, %	98.5	99.2	99.7	–

The primary analysis of organ support-free days (OSFD) and hospital survival were conducted on the REMAP-CAP Severe State cohort which included all patients enrolled in the trial who met COVID-19 Severe State criteria and were randomized within at least one domain ($n = 1928$), adjusting for other assigned treatments, age, sex, time period, site, domain and intervention eligibility and intervention assignment. Secondary analysis of organ support-free days (OSFD) and hospital survival were conducted on the Unblinded cohort which was restricted to patients randomized to an intervention in domains that have been unblinded including the COVID-19 Antiviral Therapy Domain and domains that have ceased recruitment (Corticosteroid and reported arms of the Immune Modulation Therapy Domain) ($n = 1271$)

Data on OSFD and in-hospital mortality were missing for six patients randomized to lopinavir-ritonavir, one to hydroxychloroquine, one to combination therapy and nine to control

Probability of harm is calculated as 1 of superiority

Additional secondary and sensitivity analyses are reported in Tables S7 and S8 in the Supplementary Appendix

Definitions of outcomes are provided in “Methods” and the study protocol

All models are structured such that a higher OR is favorable

CrI credible interval, OR odds ratio

Appendix). The full model was not performed for this outcome because of limited follow-up reverse transcription-polymerase chain reaction (RT-PCR) data.

Safety outcomes

Serious adverse events were reported in 13/255 (5.1%) patients randomized to lopinavir-ritonavir, 3/50 (6%) to hydroxychloroquine, 1/27 (3.7%) to combination therapy, and 12/362 (3.3%) to control. Serious ventricular arrhythmia or sudden unexpected death was reported in 6/239 (2.5%) patients randomized to lopinavir-ritonavir, 2/49 (4.1%) to hydroxychloroquine, 2/26 (7.7%) to combination therapy, and 10/435 (2.9%) to control (Table 3).

Subgroup analyses and interactions with corticosteroids and IL-6 antagonists

The effects of lopinavir-ritonavir, hydroxychloroquine and combination therapy on the primary outcome were similar across patients who were mechanically ventilated or not, and patients who were in shock or not, at the time of enrollment (Tables S9 and S10, Supplementary Appendix). There was no meaningful interaction between treatment with lopinavir-ritonavir, hydroxychloroquine, or combination therapy and the effects of corticosteroids or IL-6 receptor antagonists on organ support-free days or hospital survival. (Table S11, Table S12, and Statistical Analysis Committee Primary Analysis Report, Supplementary Appendix).

Discussion

Among critically ill patients with COVID-19, treatment with lopinavir-ritonavir, hydroxychloroquine or combination therapy did not improve outcomes and demonstrated a high probability of being harmful. The findings were robust on sensitivity analyses, including analyses restricting to patients randomized concurrently with lopinavir-ritonavir arm or patients randomized concurrently hydroxychloroquine/combination therapy arms,

and were consistent across secondary outcomes. Treatment with lopinavir-ritonavir, hydroxychloroquine, or combination therapy demonstrated similar harm regardless of concomitant therapy with corticosteroids or IL-6 receptor antagonists with no differential effects across assignments to these therapies.

The observed clinical findings are discordant with in vitro data that demonstrate antiviral activity against SARS-CoV-2 [9–11]. This may be related to several factors. It is unclear whether standard doses of lopinavir-ritonavir and hydroxychloroquine achieve adequate, safe and sustainable SARS-CoV-2 inhibitory concentrations in the lung and plasma as predicted by pharmacokinetic studies [12, 31, 32]. Both lopinavir-ritonavir and hydroxychloroquine are known for drug interactions and for their effects on prolonging QT prolongation and inducing cardiac arrhythmia. Hydroxychloroquine could worsen acute organ injury in critically ill patients with COVID-19 by inhibiting autophagy [33]. Additionally, ritonavir may increase the blood levels of hydroxychloroquine, further increasing the risk of adverse events with combination therapy [34]. We did not document significantly higher reports of serious ventricular arrhythmia or sudden unexpected death, but this analysis may be limited by the low number of events.

Previous studies have demonstrated a lack of benefit of lopinavir-ritonavir and hydroxychloroquine among hospitalized patients. These trials included predominantly patients admitted to hospital wards [19, 20]. For example, 4% of patients in the RECOVERY trial were receiving invasive mechanical ventilation, and 9% of patients in the Solidarity trial were mechanically ventilated at enrollment. On the other hand, REMAP-CAP which enrolled critically ill patients with COVID-19 receiving respiratory or cardiovascular support demonstrates a high probability of harm with these treatments. The observed harm in the current trial may reflect the fact that critically ill patients are generally at a higher risk for harm compared

(See figure on next page.)

Fig. 2 Organ support-free days and mortality. **A** Organ support-free days in patients allocated to lopinavir-ritonavir, hydroxychloroquine, combination therapy and control among critically ill patients in the COVID-19 Antiviral Therapy Domain of the REMAP-CAP trial. Distributions of organ support-free days are displayed as the cumulative proportion (y axis) for each study group by day (x axis). Curves that rise more slowly are more favorable. The height of each curve at “–1” indicates the in-hospital mortality for each intervention. The height of each curve at any time point indicates the proportion of patients who had that number of organ support-free days or fewer. The difference in the height of the curves at any point represents the difference in the percentile in the distribution of organ support-free days associated with that number of days alive and free of organ support. **B** Organ support-free days are displayed as horizontally stacked proportions by study group. Red represents worse values and blue represents better values. On primary analysis of organ support-free days, the three interventions decreased organ support-free days compared to control, with corresponding median adjusted ORs and 95% credible intervals of 0.73 (0.55–0.99), 0.57 (0.35–0.83) and 0.41 (0.24–0.72), respectively, yielding high posterior probabilities of futility (99% or greater) and high posterior probabilities of harm compared to control (98%, 99.9% and > 99.9%, respectively). **C** Empirical distribution of survival for lopinavir-ritonavir, hydroxychloroquine, combination therapy and control. Lopinavir-ritonavir, hydroxychloroquine and combination therapy resulted in reduced survival over 90 days compared to control, with adjusted median hazard ratios (95% CrI) of 0.83 (0.65, 1.07), 0.71 (0.45, 0.97), 0.58 (0.36, 0.92), yielding high probabilities of harm compared with control of 92% and 98.4% and 98.7%, respectively

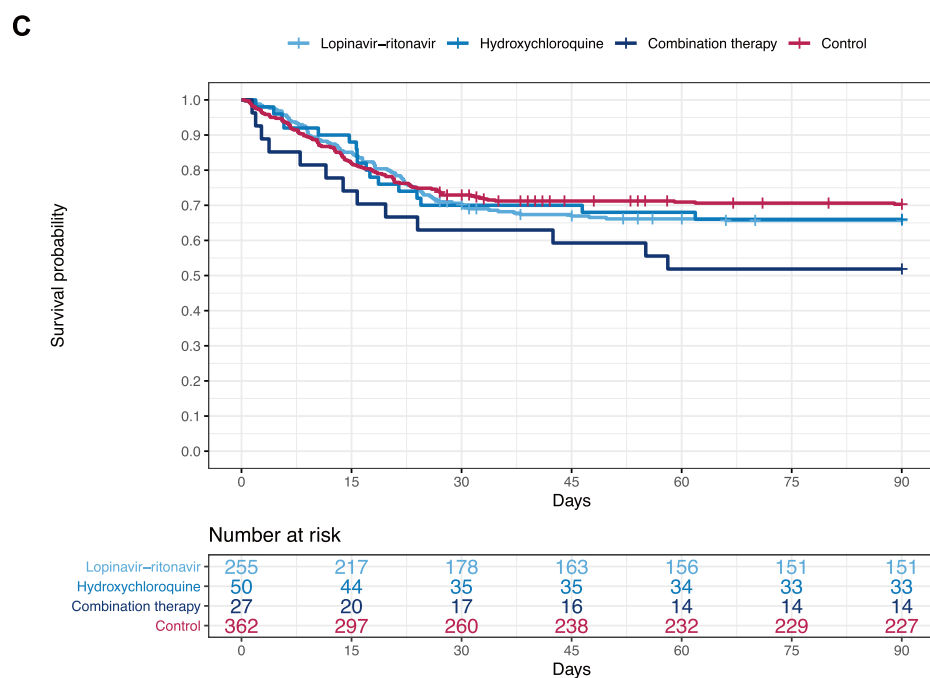
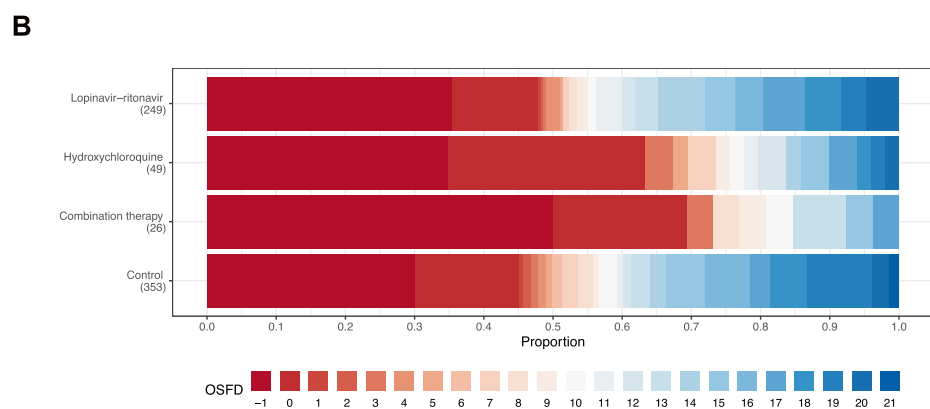
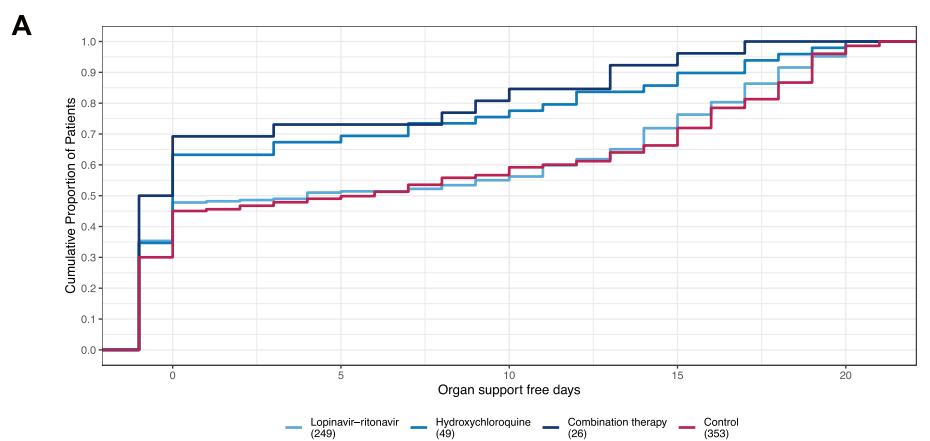


Fig. 2 (See legend on previous page.)

Table 3 Secondary and safety outcomes

Outcome/analysis	Lopinavir-ritonavir (N = 255)	Hydroxychloroquine (N = 50)	Combination therapy (N = 27)	Control (N = 362)
Secondary outcomes				
<i>90-day survival (time-to-event analysis)</i>				
Adjusted HR—median (95% CrI)	0.83 (0.65, 1.07)	0.71 (0.45, 0.97)	0.58 (0.36, 0.92)	1
Probability of harm compared to control, %	92	98.4	98.7	–
<i>Respiratory support-free days</i>				
Median (IQR)	3 (– 1, 15)	0 (– 1, 9)	–1 (– 1, 7)	5 (– 1, 16)
Adjusted OR—median (95% CrI)	0.75 (0.56, 0.99)	0.64 (0.4, 0.92)	0.47 (0.27, 0.83)	1
Probability of harm compared to control, %	97.7	99.2	99.7	–
<i>Cardiovascular support-free days</i>				
Median (IQR)	14 (– 1, 21)	13 (– 1, 19)	– 1 (– 1, 14)	18 (– 1, 21)
Adjusted OR—median (95% CrI)	0.66 (0.49, 0.89)	0.60 (0.39, 0.86)	0.39 (0.22, 0.69)	1
Probability of harm compared to control, %	99.7	99.6	> 99.9	–
<i>Time to ICU discharge</i>				
Adjusted HR—median (95% CrI)	0.87 (0.72, 1.07)	0.74 (0.52, 0.94)	0.63 (0.44, 0.89)	1
Probability of harm compared to control, %	91.2	99.4	99.7	–
<i>Time to hospital discharge</i>				
Adjusted HR—median (95% CrI)	0.83 (0.68, 0.99)	0.76 (0.56, 0.97)	0.63 (0.42, 0.89)	1
Probability of harm compared to control, %	98.1	98.5	99.6	–
<i>WHO scale at day 14</i>				
Adjusted OR—median (95% CrI)	0.85 (0.65, 1.13)	0.76 (0.49, 1.07)	0.63 (0.38, 1.08)	1
Probability of harm compared to control, %	86.6	94.4	95.5	–
<i>Progression to invasive mechanical ventilation, ECMO or death, restricted to those not intubated at baseline</i>				
n/N (%)	89/176 (50.6)	17/24 (70.8)	11/14 (78.6)	107/239 (44.8)
Adjusted OR—median (95% CrI)	0.75 (0.5, 1.12)	0.58 (0.24, 1)	0.42 (0.16, 0.95)	1
Probability of harm compared to control, %	92	97.6	98.2	–
Safety outcomes				
Serious adverse events (SAE)				
Patients with ≥ 1 SAE, n/N (%) ^a	13/255 (5.1)	3/50 (6)	1/27 (3.7)	12/362 (3.3)
Adjusted OR—median (95% CrI)	0.55 (0.24, 1.22)	0.65 (0, 2.38)	0.97 (0.24, 4.79)	1
Probability of harm compared to control, %	93	74.8	51.9	–
Serious ventricular arrhythmia or sudden unexpected death				
n/N (%)	6/239 (2.5)	2/49 (4.1)	2/26 (7.7)	10/345 (2.9)
Adjusted OR—median (95% CrI)	1.30 (0.56, 3.28)	0.88 (0.27, 3.55)	0.62 (0.18, 2.6)	1
Probability of harm compared to control, %	28.2	58.2	75	–

Secondary and safety analyses were conducted on the Unblinded cohort which included all patients the enrolled in the COVID-19 Antiviral Therapy Domain and domains that have ceased recruitment (Corticosteroid and reported arms of the Immune Modulation Therapy Domain) ($n = 1293$), adjusting for age, sex, time period, site, region, domain and intervention eligibility and intervention assignment

Probability of harm is calculated as 1 of superiority

Definitions of outcomes are provided in “Methods” and the study protocol

All models are structured such that a higher OR or HR is favorable. The WHO scale ranges from 0 (no disease) to 8 (death)

WHO World Health Organization, SD standard deviation, CrI credible interval, OR odds ratio, HR Hazard ratio

^a Denominators represent patients with available data

to those who are less ill and are hospitalized on the wards [35]. Additionally, treatment at a later time point in the disease course, when the patient becomes critically ill, may correspond to viral replication becoming

a less prominent feature in the disease pathogenesis, at which point the harm of antiviral therapy outweighs any potential benefit. The consistent findings from different sensitivity analyses, including the model restricted

to patients in the COVID-19 Antiviral Therapy Domain, demonstrated the robustness of the findings.

This study highlights some of the features of the adaptive platform trial design used in REMAP-CAP. The adaptive platform trial design allows efficient enrollment into multiple therapeutic domains simultaneously and studying interactions with several agents; a feature that explains its increasing use in other medical fields including oncology and psychiatry. The design has the flexibility to allow different interventions to be added or removed into the platform, and to allow sites to choose some or all interventions, based on the local drug availability and equipoise. These features, along with the multicenter, multinational pragmatic conduct, contribute to the efficiency of the trial and the generalizability of the results, thus facilitating quick answers to multiple questions; a highly desirable feature during a global pandemic. Our study also illustrates the efficiency that is associated with the REMAP-CAP design; the ongoing recruitment of patients into the platform even after the hydroxychloroquine interventions stopped enrolling provided more information to be included in the analytical model, with appropriate adjustment for time, to inform specific treatment effects [36, 37]. The real-time adaptive analyses, which are based on data from patients with completed outcome information, allow quick decisions about halting interventions upon reaching futility thresholds. In the case of lopinavir-ritonavir, enrollment was halted once the futility threshold was met based on available data at the time of the adaptive analysis. By definition of the statistical triggers, the futility trigger must occur prior to the harm trigger. Because of this ordered relationship, the pre-specified trigger for harm is only evaluated at the final analysis while the futility trigger is evaluated at adaptive and final analyses. Once outcome data on the remaining patients were completed, the final analysis demonstrated that the intervention was not only futile, but also harmful. This feature of frequent adaptive analyses allows for ongoing assessment for futility, thus reducing the unnecessary exposure of additional patients to non-effective or harmful therapies, compared to standard RCT. The drawback of this study design is that study groups may end up unequal in size, may not be entirely concurrent in time, or balanced in some of the baseline characteristics despite equal randomization at any given point [38]. In our study, this explains the different sizes of the study groups. Additionally, patients were enrolled in the hydroxychloroquine and combination therapy groups at a time when ICUs were under strain and corticosteroid therapy was not the standard of care. To address these recognized issues with the adaptive platform design, the primary model adjusted for time and site and corticosteroid therapy. To further address the possible effect

of concurrent control, we conducted additional analysis restricted to the concurrent controls of lopinavir-ritonavir and to the concurrent controls of hydroxychloroquine and combination therapy groups. These analyses demonstrated that baseline characteristics (including invasive mechanical ventilation) and co-interventions (including corticosteroids and remdesivir) were generally balanced between intervention groups and respected concurrent controls, and that the treatment effects are consistent results with the primary analysis. To limit potential sources of bias, we used a centralized randomization with concealed allocation and performed analysis based on the intention-to-treat principle. In addition, all analyses were specified prior to unblinding results. The study has limitations. Enrollment into the hydroxychloroquine and combination therapy study arms was halted before reaching any pre-specified internal trigger but based on external evidence. While the small sample size is a limitation of the current study, the strong signal observed in the small number of patients results in a high probability of harm. Data on the bioavailability of dissolved or crushed lopinavir-ritonavir tablets in critically ill patients are limited. The study used an open-label design, although clinician and patient awareness of study assignment likely had minimal effect on the organ support or mortality components of the primary outcome.

In conclusion, among critically ill patients with COVID-19, treatment with lopinavir-ritonavir, hydroxychloroquine, or combination therapy resulted in worse outcomes compared to no COVID-19 antiviral therapy.

Supplementary Information

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Availability of data and material

Qualified researchers registered with an appropriate institution can request access to deidentified patient data after 9 months of publication through submission of a proposal to the corresponding author. The proposal will be reviewed and approved by the REMAP-CAP ITSC to ensure that any proposed publication is of high quality, honours the commitments made to the study patients in the consent documentation and ethical approvals, and is compliant with sponsor restrictions and relevant legal and regulatory requirements (e.g., relating to data protection and privacy). The ITSC committee will have the right to review and comment on any draft manuscripts before publication. A contract will also be signed.

Declarations

Conflicts of interest

ACG reports grants from NIHR, grants from NIHR Research Professorship (RP-2015-06-18), non-financial support from NIHR Clinical Research Network, during the conduct of the study; personal fees from GlaxoSmithKline, personal fees from Bristol Myers Squibb, personal fees from 30 Respiratory, outside the submitted work; LPGD is a member of the COVID-19 guideline committee SCCM/ESICM/SSC, member of the ESICM COVID-19 taskforce, and chair of the Dutch intensivists (NVIC) taskforce acute infectious threats; AND reports grants from Health Research Board of Ireland, during the conduct of the study; AB reports grants from Minderoo, grants from Wellcome, during the conduct of the study; LRB reports grants from EU PREPARE consortium, grants from Australian National Health and Medical Research Council, grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; CAB reports personal fees from BMS pfizer, non-financial support from Bayer, personal fees from Novartis, personal fees from Janssen, non-financial support from Amgen, personal fees from Lilly, personal fees from Portola, personal fees from Ablynx, outside the submitted work; MB reports other from Breast Cancer Research Foundation, during the conduct of the study; other from Eisai Inc, other from Amgen Inc, outside the submitted work; MDJ reports receiving fees for being on the Advisory Board for Roche and Cidara. He also reports receiving fee for being on IDSMB for Janssen and GSK; MAD reports grants from EU PREPARE, grants from Australian National Health and Medical Research Council, grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; MF reports grants from EU PREPARE, grants from Australian National Health and Medical Research Council, grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; RH reports grants from Wellcome Trust, during the conduct of the study; grants from National

Institute of Health Research, outside the submitted work; AMH reports grants from National Health and Medical Research Council and from the Minderoo Foundation during the conduct of the study; TEH reports grants from Health Research Council of New Zealand, during the conduct of the study; CMH reports grants from NICHD, during the conduct of the study; DTH reports grants from The Breast Cancer Research Foundation in collaboration with the Translational Breast Cancer Research Consortium, during the conduct of the study; PRL reports personal fees from Novartis, personal fees from Brigham and Women's Hospital, personal fees from Corona LLC, personal fees from McGraw Hill Publishing, outside the submitted work; RJL reports that Berry Consultants, LLC, a statistical consulting firm that specializes in the design, conduct, oversight, and analysis of adaptive and platform clinical trials, received support for its role in the design, conduct, and analysis of REMAP-CAP. Dr. Lewis is the Senior Medical Scientist at Berry Consultants, LLC; EL reports grants from EU, grants from Australian National Health and Medical Research Council, grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; DFM reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis and Eli Lilly, and from sitting on a DMEC for a trial undertaken by Vir Biotechnology. In addition his institution has received funds from grants from several funders for studies in patients with ARDS and COVID-19. In addition, DFM has a patent (US8962032) issued to his institution for a treatment for inflammatory disease. He is a Director of Research for the Intensive Care Society and NIHR EME Programme Director; AM reports grants from EU-PREPARE, grants from Australian National Health and Medical Research Council, grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; B JM reports grants from Translational Breast Cancer Research Consortium, grants from UPMC Learning While Doing Program, during the conduct of the study; grants from NIH/NHLBI, grants from Bayer Pharmaceuticals, Inc, outside the submitted work; SCM reports grants from Health Research Council of New Zealand, during the conduct of the study; PRM reports grants from National Institute for Health Research, grants from European Union FP7 (PREPARE), during the conduct of the study; RP reports grants from Fisher and Paykel Healthcare NZ Ltd, outside the submitted work; KMR reports grants from European Union, grants from UK National Institute for Health Research, during the conduct of the study; CTS reports grants from EU PREPARE, grants from Australian National Health and Medical Research Council, grants from Health Research Council of New Zealand, grants from UPMC, during the conduct of the study; CWS reports grants from NIH, personal fees from Beckman Coulter, outside the submitted work; MSH reports other from National Institute For Health Research, outside the submitted work; AMT reports grants from Health Research Council of New Zealand, during the conduct of the study; FVV reports personal fees from Gilead, personal fees from Sobi, outside the submitted work; SB reports personal fees from Berry Consultants, during the conduct of the study; JCM reports grants from Canadian Institutes of Health Research, during the conduct of the study; personal fees from Gilead Pharmaceuticals, outside the submitted work; CM reports grants from Health Research Council of New Zealand, non-financial support from Abbvie, during the conduct of the study; DCA reports non-financial support from European Union FP7 PREPARE, grants from Breast Cancer Research Foundation, Amgen, Inc., and Eisai, Inc, during the conduct of the study; SAW reports grants from National Health and Medical Research Council, grants from Minderoo Foundation, grants from Health Research Council, during the conduct of the study. *All other authors had no conflict of interest to disclose.

Ethics approval

The trial was approved by the relevant ethics committees in all regions.

Consent to participate

Written or verbal informed consent, in accordance with regional legislation, was obtained from all patients or from their surrogates.

Consent for publication

All authors approved the manuscript for submission.

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