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► **To cite this version:**

Alisa M. Higgins, Lindsay R. Berry, Elizabeth Lorenzi, Srinivas Murthy, Zoe K. Mcquilty, et al.. Long-term (180-Day) Outcomes in Critically Ill Patients with COVID-19 in the REMAP-CAP Randomized Clinical Trial. *Journal of the American Medical Association*, 2023, 329 (1), pp.39-51. 10.1001/jama.2022.23257 . hal-03949589

**HAL Id: hal-03949589**

**<https://hal.science/hal-03949589v1>**

Submitted on 16 Mar 2023

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# Long-term (180-day) outcomes in critically ill patients with COVID-19 in the REMAP-CAP randomized clinical trial

**The REMAP-CAP Investigators\***

## **\*Author and Group Information**

The members of the writing committee appear at the end of the main text and the full list of investigators and collaborators in the Supplementary Appendix.

## **Running Head**

180-Day Outcomes in the REMAP-CAP COVID-19 RCT

## **Key words**

Adaptive platform trial; randomized controlled trial; intensive care, pneumonia; COVID-19; antiplatelet; immunoglobulin; antiviral; corticosteroid; immune modulation; anticoagulation

**Word count** 4170

**Date of Revision** 25 November 2022

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# Key points

## Question

What is the effect of treatment for critically ill patients with COVID-19 on longer-term mortality, disability and health-related quality of life (HRQoL)?

## Findings

In this Bayesian adaptive randomized clinical platform trial that included 4869 critically ill patients with COVID-19, the probability was high that interleukin-6 receptor antagonists and antiplatelet agents improved survival at 6 months (posterior probabilities of superiority >99.9% and 95.0%). Long-term outcomes were not improved with therapeutic anticoagulation (11.5%), convalescent plasma (54.7%), or lopinavir-ritonavir (31.9%), and were worsened with hydroxychloroquine (posterior probability of harm 96.8%). Corticosteroids did not improve long-term outcomes, although enrollment had been terminated early in response to external evidence.

## Meaning

Among critically ill patients with COVID-19 randomized to receive one or more therapeutic interventions, there was a high likelihood of improved 180-day mortality among patients treated with IL-6 receptor antagonists and antiplatelets.

# Abstract

**IMPORTANCE** The longer-term effects of therapies for the management of critically ill patients with COVID-19 are unknown.

**OBJECTIVE** To determine the effect of multiple interventions for critically ill adults with COVID-19 on longer-term outcomes.

**DESIGN, SETTING AND PARTICIPANTS** Pre-specified secondary analysis of an ongoing adaptive platform trial (REMAP-CAP) testing interventions within multiple therapeutic domains, in which 4869 critically ill adult patients with COVID-19 were enrolled between 9 March 2020 and 22 June 2021 from 197 sites in 14 countries. The final day-180 follow up was completed on 2 March 2022.

**INTERVENTIONS** Patients were randomized to one or more interventions within six treatment domains—immune modulators (n=2274), convalescent plasma (n=2011), antiplatelet therapy (n=1557), anticoagulation (n=1033), antivirals (n=726), and corticosteroids (n=401).

**MAIN OUTCOMES AND MEASURES** The main outcome was survival through day 180, analyzed using a Bayesian piecewise exponential model. A hazard ratio (HR) < 1 represented improved survival (superiority), while a HR > 1 represented worsened survival (harm); futility was represented by a < 20% relative improvement in outcome shown by a HR > 0.83 (1/1.2).

**RESULTS** Among 4869 patients who were randomized (mean age, 59.3 years; 1537 (32.1%) females), 4107 (84.3%) had known day 180 vital status and 2590 (63.1%) were alive. Interleukin-6 receptor antagonists and antiplatelet agents had a >99.9% and 95.0% probability of improving 6-month survival compared with control (adjusted hazard ratios [HR]

0.74 [95% CrI 0.61-0.90] and 0.85 [0.71-1.03]), while the probability of trial-defined statistical futility (HR >0.83) was high for therapeutic anticoagulation (99.9%, HR 1.13 [95% CrI 0.93-1.42]), convalescent plasma (99.2%, HR 0.99 [95% CrI 0.86-1.14]), and lopinavir-ritonavir (96.6%, HR 1.06 [95% CrI 0.82-1.38]), and the probability of harm from hydroxychloroquine and the combination of lopinavir-ritonavir and hydroxychloroquine was high (96.9% and 96.8%, HR 1.51 [95% CrI 0.98-2.29] and 1.61 [95% CrI 0.97-2.67]). The corticosteroid domain was stopped early, prior to reaching a predefined statistical trigger; there was a 57.1% to 61.6% probability of improving 6-month survival across varying hydrocortisone dosing strategies.

**CONCLUSIONS AND RELEVANCE** Among critically ill patients with COVID-19 randomized to receive one or more therapeutic interventions, treatment with an IL-6 receptor antagonist had a >99.9% probability of improved 180-day mortality compared with patients randomized to control, and treatment with an antiplatelet had a 95.0% probability of improved 180-day mortality compared with patients randomized to control. Overall, when considered with previously reported short-term results, the findings indicate that initial in-hospital treatment effects were consistent for most therapies through 6 months.

## Introduction

Randomized clinical trials in critically ill patients, including those with COVID-19, typically assess short-term outcomes such as organ failure or 28-day mortality, with fewer published trials assessing whether treatments affect long-term survival and patient-centered outcomes such as disability and health-related quality of life (HRQoL). Longer-term survival free of major disability and with an acceptable HRQoL may be more important to patients than short-term survival.<sup>1,2</sup> The World Health Organization and others have called for additional research on the effect of initial therapeutic interventions on longer-term outcomes.<sup>3</sup>

The Randomized Embedded Multifactorial Adaptive Platform for Community Acquired Pneumonia (REMAP-CAP) trial is an ongoing international, multicenter, randomized platform trial evaluating multiple treatments for patients with severe pneumonia in both pandemic and non-pandemic settings (NCT02735707) (Supplement 1).<sup>4</sup> To date, the trial has reported results for six treatment domains for patients with COVID-19—corticosteroids, antivirals, immune modulators, immunoglobulin, anticoagulation and antiplatelet therapy.<sup>5-10</sup> The trial primary outcome for patients with COVID-19 is the composite of hospital survival and organ support provision up to 21 days. The trial reported benefit on this primary outcome for interleukin-6 receptor antagonists (immune modulators), but not for antivirals, anakinra (immune modulator), convalescent plasma (immunoglobulin), therapeutic anticoagulation (in critically ill patients), or antiplatelet therapies.<sup>6-10</sup> The corticosteroid domain was closed early on the basis of external evidence but a moderate probability of benefit was observed.<sup>5</sup> Whether these initial treatment effects translate into effects on longer-term survival, disability and HRQoL is unknown. The objective of this study was to report on the effects of these treatments on pre-specified longer-term outcomes including mortality, disability and

HRQoL at 6 months for patients randomized to one or more of the reported domains in the trial.

## Methods

### Trial Design and Oversight

The design of REMAP-CAP has been reported previously.<sup>4-10</sup> In brief, patients are assessed for eligibility and potentially randomized to one or more interventions across multiple treatment domains. Domains encompass therapeutic areas and contain two or more interventions (including control). The trial enrolls both critically ill and non-critically ill patients in separate severity states, and distinct group-specific effects are estimated. This report includes only critically ill patients as follow up beyond 90 days does not include non-critically ill patients. The trial was approved by relevant regional ethics committees and conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written or verbal informed consent, in accordance with local legislation, was obtained from patients or their substitute decision maker.

### Participants

Adult patients (aged  $\geq 18$  years) admitted to an ICU with clinically suspected or microbiologically confirmed COVID-19, and receiving respiratory or cardiovascular organ support, were eligible for enrollment. Patients had to be enrolled within 48 hours of admission to ICU. Exclusion criteria along with additional inclusion and exclusion criteria for each domain are shown in Table S1.<sup>5-10</sup> Patients were enrolled from 197 sites in 14 countries

(Table S2). In view of racial and ethnic differences in outcomes during the pandemic, this trial collected self-reported race and ethnicity from either the participants or their surrogates via fixed categories appropriate to their region, where ethical approval allowed. Collection of race and ethnicity data was not approved in Asia, Canada, and continental Europe.

## **Treatment Allocation**

Patients were randomized via a centralized computer program with allocation ratios dependent on response adaptive randomization and the number of interventions available at each site. The interventions within each domain, including timing and doses, are reported previously.<sup>5-10</sup> In brief, patients in the corticosteroid domain were randomized to receive a fixed 7-day course of intravenous hydrocortisone, a shock-dependent course, or no corticosteroid; patients in the immune modulation domain were randomized to receive tocilizumab, sarilumab (both interleukin-6 receptor antagonists [IL-6 RAs]), anakinra (an interleukin-1 receptor antagonist), interferon- $\beta$ 1a, or no immune modulator; patients in the antiviral domain were randomized to receive lopinavir-ritonavir, hydroxychloroquine, the combination of both therapies, or no antiviral; patients in the immunoglobulin domain were randomized to receive 2 units of high-titer, ABO-compatible convalescent plasma, delayed convalescent plasma (given if clinical deterioration, only available in the US), or no convalescent plasma; patients in the anticoagulation domain were randomized to receive therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis in accordance with local usual care; and patients in the antiplatelet domain were randomized to receive aspirin, a P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel, or ticagrelor), or no antiplatelet therapy. Patients could be randomized to additional interventions within other domains, depending on domains active at the site, patient eligibility, and consent (see



www.remapcap.org).<sup>4</sup> Other aspects of care were provided as per each site's standard of care.

## Outcome Measures

The main outcome for this prespecified secondary analysis of longer-term outcomes was all-cause mortality within 6 months (day 180 after randomization), a prespecified secondary outcome in the REMAP-CAP core protocol. This was modelled as a time to event outcome for this analysis. Additional secondary outcomes were prespecified in the Core Protocol and included day 90 mortality, HRQoL at day 180 measured using the EQ-5D-5L utility score and visual analogue score (VAS), and disability at day 180, measured using the 12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0. The EQ-5D-5L is a preference-based HRQoL instrument comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L utility score is calculated from the individual response to each item and ranges from -0.593 (where a score of 0 is equivalent to death, negative values representing values as worse than dead) to 1.00 (the value of full health), with higher values indicating better health states.<sup>11</sup> An EQ-5D-5L utility score of 0 was imputed for all patients known or imputed to be deceased at Day 180. For the EQ VAS, respondents are asked to indicate their present health state on a visual analogue scale ranging from the worst imaginable health state ("0") to the best imaginable health state ("100").<sup>12,13</sup> The EQ-5D-5L utility score and EQ VAS have no established minimal clinically important difference among critically ill patients. The WHODAS 2.0 covers six domains of functioning with scores for each item from 0 (no difficulty) to 4 (extreme difficulty) and a total score ranging from 0 to 48, with higher scores representing greater disability.<sup>14</sup> The total score is divided by 48 and multiplied by 100 to convert it to a percentage of maximum

disability, with the percent score used to determine five mutually exclusive disability categories, from no disability to complete disability.<sup>15</sup> The MCID for the WHODAS in critically ill patients is 10%.<sup>16</sup>

Day 90 mortality was collected at all sites, whereas day 180 outcomes were collected only by a subset (174/197, 88.3%) of sites. The decision to participate in the collection of longer-term outcomes was made regionally or locally reflecting funding, regulatory approval, and site resource availability. In the UK, the large numbers of recruited participants from 5 January 2021 to 25 February 2021 exceeded the capacity for extended follow-up of all patients within the required time window. Accordingly, at the time, a subset of participants was randomly selected not to be followed-up. Overall, 587/787 (74.6%) survivors enrolled during this period were followed through 6 months.

Survival status was assessed at days 90 and 180 and determined using medical records, or contact with the participant, their next of kin, or other healthcare professional. Where a participant was deceased, the date of death was recorded. Day 180 HRQoL and disability in survivors were collected by central trial staff or site staff by telephone, with the patient or a proxy where the patient was not available. EQ-5D-5L utility scores were calculated using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system, using the UK time trade off (TTO) value set.<sup>11</sup> EQ-5D-5L and WHODAS scores were only included when the questionnaire was completed within the 12 weeks following day 180 (additional details in Supplemental Methods).

## **Statistical Analysis**

This study reports the analysis of longer-term secondary outcomes prespecified in the REMAP-CAP trial Core Protocol (Supplement 1). The analysis plan for evaluating these outcomes was finalized in a Statistical Analysis Plan (Supplement 1) on 10th March 2022, prior to unblinding the day 180 outcomes. All patients were analyzed in the groups to which they were originally randomized. The full analysis set included all critically ill patients with suspected or proven COVID-19 randomized to an intervention in one or more of the six domains which have been closed and reported, excluding patients who had withdrawn consent. For consistency with the original analyses,<sup>5-10</sup> the P2Y12 inhibitor and aspirin groups are reported as a pooled antiplatelet group, and the tocilizumab and sarilumab groups as a pooled IL-6 RA group, given that both sets of interventions reached the prespecified definition of equivalence on organ support-free days in the original analysis. Due to the low number of patients randomized, the interferon-beta-1a group within the immune modulation domain and the delayed convalescent plasma intervention within the immunoglobulin domain were not analyzed.

The primary analysis was performed using a Bayesian piecewise exponential model. The underlying hazard rate was piecewise constant for each 15-day period up to day 90 and the 90-day period from day 90 to 180. The prior distribution for each hazard rate was a gamma distribution with 1 day of exposure and a mean equal to the total exposure (in days) divided by the total number of events. The primary model estimated treatment effects (log HRs) for each intervention relative to control within each domain with standard normal priors. The primary model included variables for each domain with each domain treatment as a category (with control interventions from each domain set as the referent) and was adjusted for location (site nested within country), patient age (categorized into 6 groups), sex, and time-

period (2-week epochs). The posterior distributions of the interventions' hazard ratios (HR) was summarized with medians, 95% credible intervals (CrIs) and the probability that an intervention was superior to the control for that domain (i.e. a HR less than 1.0). Harm was defined as the probability the HR was greater than 1. Futility was defined as the probability that there was not more than a 20% relative improvement in outcome ( $HR > 0.83$  or  $1/1.2$ ). A pre-specified interaction was modelled between antiplatelet therapy (pooled P2Y12 inhibitor and aspirin group) in the antiplatelet domain and therapeutic-dose heparin in the anticoagulation domain. Statistical thresholds based on posterior probabilities for superiority and harm were used for the primary outcome to determine trial stopping rules but not used to guide interpretation of other findings; rather, effect sizes along with posterior probabilities are presented for all analyses.

Day 90 mortality was analyzed with a Bayesian logistic regression model. The EQ-5D-5L utility score was analyzed with a two-part/mixture model including two components: 1) a continuous distribution of EQ-5D-5L utility scores for patients who survived to day 180, and 2) a point mass at 0 for patients who died before day 180. The posterior distributions of the mean difference between treatment and control for EQ-5D-5L utility scores were summarized with medians, 95% CrIs and the probability that an intervention was superior to the control for that domain (i.e. a mean difference less than 0). Treatment effects were estimated for all patients, along with estimates for survivors only. The EQ VAS was reported using descriptive statistics only. The WHODAS disability category was analyzed with a two-part/mixture model including two components: 1) an ordinal model of disability category for patients that survived to day 180, and 2) the worst category of "death" for patients that died before day 180. Similarly, the posterior distributions of the interventions' odds ratio (OR) for

WHODAS disability category for survivors were summarized with medians, 95% CIs and the probability that an intervention was superior to the control for that domain (i.e. a OR less than 1). The EQ-5D-5L utility score and WHODAS category were multiply imputed as a function of the patient's covariates for patients censored alive before day 180 or missing the HRQoL outcome. Sampling was from all patients enrolled in the timeframe and the sampling probability was independent of treatment assignment. The relationship between shorter- and longer-term endpoints was assessed by plotting the OSFD OR versus Day 180 mortality HR for each intervention and reporting the coefficient of determination ( $R^2$ ).

Sensitivity analyses for the main outcome included, 1) excluding patients with negative SARS-CoV-2 testing, 2) removing adjustments for assignments in other domains and 3) estimating independent effects of the two interleukin-6 receptor antagonist interventions and the two antiplatelet interventions. For secondary outcomes, sensitivity analyses included no imputation of missing EQ-5D-5L utility and WHODAS scores. Post hoc sensitivity analyses were conducted to evaluate the main outcome model and robustness to model assumptions, including 1) the assumption of proportional hazards for treatment effects; 2) the assumption of a parametric distribution of survival times (piecewise exponential); and 3) the use of prior distributions in the Bayesian framework (Supplemental Methods).

Two subgroup analyses were performed stratifying treatment effects on day 180 mortality based on the binary categories of receipt of invasive mechanical ventilation at baseline and pre-existing immunosuppression. Further details of all analyses are provided in the Statistical Analysis Plan in Supplement 1. Data management and summaries were created using R version 3.6.0, with the primary analysis computed in R version 4.1.2 using the rstan package

version 2.21.1. Additional data management and analyses were performed in SQL 2016, and Stata version 17.0.

## Results

### Enrollment and Participant Characteristics

A total of 4869 patients were enrolled from 9 March 2020 through 24 June 2021 to one or more of the six reported domains in the trial. Seventy-eight patients withdrew consent, resulting in 4791 patients included in the analysis of longer-term outcomes (Figure 1). Of these, 473 were randomized at 19 sites that only participated in the 90-day follow-up, including all sites in Nepal, India, and the United States. Details of recruitment and follow up by country of enrollment are shown in Table S2. The final day 180 follow up was completed on 2 March 2022. The baseline characteristics of the included patients are shown in Table 1. Baseline characteristics by intervention within each domain are shown in Tables S3 to S8.

### Main Outcome

Of the 4318 patients randomized at sites participating in day 180 follow-up, day 180 mortality status was available for 4107 (95.1%) patients. Patients with known day 180 mortality status differed from those with unknown status; patients with unknown status were younger, had higher frequencies of non-invasive ventilation receipt at baseline, lower frequencies of invasive mechanical ventilation and vasopressor use at baseline, lower APACHE II scores, and were less likely to have prevalent asthma or COPD, immunosuppressive disease, or to be receiving chronic immunosuppressive therapy (Table

S9). Of patients with known day 180 mortality status, 1517 (36.9%) patients had died. (Table 2 and Figure 2) Of patients who died by day 180, 6.0% (91/1516) of deaths occurred between hospital discharge and day 180. The pooled interleukin-6 receptor antagonists and anti-platelet treatment groups each had a high probability of benefit (>99.9% and 95.0% respectively) compared with their control groups. The probability of benefit for fixed dose corticosteroids and shock-dependent corticosteroids compared to no corticosteroids was 61.6% and 57.1%, respectively. The probability of trial-defined statistical futility was high for therapeutic anticoagulation in the critically ill (99.9%, HR 1.13 [95% CrI 0.93-1.42]), convalescent plasma (99.2%, HR 0.99 [95% CrI 0.86-1.14]), and lopinavir-ritonavir (96.6%, HR 1.06 [95% CrI 0.82-1.38]). Hydroxychloroquine and its combination with lopinavir-ritonavir had a high probability of harm (96.9% and 99.5%, HR 1.51 [95% CrI 0.98-2.29] and 1.61 [95% CrI 0.97-2.67] respectively) (Table 2 and Figure S1). Results of the sensitivity analyses for non-negative COVID patients and in domain-specific populations were consistent with the primary analysis (see Tables S10 to S12 and Figure S2). Post hoc sensitivity analyses found the results were robust to model assumptions including the proportional hazards assumption (Figures S3-S4 and Model Evaluation Report in the supplement). Across interventions there was a strong association ( $R^2 = 0.84$ ) between the ORs for the composite of in-hospital mortality and organ support free days to day 21 (primary outcome in the trial) and the reciprocals of day 180 mortality hazard ratios (Figure S5).

## Secondary Outcomes

The ORs for day 90 mortality are shown in Table S13 and Figure S6. Results were consistent with the day 180 mortality analysis.

Of the 2589 survivors at sites participating in follow up, the EQ VAS was available in 1009 patients (39.0%), the EQ-5D-5L utility score in 989 patients (38.2%), and the WHODAS in 720 patients (27.8%) (Figure 1). Patients without EQ-5D-5L utility and WHODAS scores differed from those with scores - patients missing scores were younger; received less high-flow nasal oxygen and more non-invasive and invasive ventilation, and were less likely to have immunosuppressive disease or be receiving chronic immunosuppressive therapy (Tables S14 and S15).

In the overall cohort, the median (IQR) EQ-5D-5L utility score in survivors was 0.74 (0.55 to 0.88; n=989). The median (IQR) EQ VAS score was 75 (50 to 85; n=1009). The proportion of patients reporting problems in each domain and the EQ VAS scores are shown in Tables S16 and S17. Among survivors, the adjusted mean difference (95% CrI) in the EQ-5D-5L utility score in the pooled antiplatelet group was 0.08 (0.00 to 0.15) higher compared with control, with a posterior probability of superiority of 97.4%, while among all patients (survivors and non-survivors) the adjusted mean difference (95% CrI) was 0.08 (0.02 to 0.13) with a probability of superiority of 99.6% (Table 3). Among all patients, the adjusted mean difference in the pooled IL-R RAs was 0.08 (0.02 to 0.13) higher compared with control, with a posterior probability of 99.5%. The mean EQ-5D-5L utility score in the lopinavir-ritonavir group was lower than the control group, with a posterior probability of harm of 98.7% among survivors, and 98.4% among all patients. The mean difference in EQ-5D-5L utility scores between each remaining intervention and their control group are shown in Table 3 and Figure S7.

Disability in survivors is shown in Tables S18 and S19. 37.9% (273/720) of survivors had moderate, severe, or complete disability at day 180. The 95% CrIs for the ORs for WHODAS



disability category were wide, with intervals crossing 1 for all interventions (Figure S8).

Among these interventions, pooled interleukin-6 receptor antagonists and anakinra had a 92.6% and 90.8% probability of reducing disability and lopinavir-ritonavir had a 91.7% probability of worsening disability.

Results for the sensitivity analyses of the EQ-5D-5L utility score and WHODAS without imputation for missing scores were consistent with the imputed analysis (Tables S20-S21).

## **Subgroup Analyses**

Treatment effects on day 180 mortality did not meaningfully vary by invasive mechanical ventilation status at baseline (Tables S22-S23 and Figure S9). In patients with immunodeficiency at baseline, therapeutic anticoagulation and antiplatelet therapy had posterior probabilities of worsened day 180 mortality of 98.8% and 92.4% (Table S24-S25 and Figure S10).

## **Discussion**

In this prespecified secondary analysis of a Bayesian adaptive randomized clinical platform trial that included 4791 critically ill patients with COVID-19, there was a >99.9% and 95.0% probability that interleukin-6 receptor antagonists and antiplatelet agents improved survival through 6 months respectively. In contrast, survival was not improved with therapeutic anticoagulation, convalescent plasma, or lopinavir-ritonavir, and the probability that survival was worsened with hydroxychloroquine alone or in combination with lopinavir-ritonavir was 96.8%. Corticosteroids did not confer a high probability of improved longer-term survival, but enrollment into this domain was closed early in response to external evidence which may

limit statistical power to detect any potential effect. Although the majority of deaths occurred early, 6% of all deaths occurred between hospital discharge and day 180.

Interventions are delivered in critically ill patients with the goal of increasing long-term survival as well as improving HRQoL and functional status in survivors. However most clinical trials in critically ill patients have evaluated shorter-term outcomes, many of which may not be patient-centered.<sup>17</sup> Longer-term trajectories after critical illness, including acute respiratory distress syndrome (ARDS) and sepsis, are characterized by frequent rehospitalization, sustained impairments in HRQoL and functional status, an excess hazard of mortality, and exacerbation of chronic comorbidities which may persist for years after initial hospitalization.<sup>18-23</sup> Patients who initially survive face later mortality and morbidity hazards that may offset potential benefits of treatment. Accordingly, the effect of many treatments administered in the ICU on long-term outcomes after critical illness – including COVID-19 – remain uncertain. Although the REMAP-CAP trial evaluated a hospital-based primary outcome reflecting survival to discharge and, in survivors, receipt of ICU-level organ support, the protocol included the collection of longer-term (6-month) outcomes reflecting survival, HRQoL and disability. Overall, there was a strong correlation between the trial primary outcome and 6-month outcomes.

There was broad variation in 6-month HRQoL and disability scores. The majority of survivors reported favorable HRQoL and functional status, although approximately 1 in 3 patients had at least moderate disability that persisted through 6 months (although participants' baseline disability was not known). Interleukin-6 receptor antagonists, which improved organ support-free days, also had a >99.9% probability of improving survival over 6 months compared to no immune modulator. Furthermore, among survivors, there was an 87.0% probability of

improved HRQoL and 92.6% probability of reduced disability, suggesting that improvement in survival was not occurring at the expense of poor-quality survival. Although antiplatelet agents did not improve the organ support-free days outcome, they had a 92.3% and 95.0% probability of improved day 90 and day 180 survival, and a 97.4% probability of improved HRQoL in survivors at 6 months. When death and HRQoL were evaluated as a composite, the probability of superiority was 99.6%.

Although there was a 93% probability that fixed dose hydrocortisone improved organ support-free days, no early or late effect on survival was observed. Other treatments that did not improve organ support-free days, including therapeutic anticoagulation, convalescent plasma, lopinavir-ritonavir, and hydroxychloroquine, were similarly ineffective in improving longer-term outcomes. Overall, there was a strong correlation between organ support-free days and longer-term outcomes in critically ill patients with COVID-19.

To the best of our knowledge this is the largest trial that has reported on the effect of treatments for COVID-19 on longer-term mortality, HRQoL and disability in critically ill patients. The HRQoL and disability outcomes in this trial are similar to observational cohort reports of critically ill survivors of COVID-19,<sup>24-26</sup> and similar to both observational and trial cohorts of critically ill patients prior to the pandemic.<sup>24,27,28</sup> Although there do not appear to be large effects of ICU-based treatments on either HRQoL or disability, it is encouraging that overall increases in longer-term survival are not accompanied by a decrement in HRQoL or increased disability. There is a theoretical risk that a treatment that saves lives amongst critically ill patients may convert non-survivors into survivors who have poor quality of survival. A recent systematic review evaluating HRQoL in randomized trials reporting a survival benefit in critically ill patients found only 2.9% of studies reporting a significant

reduction in mortality also reported on HRQoL.<sup>29</sup> Of those trials reporting HRQoL, results were inconsistent, with 2 studies reporting improvements in both survival and HRQoL, 3 reporting no difference in HRQoL in survivors, and 2 reporting lower HRQoL in survivors.<sup>29</sup> The present study demonstrates that the improved survival associated with interleukin-6 receptor antagonists and antiplatelet agents does not result in a lower HRQoL in survivors. Given the global effect of COVID-19, small differences in mortality or other patient-centred outcomes such as HRQoL and disability can result in important clinical and health economic benefits at the population level, particularly in a global pandemic.

## Limitations

This study has several limitations. First, the trial used an open-label design, although the mortality outcome is at a lower risk for bias. Second, the collection of outcomes beyond day 90 was not mandated although 6-month survival status was available for 85.7% of patients. Not all regions and sites collected HRQoL and disability outcomes and there was a substantial amount of missing data for these outcomes. Bayesian multiple imputation techniques were used to account for missing data and sensitivity analyses without imputation did not meaningfully change the results. Third, HRQoL and disability scores could not be collected at baseline while patients were critically ill, and therefore this trial could not assure balance across randomization groups, nor could this trial evaluate change in score over time. As such, it is possible that differences in HRQoL or disability may have been due to imbalances in these measures at baseline, although randomization and temporal and site adjustment in the models would have been expected to balance these across the treatment arms. Fourth, the results relate to the effectiveness of interventions on prior variants of COVID-19 and prior to

widespread availability of vaccination, and the effectiveness on newer variants and vaccinated patients is unknown. Further study is needed to determine whether the observed impacts are sustained through different waves of the pandemic.

## Conclusions

Among critically ill patients with COVID-19 randomized to receive one or more therapeutic interventions, treatment with an IL-6 receptor antagonist had a >99.9% probability of improved 180-day mortality compared with patients randomized to control, and treatment with an antiplatelet had a 95.0% probability of improved 180-day mortality compared with patients randomized to control. Overall, when considered with previously reported short-term results, the findings indicate that initial in-hospital treatment effects were consistent for most therapies.

# Article Information

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Dr Higgins had full access to all the data in the trial and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### **Conflict of Interest Disclosures**

See submitted ICMJE forms for declared potential conflict of interests.

### **Funding/Support:**

The Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) consortium by the European Union, FP7-HEALTH-2013-INNOVATION-1 (#602525), the Rapid European COVID-19 Emergency Research response (RECOVER) consortium by the European Union's Horizon 2020 research and innovation programme (#101003589), the Australian National Health and Medical Research Council (#APP1101719), the Australian Medical Research Future Fund (#APP2002132), the Health Research Council of New Zealand (#16/631), the Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program Grant (#158584) and the Canadian Institute of Health Research COVID-19 Rapid Research Funding (#447335), the UK National Institute for Health Research (NIHR) and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (CTN 2014-012), the UPMC Learning While Doing Program, the Translational Breast Cancer Research Consortium, the French Ministry of Health (PHRC-20-0147), the Wellcome Trust Innovations Project (215522), the Minderoo Foundation, the EU Programme Emergency Support Instrument, the NHS Blood and Transplant Research and Development Programme, the Translational Breast Cancer Research Consortium, the NSW Office of Health

and Medical Research, Amgen, Eisai, and the Pittsburgh Foundation. Dr Higgins is funded by an NHMRC Emerging Leadership Fellowship (GNT2008447). A/Prof McQuilten is funded by an NHMRC Emerging Leadership Fellowship (APP194811). Prof Gordon is funded by an NIHR Research Professorship (RP-2015-06-18) and Prof Shankar-Hari by an NIHR Clinician Scientist Fellowship (CS-2016-16-011). Prof Turgeon is the Chairholder of the Canada Research Chair in Critical Care Neurology and Trauma. Dr Lawler is supported by a career award from the Heart and Stroke Foundation of Canada.

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

### **Role of the Funder/Sponsor**

The funders had no role in the design and conduct of the trial; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The platform trial has six regional non-profit sponsors (Monash University, Melbourne, Australia (sponsor for Australia, India, Pakistan, Nepal, Saudi Arabia and Colombia); Medical Research Institute of New Zealand (New Zealand sponsor); Utrecht Medical Center, Utrecht, the Netherlands (European sponsor); Unity Health, Toronto, Canada (Canadian sponsor); Global Coalition for Adaptive Research (GCAR), San Francisco, USA (US sponsor); and St Marianna University Hospital, Japan (Japanese sponsor)). Several authors are employees of these organizations. However, beyond the declared author contributions, the sponsors had no additional role.

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See Supplement 2 'The REMAP-CAP Investigators and Collaborators'.

## **Acknowledgements**

We are grateful to the NIHR Clinical Research Network (UK), UPMC Health System Health Services Division (US), and the Direction de la Recherche Clinique et de l'Innovation de l'AP-HP (France) for their support of participant recruitment. We are also very thankful to the patients who have participated in this trial.

Data Sharing Statement: See Supplement 3

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# Summary of Supplements

## Supplement 1. Protocol Supplement

- Brief introduction to explain the protocol structure given modular nature of ongoing platform trial
- REMAP-CAP Core Protocol (Version 3.0, 10th July 2019, the Original Version - predating any Covid-19 screening and inclusion)
- Pandemic Appendix to Core (PATC) protocol (Final Version 2.0, 18th May 2020 including summary of changes from version 1.1 and Original Version 1.1, 12th February 2020)
- REMAP-COVID Core Protocol (Version 1.0, 27th March 2020)
- Statistical Analysis Plan for the secondary analysis of long-term survival and disability in relation to randomized treatments in patients with suspected or proven COVID-19 in the REMAP-CAP trial (Version 1.1, 10<sup>th</sup> March 2022)

## Supplement 2.

- REMAP CAP Investigators and Collaborators
- Supplementary Methods
- Supplemental Tables

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Table S14: Baseline characteristics of survivors with and without EQ-5D-5L utility scores

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Table S16: Day 180 EQ-5D-5L results

Table S17: Day 180 EQ VAS results

Table S18: Day 180 Disability Categories

Table S19: Day 180 Disability

Table S20: Sensitivity Analysis of EQ-5D-5L utility score without imputation

Table S21: Sensitivity Analysis of WHODAS disability category without imputation

Table S22: Day 180 mortality in patients mechanically ventilated at baseline

Table S23: Day 180 mortality in patients not mechanically ventilated at baseline

Table S24: Day 180 mortality in immune deficient patients

Table S25: Day 180 mortality in non-immune deficient patients

- **Supplemental Figures**

Figure S1: Forest plot of Day 180 mortality hazard ratios in unblinded ITT population

Figure S2: Forest plot of Day 180 mortality hazard ratios in sensitivity analyses

Figure S3: Fitted Kaplan-Meier curves for mortality through Day 180 with proportional hazard ratios, adjusting for covariates

Figure S4: Fitted Kaplan-Meier curves for mortality through Day 180 with time-varying hazards, adjusting for covariates

Figure S5: Association between OSFD odds ratios and the reciprocal of day 180 mortality hazard ratios

Figure S6: Forest plot of Day 90 mortality odds ratios in unblinded ITT population

Figure S7: Forest plot of expected effect on EQ-5D-5L utility score in all patients (assuming patients who died within 180 days have a utility score of 0)

Figure S8: Forest plot of the odds ratio on WHODAS disability category in survivors in unblinded ITT analysis

Figure S9: Forest plot of Day 180 mortality hazard ratios in unblinded ITT population comparing mechanical ventilation status at baseline

Figure S10: Forest plot of Day 180 mortality hazard ratios in unblinded ITT population comparing immune deficient status at baseline

- Model Evaluation Report

### **Supplement 3. Data Sharing Statement**

# Figures

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Figure 1. Cohort development in an analysis of longer-term follow-up of critically ill participants in the REMAP-CAP COVID-19 Clinical Trial

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Figure 2. Kaplan Meier Curves for Mortality through Day 180

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Each Kaplan-Meier curve summarizes 180-day all-cause mortality in critically ill patients for each treatment within each domain. The probability of superiority of each active intervention to control for 180-day mortality is reported from the fully adjusted Bayesian model (adjusting for other treatments from other domains, site, time, sex, and age). Censored subjects are indicated on the Kaplan-Meier curve as vertical tick marks.

# Tables

Table 1: Baseline characteristics of patients in one or more domains included in the analysis of mortality at 180 days <sup>a</sup>

Characteristic	N=4791
Age in years, median (IQR)	60 (51 - 68) [N=4790]
Male sex, n/N (%)	3253/4790 (67.9)
Female sex, n/N (%)	1537/4790 (32.1)
Race/Ethnicity <sup>a</sup> , n/N (%)	
Asian	504/3557 (14.2)
Black	160/3557 (4.5)
Mixed	69/3557 (1.9)
Other <sup>b</sup>	159/3557 (4.5)
White	2665/3557 (74.9)
Confirmed SARS-CoV2 infection, n/N (%) <sup>c</sup>	4139/4764 (86.9)
Body mass index, kg/m <sup>2</sup> , median (IQR)	30.5 (26.6 – 35.8) [N=4317]
APACHE II score <sup>d</sup> , median (IQR)	13 (8-19) [N=4673]
Pre-existing conditions, n/N (%) <sup>e</sup>	
Diabetes mellitus	1404/4788 (29.3)
Respiratory disease <sup>ex</sup>	1067/4788 (22.3)
Asthma/COPD	897/4788 (18.7)
Other	218/4788 (4.6)
Kidney disease	370/4427 (8.4)
Severe cardiovascular disease	376/4703 (8.0)
Immunosuppressive disease	190/4788 (4.0)
Chronic immunosuppressive therapy	175/4788 (3.7)
Time to enrolment, median (IQR)	
From hospital admission, days	1.7 (0.9 – 3.3)
From ICU admission, hours	16.7 (9.1 – 22.5)
Acute respiratory support, n (%)	
None/supplemental oxygen only	7 (0.2)
High flow nasal cannula	1198 (25.0)
Non-invasive ventilation only	1848 (38.6)
Invasive mechanical ventilation	1746 (36.4)
ECMO, n/N (%)	4/4729 (0.1)
Vasopressor support, n (%)	1005 (21.0)
Median (IQR) acute physiology and laboratory values <sup>f</sup>	
PaO <sub>2</sub> /FI <sub>O</sub> <sub>2</sub>	116 (89 - 158) [N=4368]
C-reactive protein, µg/mL	117 (65 - 192) [N=3585]
Creatinine, mg/dL	0.8 (0.7 - 1.1) [N=4681]
Lactate, mmol/L	1.3 (1.0 - 1.8) [N=4205]
Platelets, x10 <sup>9</sup> /L	245 (183 - 314) [N=4626]
Bilirubin, mg/dL	0.5 (0.4 - 0.8) [N=4443]

Percentages may not sum to 100 because of rounding. SD denotes standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.

<sup>a</sup> Baseline characteristics by intervention in each of the six domains can be found in Tables S3-S8

<sup>b</sup> Self-reported via fixed categories. Data collection was not approved in Asia, Canada, and continental Europe. "Other" includes "other ethnic group" and those who declined to respond or were not asked by registration personnel.

<sup>c</sup> SARS-CoV2 infection was confirmed by respiratory tract polymerase chain reaction test.

<sup>d</sup> Measures the severity of illness based on age, medical history, and physiological variables. Scores range from 0 to 71; higher numbers represent greater risk of death. The median score of 12 is typical for patients with COVID-19 admitted to intensive care units (ICUs).

<sup>e</sup> Kidney disease was determined from the most recent stable serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 130  $\mu\text{mol/L}$  or greater (1.5 mg/dL) for males or 100  $\mu\text{mol/L}$  or greater (1.1 mg/dL) for females not previously receiving dialysis. Cardiovascular disease was defined as New York Heart Association class IV symptoms. Immunosuppression was defined by the receipt of recent chemotherapy, radiation, high-dose or long-term steroid treatment, or presence of immunosuppressive disease.

<sup>f</sup> Laboratory results available when captured for clinical care. Although specific laboratory cut-offs may vary, ranges for the following variables are generally considered normal:  $P_aO_2/F_iO_2$  ratio  $\geq 400$ ; creatinine  $< 1.2$  mg/dL; platelets  $\geq 150 \times 10^9/L$ ; and bilirubin  $< 1.2$  mg/dL.

**Table 2: Day 180 mortality**

	N	Day 180 mortality <sup>a</sup> , n/N (%)	Adjusted Hazard Ratio <sup>b</sup> (95% CrI)	Estimated Difference in Day 180 mortality (95% CrI) <sup>c</sup>	Probability of Superiority of Intervention (%) <sup>d</sup>	Probability of Futility of Intervention (%) <sup>d</sup>	Probability of Superiority of Intervention for organ support free days (%) <sup>e</sup>
<b>Immune Modulation Domain<sup>f</sup></b>							
IL-6 receptor antagonists	1433	436/1248 (34.9)	0.74 (0.61 to 0.90)	-7.9% (-13.2% to -2.7%)	>99.9%	12.2%	>99.9%
Anakinra	371	138/325 (42.5)	0.96 (0.75 to 1.23)	-1.3% (-6.9% to 4.5%)	63.7%	85.9%	50.0%
No immune modulator	406	140/350 (40.0)	1 (referent)	-	-	-	-
<b>Immunoglobulin Domain</b>							
Convalescent plasma	1078	370/944 (39.2)	0.99 (0.88 to 1.14)	-0.3% (-4.1% to 3.5%)	54.7%	99.2%	26.6%
No convalescent plasma	911	324/790 (41.0)	1 (referent)	-	-	-	-
<b>Antiplatelet Domain</b>							
Antiplatelet agent <sup>g</sup>	1019	274/871 (31.5)	0.85 (0.71 to 1.03)	-3.5% (-7.9% to 0.7%)	95.0%	57.7%	62.8%
No antiplatelet agent	527	143/441 (32.4)	1 (referent)	-	-	-	-
<b>Anticoagulation Domain</b>							
Therapeutic anticoagulation <sup>g</sup>	499	165/403 (40.9)	1.13 (0.93 to 1.42)	3.2% (-1.7% to 8.5%)	11.5%	99.9%	10.8%
Usual care thromboprophylaxis	511	147/418 (35.2)	1 (referent)	-	-	-	-
<b>Antiviral Domain</b>							
Lopinavir-ritonavir	256	81/226 (35.8)	1.06 (0.82 to 1.38)	1.8% (-4.3% to 7.3%)	31.9%	96.6%	11.4%
Hydroxychloroquine	50	16/41 (39.0)	1.51 (0.98 to 2.29)	11.6% (1.7% to 21.6%)	3.2%	99.6%	0.4%
Combination antiviral therapy	27	13/26 (50.0)	1.61 (0.97 to 2.67)	13.8% (2.6% to 24.7%)	3.2%	99.5%	0.3%
No antiviral	362	107/311 (34.4)	1 (referent)	-	-	-	-
<b>Corticosteroid Domain</b>							
Fixed dose corticosteroids	137	34/109 (31.2)	0.93 (0.61 to 1.47)	-1.4% (-11.7% to 7.8%)	61.6%	69.1%	94.6%
Shock-dependent corticosteroids	147	39/137 (28.5)	0.96 (0.61 to 1.50)	0.0% (-11.5% to 10.4%)	57.1%	72.5%	75.6%
No corticosteroid	101	27/79 (34.2)	1 (referent)	-	-	-	-

CrI denotes credible interval; OSFD, organ support free days.

<sup>a</sup> Due to censoring, reported day 180 mortality rates are restricted to patients at sites participating in day 180 follow-up with known day 180 vital status. The Kaplan Meier curves in Figure 2 include additional exposure and events from patients that were censored before day 180 or enrolled at sites that did not participate in day 180 follow-up.

<sup>b</sup> Hazard ratios <1 indicate improved survival while hazard ratios >1 indicate worsened survival

<sup>c</sup> The difference in Day 180 mortality is determined from the Day 180 mortality rates which are estimated from the primary analysis model. For each domain, day 180 mortality rates are estimated for the population of patients randomized within that domain based on their baseline covariates and the estimated model parameters. For each patient within the domain population, separate survival curves are predicted assuming the patient received each intervention within the domain. The survival curves are averaged across patients to summarize the average survival for each intervention within the domain population.

<sup>d</sup> The probability of superiority ( $HR < 1$ ) and futility ( $HR > 1/1.2$ ) is computed from a Bayesian piecewise exponential model using the posterior distribution.

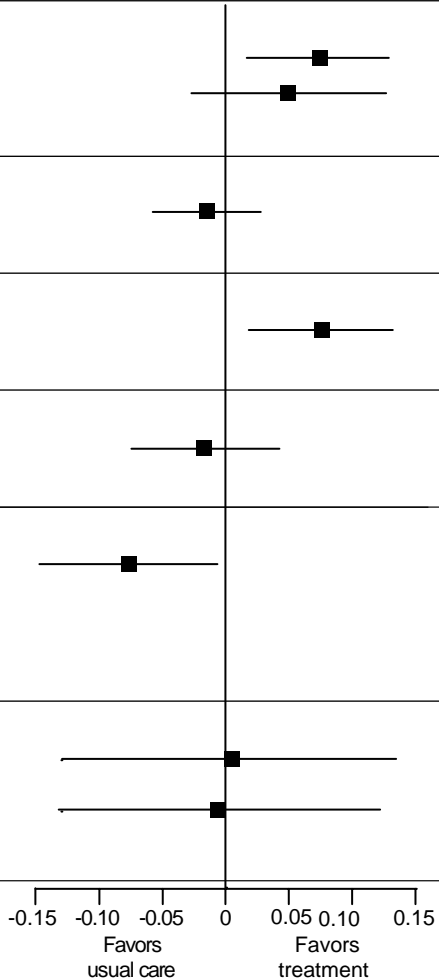
<sup>e</sup> OSFD are a composite ordinal scale consisting of survival to hospital discharge and days free of organ support to day 21. Probabilities may differ from those presented in the original manuscript for each domain due to changes in patient consent.

<sup>f</sup> Domains are ordered based on the total number of patients enrolled in the domain from largest to smallest

<sup>g</sup> 35 patients within the antiplatelet and anticoagulation domains were randomized to the prespecified combination of therapeutic anticoagulation and an antiplatelet agent. The combination effect provides the effect of giving both therapeutic anticoagulation and antiplatelet interventions together in combination (relative to giving control in both domains). This is estimated by multiplying the hazard ratio for antiplatelet, therapeutic anticoagulation and the interaction effect for antiplatelet and therapeutic anticoagulation. The HR for the combination effect is 1.34 (0.82 to 2.23) with a probability of superiority of 11.6%. The HR for the therapeutic anticoagulation/antiplatelet interaction is 1.39 (0.87 to 2.19).



**Table 3: Day 180 HRQoL <sup>a</sup>**

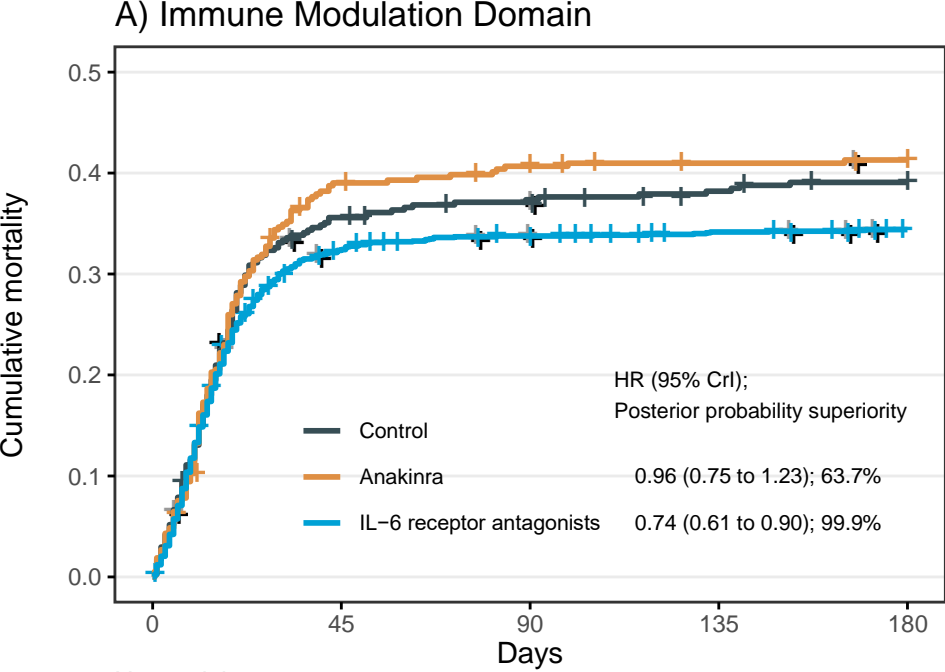
	EQ-5D-5L utility score, mean (SD) [N]	Adjusted Mean Difference in Survivors (95% CrI) <sup>b</sup>	Probability of Superiority of Intervention in Survivors (%) <sup>a</sup>	Adjusted Mean Difference in Survivors and Non-Survivors (95% CrI) <sup>b</sup>		Probability of Superiority of Intervention in Survivors and Non-Survivors (%) <sup>a</sup>
<b>Immune Modulation Domain <sup>c</sup></b>						
IL-6 receptor antagonists	0.66 (0.29) [N=302]	0.04 (-0.03 to 0.12)	87.0%	0.08 (0.02 to 0.13)		99.5%
Anakinra	0.72 (0.28) [N=78]	0.07 (-0.03 to 0.18)	91.5%	0.05 (-0.03 to 0.13)		89.6%
Control	0.64 (0.29) [N=92]	0 (referent)	-	0 (referent)		-
<b>Immunoglobulin Domain</b>						
Convalescent plasma	0.62 (0.32) [N=216]	-0.03 (-0.09 to 0.03)	18.8%	-0.02 (-0.06 to 0.03)		25.2%
Control	0.64 (0.29) [N=174]	0 (referent)	-	0 (referent)		-
<b>Antiplatelet Domain</b>						
Antiplatelet	0.69 (0.27) [N=163]	0.08 (0.00 to 0.15)	97.4%	0.08 (0.02 to 0.13)		99.6%
Control	0.63 (0.30) [N=95]	0 (referent)	-	0 (referent)		-
<b>Anticoagulation Domain</b>						
Therapeutic anticoagulation	0.67 (0.28) [N=116]	0.01 (-0.07 to 0.09)	59.2%	-0.02 (-0.07 to 0.04)		28.8%
Thromboprophylaxis	0.67 (0.30) [N=124]	0 (referent)	-	0 (referent)		-
<b>Antiviral Domain</b>						
Lopinavir-ritonavir	0.62 (0.3) [N=74]	-0.10 (-0.19 to -0.01)	1.3%	-0.08 (-0.15 to -0.01)		1.6%
Hydroxychloroquine	1.00 (NA) [N=1]	NA	NA	NA		NA
Combination antiviral therapy	0.58 (0.19) [N=2]	NA	NA	NA		NA
Control	0.71 (0.27) [N=101]	0 (referent)	-	0 (referent)		-
<b>Corticosteroid Domain</b>						
Fixed dose corticosteroids	0.79 (0.20) [N=27]	-0.01 (-0.18 to 0.16)	45.9%	0.006 (-0.13 to 0.14)		53.1%
Shock-dependent corticosteroids	0.77 (0.17) [N=34]	-0.02 (-0.18 to 0.14)	41.0%	-0.006 (-0.13 to 0.12)		46.7%
Control	0.75 (0.28) [N=21]	0 (referent)	-	0 (referent)		-

SD denotes standard deviation; IQR, interquartile range; NA, not available; CrI, credible interval.

<sup>a</sup>Results for the EQ VAS and the WHODAS are available in Supplement Tables S17 to S19

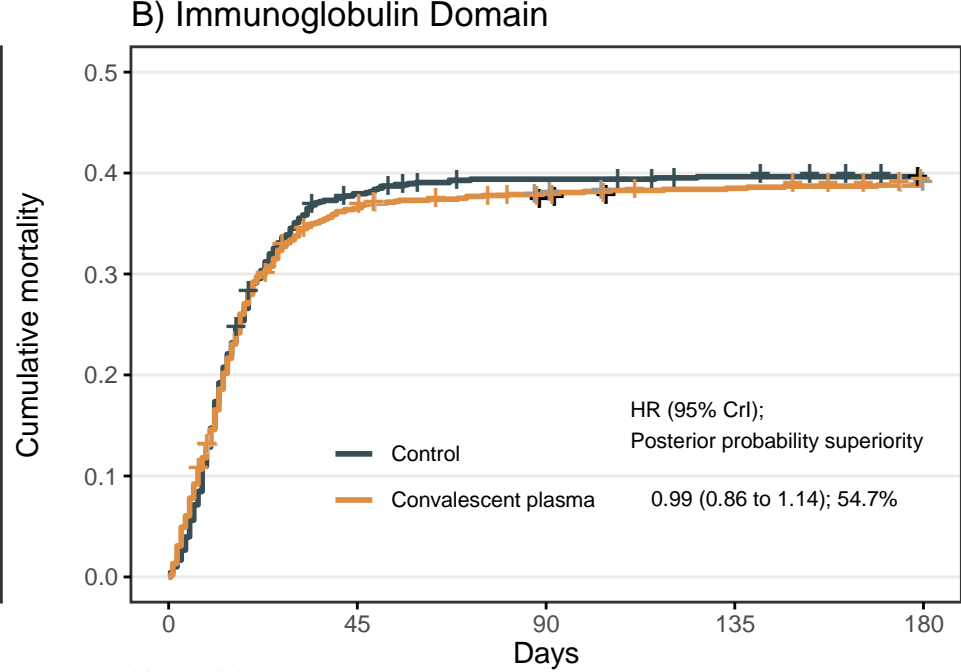
<sup>b</sup>The probability of superiority and adjusted mean difference are computed from the posterior distribution of a Bayesian two-part/mixture model that multiply imputes EQ-5D-5L utility scores using patients' baseline covariates for 1) patients censored alive before 6 months and 2) patients known to be alive at 6 months with unknown HRQoL. For patients that are censored before 6 months, first 6-month mortality outcomes are multiply imputed from the piecewise exponential component of the Bayesian two-part/mixture model. For patients that are known or imputed to be alive at 6 months, a value of EQ-5D-5L is multiply imputed from the continuous component of the two-part/mixture model. For patients that are imputed as dead by 6 months, EQ-5D-5L is set to 0 and they do not contribute to the analysis of EQ-5D-5L in survivors. In this analysis, 4307 of 4791 patients (90%) have known survival status at 6 months and a mortality outcome is multiply imputed for the remaining 484 (10%) of patients. Of the 2590 patients known to be alive at 6 months, 852 (33%) have known EQ-5D-5L utility score and the remaining 1738 (67%) are imputed.

<sup>c</sup>Domains are ordered based on the total number of patients enrolled in the domain from largest to smallest



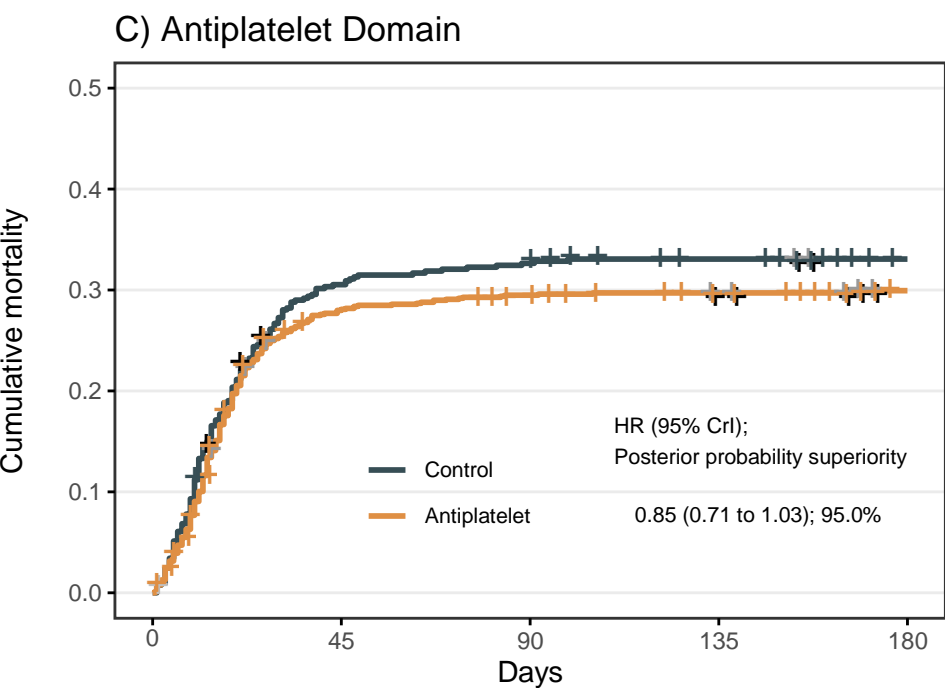
No. at risk

406	25	248	215	210
371	22	215	190	187
1433	95	928	825	812

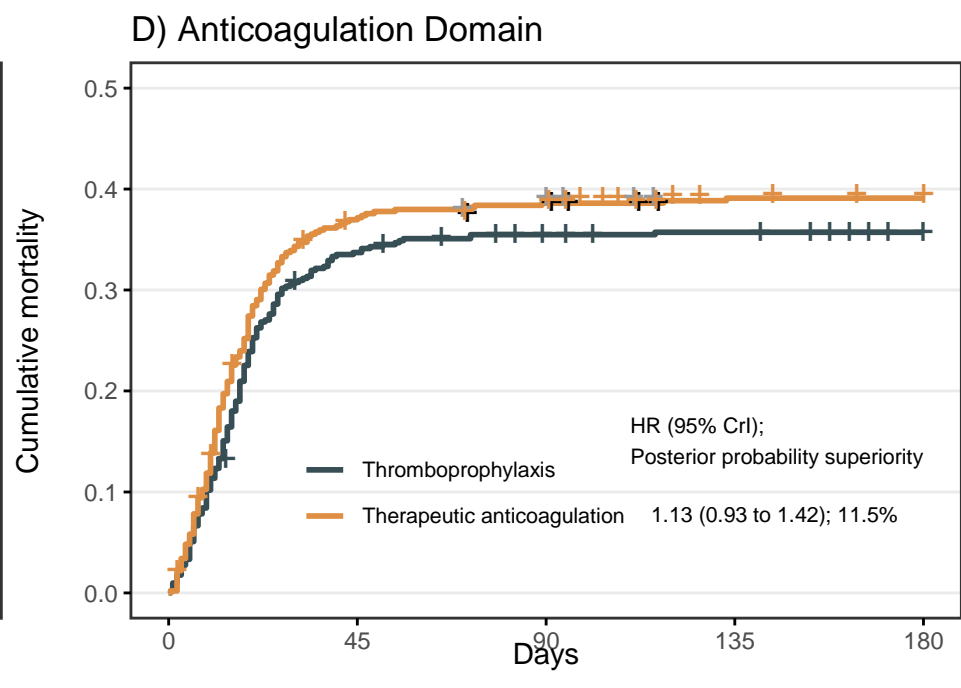


No. at risk

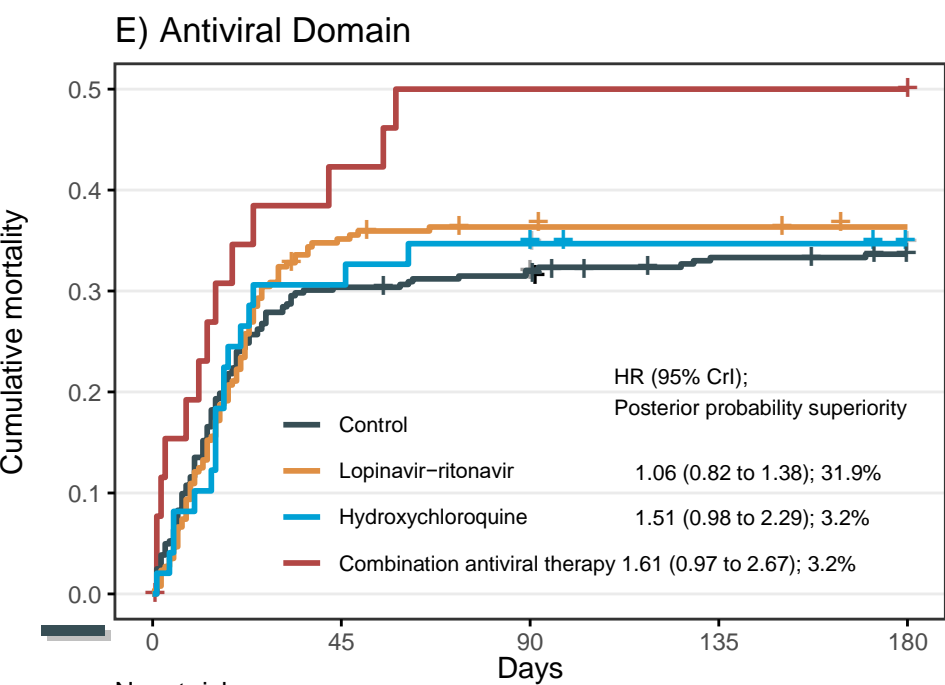
911	56	543	473	466
1078	68	659	582	574



527	362	351	308	298
1019	722	704	614	597

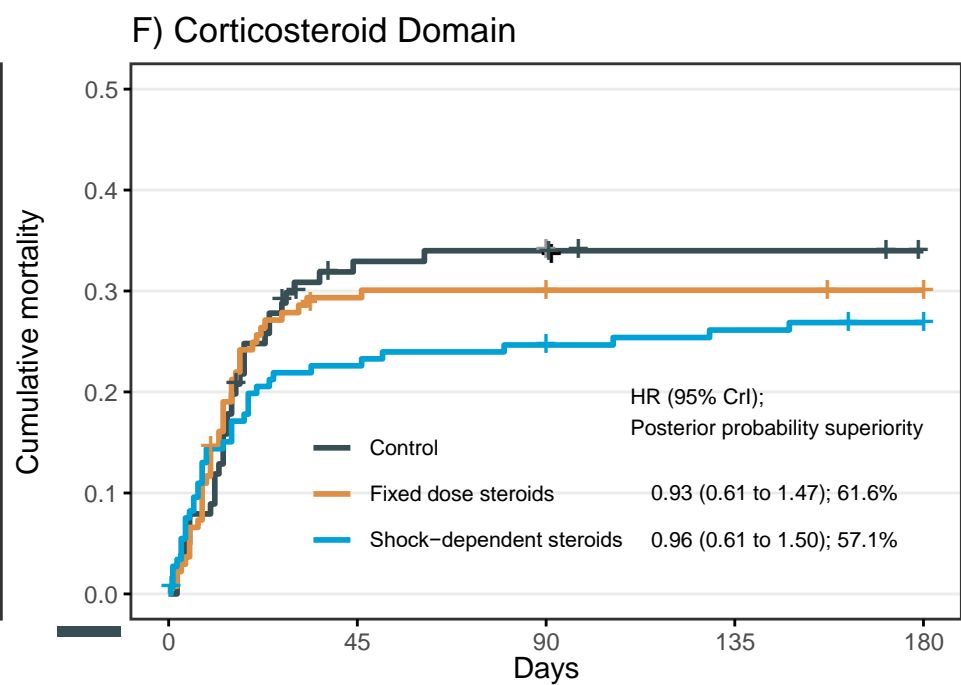


511	337	323	277	271
499	309	299	240	238



No. at risk

362	252	245	207	204
256	165	160	147	145
50	34	32	26	25
27	15	13	13	13



No. at risk

101	64	63	53	52
137	95	94	76	75
147	113	110	100	98

Supplement to:

# 180-Day Outcomes in Critically Ill Patients with COVID-19 in the REMAP-CAP Randomized Clinical Trial.

## The REMAP-CAP Investigators

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The REMAP-CAP platform is supported by the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Canadian Critical Care Clinical Trials Group, the Irish Critical Care Clinical Trials Network, the UK Critical Care Research Group and the International Forum of Acute Care Trialists.

REMAP-CAP was supported in the UK by the NIHR Clinical Research Network and we acknowledge the contribution of Kate Gilmour, Karen Pearson, Chris Siewerski, Sally-Anne Hurford, Emma Marsh, Debbie Campbell, Penny Williams, Kim Shirley, Meg Logan, Jane Hanson, Anne Oliver, Mihaela Sutu, Sheenagh Murphy, Latha Aravindan, Joanne Collins, Holly Monaghan, Adam Unsworth, Seonaid Beddows, Laura Ann Dawson, Sarah Dyas, Adeeba Asghar, Kate Donaldson, Tabitha Skinner, Nhlanhla Mguni, Natasha Muzengi, Ji Luo, Joanna O'Reilly, Chris Levett, Alison Potter, David Porter, Teresa Lockett, Jazz Bartholomew, Clare Rook, Hannah Williams, Alistair S Hall, Hilary Campbell, Holly Speight, Sandra Halden, Susan Harrison, Mobeena Naz, Charles Rounds, Kaatje Lomme, Johnathan Sheffield, William Van't Hoff, James D Williamson, Catherine Birch, Morwenna Brend, Emma Chambers, Sarah Crawshaw, Chelsea Drake, Heather Harper, Stephen Lock, Eleanor OKell, Amber Hayes, Susan Walker, Jayne Goodwin, Helen Hodgson, Yvette Ellis, Dawn Williamson, Madeleine Bayne, Shane Jackson, Rahim Byrne, Sonia McKenna, Alison Clinton, NIHR Urgent Public Health Group: <https://www.nihr.ac.uk/documents/urgent-public-health-group-members/24638#Members>

REMAP-CAP was supported in France by the CRICS-TRIGGERSEP network

REMAP-CAP was supported in Ireland by the Irish Critical Care Clinical Trials Network and we acknowledge the contribution of Kate Ainscough, Kathy Brickell and Peter Doran.

REMAP-CAP was supported in the Netherlands by the Research Collaboration Critical Care the Netherlands (RCC-Net).

REMAP-CAP was supported in Canada by the Canadian Institutes of Health Research, St. Michael's Unity Health, and the Canadian Critical Care Trials Group

REMAP-CAP was supported in the United States by the Translational Breast Cancer Research Consortium, the UPMC Learning While Doing Program, and the Global Coalition for Adaptive Research

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*Royal Melbourne Hospital:* Jeffrey Presneill, Deborah Barge, Kathleen Byrne;  
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*Royal Perth Hospital:* Sharon Waterson, Steve Webb, Robert McNamara, Melanie Boardman;  
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*Sir Charles Gairdner Hospital:* Sacha Schweikert, Bradley Wibrow, Matthew Anstey, Rashmi Rauniyar;  
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*St. Vincent's Hospital (VIC):* John Santamaria, Leanne Barbazza, Jennifer Homes, Roger Smith;  
*Sunshine Coast University Hospital:* Peter Garrett, Lauren Murray, Jane Brailsford;  
*Sunshine Hospital:* Craig French, Gerard Fennessy, John Mulder, Rebecca Morgan;  
*The Sutherland Hospital:* Anas Naeem, Laura Fagan, Emily Ryan;  
*Toowoomba Hospital:* Vasanth Mariappa, Judith Smith;  
*University Hospital Geelong:* Scott Simpson, Matthew Maiden, Michelle Horton, Jemma Trickey;  
*Werribee Mercy Hospital:* Umesh Kadam, Marlene Gojanovic;  
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*William Osler Health System:* Alexandra Binnie, Elizabeth Powell, Alexandra McMillan, Tracy Luk, Noah Aref;

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*Middlemore Hospital*: Tony Williams, Susan Morpeth, Rima Song, Vivian Lai, Hannah Habraken;

*North Shore Hospital*: Robert Everitt, Danielle Hacking;

*Rotorua Hospital*: Ulrike Buehner, Erin Williams;

*Taranaki Base Hospital*: Jonathan Albrett, Carolyn Jackson, Simon Kirkham;

*Tauranga Hospital*: Troy Browne, Kate Grimwade, Jennifer Goodson, Owen Keet, Owen Callender;

*Waikato Hospital*: Robert Martynoga, Kara Trask, Amelia Butler;

*Wellington Regional Hospital*: Paul Young, Chelsea Young, Eden Lesona, Leanlove Navarra, Raulle Sol Cruz, Kirsha Delaney, Rhoze Sol Cruz, April Aguilar-Dano;

*Whangarei Hospital*: Ralph Fuchs, Bridget Lambert;

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*Alexandra Hospital Redditch:* Olivia Kelsall, Nicholas Cowley, Laura Wild, Jessica Thrush, Hannah Wood, Karen Austin;

*Altnagelvin Hospital:* Adrian Donnelly, Martin Kelly, Naoise Smyth, Sinéad O'Kane, Declan McClintock, Majella Warnock, Ryan Campbell, Edmund McCallion;

*Antrim Area Hospital:* Paul Johnson, Shirley McKenna, Joanne Hanley, Andrew Currie, Barbara Allen, Clare McGoldrick, Moyra McMaster;

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*Belfast Health and Social Care Trust (Belfast City Hospital, Mater Infirmorum, Royal Victoria Hospital):* Jon Silversides, Peter McGuigan, Kathryn Ward, Aisling O'Neill, Stephanie Finn, Chris Wright, Jackie Green, Érin Collins;

*Brighton and Sussex University Hospitals Trust:* Barbara Phillips, Laura Ortiz-Ruiz de Gordo;

*Calderdale and Huddersfield Foundation Trust:* Jez Pinnell, Matt Robinson, Lisa Gledhill, Tracy Wood;

*Cardiff and Vale University Health Board:* Matt Morgan, Jade Cole, Helen Hill, Michelle Davies, Angharad Williams, Emma Thomas, Rhys Davies, Matt Wise;

*Charing Cross Hospital:* David Antcliffe, Maie Templeton, Roceld Rojo, Phoebe Coghlan, Joanna Smee, Gareth Barker;

*Chesterfield Royal Hospital:* Euan Mackay, Jon Cort, Amanda Whileman, Thomas Spencer, Nick Spittle, Sarah Beavis, Anand Padmakumar, Katie Dale, Joanne Hawes, Emma Moakes, Rachel Gascoyne, Kelly Pritchard, Lesley Stevenson, Justin Cooke, Karolina Nemeth-Rozpopa;

*The Christie NHS Foundation Trust:* Vidya Kasipandian, Amit Patel, Suzanne Allibone, Roman Mary-Genetu;

*Colchester Hospital:* Mohamed Ramali, Ooi HC, Alison Ghosh, Rawlings Osagie, Malka Jayasinghe Arachchige, Melissa Hartley;

*Countess of Chester Hospital:* Peter Bamford, Andrew Reid, Kathryn Cawley, Maria Faulkner, Charlotte Pickering;

*Croydon University Hospital:* Ashok Sundar Raj, Georgios Tsinaslanidis, Reena Nair Khade, Gloria Nwajei Agha, Rose Nalumansi Sekiwala;

*Cumberland Infirmary:* Tim Smith, Chris Brewer, Jane Gregory;

*Darlington Memorial Hospital:* James Limb, Amanda Cowton, Julie O'Brien, Kelly Postlethwaite;

*Derriford Hospital:* Nikitas Nikitas, Colin Wells, Liana Lankester, Helen McMillan;

*Dorset County Hospital:* Mark Pulletz, Patricia Williams, Jenny Birch, Sophie Wiseman, Sarah Horton;

*East Kent Hospitals (Queen Elizabeth the Queen Mother Hospital):* Ana Alegria, Salah Turki, Tarek Elsefi, Nikki Crisp, Louise Allen;

*East Lancashire Hospitals NHS Trust (Royal Blackburn Hospital):* Nicholas Truman, Matthew Smith, Sri Chukkambotla, Wendy Goddard, Stephen Duberley, Meherunnisa Khan, Aayesha Kazi;

*Freeman Hospital and Royal Victoria Infirmary, Newcastle upon Tyne:* Iain J McCullagh, Tom Cairns, Helen Hanson, Bijal Patel, Ian Clement;

*Frimley Health NHS Foundation Trust:* George Evetts, Omar Touma, Susan Holland, Christopher Hodge, Holly Taylor, Meera Alderman, Nicky Barnes, Joana Da Rocha, Catherine Smith, Nicole Brooks, Thanuja Weerasinghe, Julie-Ann Sinclair, Yousuf Abusamra, Ronan Doherty, Joanna Cudlipp, Rajeev Singh, Haili Yu, Admad Daebis, Christopher Ng, Sara Kendrick, Anita Saran, Ahmed Makky, Danni Greener, Louise Rowe-Leete, Alexandra Edwards, Yvonne Bland, Rozzie Dolman, Tracy Foster;

*Gateshead Health NHS Trust:* Vanessa Linnett, Amanda Sanderson, Jenny Ritzema, Helen Wild, Rachael Lucas, Yvonne Marriott;

*George Eliot Hospital:* Divya Khare, Meredith Pinder, Amitha Gopinath, Thogulava Kannan, Steven Dean, Piyush Vanmali;

*Glan Clwyd Hospital:* Richard Pugh, Richard Lean, Xinyi Qiu, Jeremy Scanlan, Andrew Evans, Gwyneth Davies, Joanne Lewis;

*Glangwili General Hospital:* Yvonna Plesnikova, Ahmed Ben Khoud, Samantha Coetzee;

*Glasgow Royal Infirmary:* Kathryn Puxty, Susanne Cathcart, Dominic Rimmer, Catherine Bagot, Kathryn Scott, Laila Martin;

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*Guy's & St Thomas' NHS Foundation Trust:* Manu Shankar-Hari, Gill Arbane, Marina Marotti, Aneta Bociek, Sara Campos;

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## 2. Supplementary methods

### 2.1 Outcomes:

#### EQ-5D-5L

The EQ-5D-5L is a preference-based QoL instrument comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents are asked to choose the most appropriate option from five alternatives (no, slight, moderate, severe or extreme problems). In addition, respondents were asked to indicate their present health state on a visual analogue scale (EQ VAS) ranging from the worst imaginable health state ("0") to the best imaginable health state ("100"). EQ-5D-5L utility scores were calculated where a valid response (1 to 5) was available for each of the 5 EQ-5D-5L domains, and the EQ-5D-5L was conducted within the 12 weeks following day 180. Scores were calculated using the crosswalk link function and the individual responses to the EQ-5D-5L descriptive system, using the UK time trade off (TTO) value set, with values between -0.594 and 1.00.

#### WHODAS

The 12-item WHODAS 2.0 covers six domains of functioning with scores from 0 (no difficulty) to 4 (extreme difficulty) and a total score ranging from 0 to 48, with higher scores representing greater disability. The total score is divided by 48 and multiplied by 100 to convert it to a percentage of maximum disability. Where a single WHODAS item was missing, the mean value of the remaining 11 items was assigned to the missing item. Scores were only calculated where the WHODAS was conducted within the 12 weeks following day 180. WHODAS percentage scores were used to determine mutually exclusive disability categories: 1) no disability (0–4.5%); 2) mild disability (4.5–24.5%); 3) moderate disability (24.5–49.5%); 4) severe disability (49.5–95.5%); and 5) complete disability (95.5–100%).

## Supplemental Results Tables

Table S1: Platform and domain-specific inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria (including intervention-specific exclusion criteria)
Platform	<ul style="list-style-type: none"> <li>Adult patient admitted to an ICU for acute severe CAP within 48 hours of hospital admission with a. symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND b. Radiological evidence of new onset infiltrate of infective origin (in patients with preexisting radiological changes, evidence of new infiltrate)</li> <li>Up to 48 hours after ICU admission, receiving organ support with one or more of: a. Non-invasive or invasive ventilatory support; b. Receiving infusion of vasopressor or inotropes or both</li> </ul>	<ul style="list-style-type: none"> <li>Healthcare-associated pneumonia: a. Prior to this illness, is known to have been an inpatient in any healthcare facility within the last 30 days b. Resident of a nursing home or long-term care facility</li> <li>Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment</li> <li>Previous participation in this REMAP within the last 90 days</li> </ul>
Immune modulation	<ul style="list-style-type: none"> <li>COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing</li> <li>Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur</li> </ul>	<ul style="list-style-type: none"> <li>More than 24 hours has elapsed since ICU admission</li> <li>Patient has already received any dose of one or more of any form of interferon, anakinra, tocilizumab, or sarilumab during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission</li> <li>Known condition or treatment resulting in ongoing immune suppression including neutropenia prior to this hospitalization</li> <li>Patient has been randomized in a trial evaluating an immune modulation agent for proven or suspected COVID-19 infection, where the protocol of that trial requires ongoing administration of study drug</li> <li>The treating clinician believes that participation in the domain would not be in the best interests of the patient</li> <li>Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent</li> <li>Intention to prescribe systemic corticosteroids for any reason, other than participation in the Corticosteroid Domain of this platform, will result in exclusion from receiving IFN-β1a</li> <li>Known hypersensitivity to proteins produced by E. coli will result in exclusion from receiving anakinra</li> <li>Known or suspected pregnancy will result in exclusion from the anakinra, IFN-β1a, tocilizumab and sarilumab interventions.</li> <li>A baseline alanine aminotransferase or an aspartate aminotransferase that is more than five times the upper limit of normal will result in exclusion from receiving tocilizumab or sarilumab</li> <li>A baseline platelet count &lt; 50 x 10<sup>9</sup> /L will result in exclusion from receiving tocilizumab or sarilumab</li> </ul>

Table S1 continued: Platform and domain-specific inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria (including intervention-specific exclusion criteria)
<p>Immunoglobulin</p> <ul style="list-style-type: none"> <li>• COVID-19 infection is confirmed by microbiological testing</li> </ul>	<ul style="list-style-type: none"> <li>• More than 48 hours have elapsed since ICU admission</li> <li>• Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission</li> <li>• More than 14 days have elapsed since hospital admission</li> <li>• The treating clinician believes that participation in the domain would not be in the best interests of the patient</li> <li>• Known hypersensitivity to an agent specified as an intervention in this domain</li> <li>• Known previous history of transfusion-related acute lung injury</li> <li>• Known objection to receiving plasma products</li> </ul>
<p>Antiplatelet</p> <ul style="list-style-type: none"> <li>• COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing</li> <li>• Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur</li> </ul>	<ul style="list-style-type: none"> <li>• More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support)</li> <li>• Clinical or laboratory bleeding risk or both that is sufficient to contraindicate antiplatelet therapy</li> <li>• Patient is already receiving antiplatelet therapy or NSAID (non-steroidal anti-inflammatory drug) or a clinical decision has been made to commence antiplatelet or NSAID therapy</li> <li>• Enrolment in a trial evaluating anticoagulation or antiplatelet therapy for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial</li> <li>• Patients otherwise eligible for the Therapeutic Anticoagulation Domain will be excluded from the Antiplatelet Domain if age is more than 75 years</li> <li>• Creatinine Clearance &lt;30ml/min, or receiving renal replacement therapy or ECMO</li> <li>• The treating clinician believes that participation in the domain would not be in the best interests of the patient</li> <li>• Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent</li> <li>• Known or suspected pregnancy will result in exclusion from the P2Y12 inhibitor intervention</li> <li>• Administration or intention to administer lopinavir/ritonavir will result in exclusion from the P2Y12 inhibitor intervention at sites that are using clopidogrel and ticagrelor as the P2Y12 inhibitor</li> </ul>

Table S1 continued: Platform and domain-specific inclusion and exclusion criteria

Domain	Inclusion Criteria	Exclusion Criteria (including intervention-specific exclusion criteria)
Anticoagulation	<ul style="list-style-type: none"> <li>• COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing</li> <li>• Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur</li> </ul>	<ul style="list-style-type: none"> <li>• More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of organ failure support)</li> <li>• Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual anti-platelet therapy</li> <li>• Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation</li> <li>• Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial</li> <li>• Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT).</li> <li>• The treating clinician believes that participation in the domain would not be in the best interests of the patient</li> </ul>
Antiviral	<ul style="list-style-type: none"> <li>• COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing</li> <li>• Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur</li> </ul>	<ul style="list-style-type: none"> <li>• More than 48 hours has elapsed since ICU admission</li> <li>• Patient has already received more than 36 hours of treatment with any non-trial prescribed systemic antiviral medication, other than remdesivir, intended to be active against COVID-19 during this hospital admission</li> <li>• Patient has been randomized in a trial evaluating an antiviral intended to be active against COVID-19, where the protocol of that trial requires ongoing administration of study drug</li> <li>• In areas where MERS-CoV infection is endemic, the patient has laboratory confirmed MERS-CoV infection</li> <li>• The treating clinician believes that participation in the domain would not be in the best interests of the patient</li> <li>• Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent</li> <li>• Receiving an agent that is specified as an intervention in this domain as a usual medication prior to this hospitalization will exclude a patient from receiving that agent</li> <li>• Known HIV infection will exclude a patient from receiving lopinavir/ritonavir</li> <li>• Known or suspected pregnancy will result in exclusion from any intervention that includes lopinavir/ritonavir or hydroxychloroquine</li> <li>• Receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 hours prior to assessment of eligibility will exclude a patient from receiving lopinavir/ritonavir</li> <li>• High clinical risk of sustained ventricular dysrhythmia will exclude a patient from receiving hydroxychloroquine</li> </ul>

Table S1 continued: Platform and domain-specific inclusion and exclusion criteria

Domain	Inclusion Criteria	Exclusion Criteria (including intervention-specific exclusion criteria)
Corticosteroid	No domain-specific inclusion criteria	<ul style="list-style-type: none"> <li>• Known hypersensitivity to hydrocortisone</li> <li>• An indication to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP (or direct complications of CAP), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven <i>Pneumocystis jiroveci</i> pneumonia</li> <li>• More than 24 hours have elapsed since ICU admission; or In France, more than 36 hours have elapsed since ICU admission</li> <li>• The treating clinician believes that participation in the domain would not be in the best interests of the patient</li> </ul>



**Table S2: Patients and follow up by country of enrolment**

Country	Number of sites	Sites completing Day 180 vital status follow up (n)	Sites completing HRQoL or disability follow up (n)	Number of patients randomized <sup>a</sup>	Patients with Day 90 vital status follow up, n/N (%)	Patients with Day 180 vital status follow up, n/N (%) <sup>b</sup>	Patients with HRQoL or disability follow up, n/N (%) <sup>c</sup>
Australia	16	16	16	39	39/39 (100)	38/39 (97.4)	29/34 (85.3)
Canada	17	17	17	203	201/203 (99.0)	199/203 (98.0)	116/127 (91.3)
Finland	1	1	1	3	3/3 (100)	3/3 (100)	1/1 (100)
France	6	5	5	65	63/65 (96.9)	58/62 (93.5)	26/45 (57.8)
Germany	1	1	1	7	6/7 (85.7)	3/7 (42.9)	0/3 (0.0)
India	4	0	0	62	55/62 (88.7)	NA <sup>d</sup>	NA <sup>d</sup>
Ireland	3	3	3	51	51/51 (100)	51/51 (100)	30/32 (93.8)
Italy	1	1	0	13	13/13 (100)	12/13 (92.3)	0/10 (0.0)
Nepal	5	0	0	64	62/64 (96.9)	NA <sup>d</sup>	NA <sup>d</sup>
Netherlands	11	11	10	216	215/216 (99.5)	208/216 (96.3)	133/155 (85.8)
New Zealand	4	4	4	4	4/4 (100)	4/4 (100)	2/2 (100)
Saudi Arabia	1	1	1	111	111/111 (100)	108/111 (97.3)	60/61 (98.4)
United Kingdom	126	117	112	3885	3832/3885 (98.6)	3423/3609 (94.8)	579/2119 (27.3)
United States of America	1	0	0	68	64/68 (94.1)	NA <sup>d</sup>	NA <sup>d</sup>

NA denotes Not Applicable

<sup>a</sup> The denominator presented is the number of patients randomized to one or more of the six closed domains who have not withdrawn consent.

<sup>b</sup> The denominator presented is the number of patients randomized to one or more of the six closed domains who have not withdrawn consent and were randomized at a site participating in day 180 vital status follow-up.

<sup>c</sup> The denominator presented is the number of patients randomized to one or more of the six closed domains who have not withdrawn consent, were known to be alive at day 180, and were randomized at a site participating in HRQoL or disability follow-up.

<sup>d</sup> No sites participating in day 180 follow-up

**Table S3: Baseline characteristics of patients in the immune modulation domain**

Characteristic	Tocilizumab N=948	Sarilumab N=485	Anakinra N=371	No immune modulator N=406
Age in years, median (IDR)	61 (54 - 70)	59 (51 - 68)	61 (52-68)	62 (53-70)
Male sex, n (%)	654 (69.0)	326 (67.2)	267 (72.0)	285 (70.2)
Female sex, n (%)	294 (31.0)	159 (32.8)	104 (28.0)	121 (29.8)
Race/Ethnicity <sup>a</sup> , n/N (%)				
Asian	124/730 (17.0)	54/462 (11.7)	40/254 (15.8)	53/318 (16.7)
Black	37/730 (5.1)	10/462 (2.2)	9/254 (3.5)	10/318 (3.1)
Mixed	13/730 (1.8)	2/462 (0.4)	6/254 (2.4)	6/318 (1.9)
Other <sup>a</sup>	36/730 (4.9)	22/462 (4.8)	16/254 (6.3)	14/318 (4.4)
White	520/730 (71.2)	374/462 (81.0)	183/254 (72.1)	235/318 (73.9)
Confirmed SARS-CoV2 infection, n/N (%) <sup>b</sup>	803/945 (85.0)	430/485 (88.7)	321/371 (86.5)	349/406 (86.0)
Body mass index, kg/m <sup>2</sup> , median (IQR)	30.4 (36.6 – 34.9) [N=860]	31.3 (27.7 – 36.3) [N=419]	29.7 (26.3 – 35.3) [N=331]	30.9 (27.1 – 34.9) [N=385]
APACHE II score <sup>c</sup> , median (IQR)	13 (8-19) [N=933]	12 (7-20) [N=477]	13 (8-19) [N=367]	12 (8-18) [N=394]
Pre-existing conditions, n/N (%) <sup>d</sup>				
Diabetes mellitus	280/946 (29.6)	108/485 (22.3)	125/371 (33.7)	152/406 (37.4)
Respiratory disease	217/946 (22.9)	117/485 (24.1)	82/371 (22.1)	100/406 (24.6)
Asthma/COPD	182/946 (19.2)	99/485 (20.4)	68/371 (18.3)	89/406 (21.9)
Other	40/946 (4.2)	26/485 (5.4)	17/371 (4.6)	17/406 (4.2)
Kidney disease	65/863 (7.5)	30/447 (6.7)	23/342 (6.7)	43/377 (11.4)
Severe cardiovascular disease	86/927 (9.3)	33/475 (7.0)	41/368 (11.1)	47/401 (11.7)
Immunosuppressive disease	20/946 (2.1)	5/485 (1.0)	6/371 (1.6)	15/406 (3.7)
Chronic immunosuppressive therapy	10/946 (1.1)	8/485 (1.7)	4/371 (1.1)	7/406 (1.7)
Time to enrolment, median (IQR)				
From hospital admission, days	1.4 (0.9 – 3.3)	1.6 (0.9 – 3.5)	1.6 (0.9 – 3.8)	1.2 (0.8 – 2.8)
From ICU admission, hours	13.5 (6.9 – 19.1)	15.1 (7.8 – 19.9)	13.6 (7.3 – 19.9)	14.0 (6.8 – 19.5)
Acute respiratory support, n (%)				
None/supplemental oxygen only	1 (0.1)	0 (0.0)	1 (0.3)	2 (0.5)
High flow nasal cannula	225 (23.7)	96 (19.8)	101 (27.2)	110 (27.1)
Non-invasive ventilation only	403 (42.5)	241 (49.7)	132 (35.6)	171 (42.1)
Invasive mechanical ventilation	319 (33.7)	148 (30.5)	137 (36.9)	123 (30.3)
ECMO, n/N (%)	1/936 (0.1)	0/478 (0.0)	0/369 (0.0)	1/396 (0.3)
Vasopressor support, n (%)	179 (18.9)	77 (15.9)	80 (21.6)	79 (19.5)
Median (IQR) acute physiology and laboratory values <sup>e</sup>				
PaO <sub>2</sub> /FIO <sub>2</sub>	111 (86 - 149) [N=872]	116 (89 - 153) [N=430]	106 (84 - 147) [N=331]	118 (89 - 170) [N=359]
C-reactive protein, µg/mL	132 (69 - 201) [N=779]	120 (70 - 199) [N=418]	112 (70 - 190) [N=324]	128 (72 - 208) [N=256]
Creatinine, mg/dL	0.9 (0.7 - 1.1) [N=940]	0.8 (0.7 - 1.1) [N=479]	0.8 (0.7 - 1.1) [N=371]	0.9 (0.7 - 1.2) [N=404]
Lactate, mmol/L	1.3 (1.0 - 1.7) [N=850]	1.3 (1.0 - 1.7) [N=418]	1.3 (1.0 - 1.7) [N=335]	1.4 (1.0 - 1.9) [N=360]
Platelets, x10 <sup>9</sup> /L	241 (181 - 311) [N=937]	238 (185 - 308) [N=481]	252 (193 - 331) [N=371]	235 (177 - 296) [N=404]
Bilirubin, mg/dL	0.5 (0.4 - 0.8) [N=908]	0.6 (0.4 - 0.8) [N=463]	0.6 (0.4 - 0.8) [N=365]	0.5 (0.4 - 0.8) [N=389]

Footnotes for Tables S3 to S9 are at the bottom of Table S9

**Table S4: Baseline characteristics of patients in the immunoglobulin domain**

Characteristic	Convalescent plasma N=1078	No Convalescent plasma N=911
Age in years, median (IQR)	61 (52 - 69)	61 (52 - 70)
Male sex, n (%)	727 (67.4)	619 (68.0)
Female sex, n (%)	351 (32.6)	292 (32.1)
Race/Ethnicity <sup>a</sup> , n/N (%)		
Asian	146/983 (14.9)	133/836 (15.9)
Black	51/983 (5.2)	38/836 (4.6)
Mixed	16/983 (1.6)	8/836 (1.0)
Other <sup>a</sup>	34/983 (3.5)	34/836 (4.1)
White	736/983 (74.9)	623/836 (74.5)
Confirmed SARS-CoV2 infection, n (%) <sup>b</sup>	997 (92.5)	843 (92.5)
Body mass index, kg/m <sup>2</sup> , median (IQR)	30.8 (26.9 – 35.6) [N=958]	31.1 (26.9 – 36.5) [N=818]
APACHE II score <sup>c</sup> , median (IQR)	13 (8-19) [N=1056]	12 (8-19) [N=896]
Pre-existing conditions, n/N (%) <sup>d</sup>		
Diabetes mellitus	338/1078 (31.4)	269/911 (29.5)
Respiratory disease	245/1078 (22.7)	216/911 (23.7)
Asthma/COPD	206/1078 (19.1)	178/911 (19.5)
Other	51/1078 (4.7)	48/911 (5.3)
Kidney disease	106/1000 (10.6)	83/840 (9.9)
Severe cardiovascular disease	96/1053 (9.1)	67/893 (7.5)
Immunosuppressive disease	52/1078 (4.8)	41/911 (4.5)
Chronic immunosuppressive therapy	47/1078 (4.4)	44/911 (4.8)
Time to enrolment, median (IQR)		
From hospital admission, days	1.8 (1.0 – 3.3)	1.7 (0.9 – 3.5)
From ICU admission, hours	17.7 (10.1 – 23.5)	17.2 (10.6 – 23.3)
Acute respiratory support, n (%)		
None/supplemental oxygen only	2 (0.2)	1 (0.1)
High flow nasal cannula	227 (21.1)	211 (23.2)
Non-invasive ventilation only	494 (45.8)	408 (44.8)
Invasive mechanical ventilation	357 (33.1)	291 (31.9)
ECMO, n/N (%)	2/1060 (0.2)	1/897 (0.1)
Vasopressor support, n (%)	207 (19.2)	175 (19.2)
Median (IQR) acute physiology and laboratory values <sup>e</sup>		
PaO <sub>2</sub> /FiO <sub>2</sub>	118 (92 - 159) [N=971]	115 (90 - 154) [N=816]
C-reactive protein, µg/mL	121 (68 - 195) [N=908]	125 (72 - 196) [N=759]
Creatinine, mg/dL	0.8 (0.7 - 1.1) [N=1070]	0.8 (0.7 - 1.2) [N=901]
Lactate, mmol/L	1.3 (1.0 - 1.7) [N=963]	1.3 (1.0 - 1.7) [N=811]
Platelets, x10 <sup>9</sup> /L	235 (177 - 304) [N=1068]	243 (182 - 307) [N=902]
Bilirubin, mg/dL	0.5 (0.4 - 0.8) [N=1028]	0.5 (0.4 - 0.8) [N=874]

Footnotes for Tables S3 to S9 are at the bottom of Table S9

**Table S5: Baseline characteristics of patients in the antiplatelet domain**

Characteristic	Aspirin N=564	P2Y12 inhibitor N=455	No Antiplatelet N=527
Age in years, median (IQR)	57 (48 – 64)	57 (49 – 65)	57 (48 – 63)
Male sex, n (%)	365 (64.7)	316 (69.5)	345 (65.5)
Female sex, n (%)	199 (35.3)	139 (30.6)	182 (34.5)
Race/Ethnicity <sup>a</sup> , n/N (%)			
Asian	46/459 (10.0)	36/372 (9.7)	58/419 (13.8)
Black	16/459 (3.5)	9/372 (2.4)	16/419 (3.8)
Mixed	19/459 (4.1)	5/372 (1.3)	10/419 (2.4)
Other <sup>a</sup>	27/459 (5.9)	15/372 (4.0)	26/419 (6.2)
White	351/459 (76.5)	307/372 (82.5)	309/419 (73.8)
Confirmed SARS-CoV2 infection, n/N (%) <sup>b</sup>	507/564 (89.9)	406/455 (89.2)	469/527 (89.0)
Body mass index, kg/m <sup>2</sup> , median (IQR)	31.7 (27.2 – 37.6) [N=495]	31.3 (26.8 – 37.4) [N=384]	31.0 (26.8 – 35.9) [N=458]
APACHE II score <sup>c</sup> , median (IQR)	12 (8-17) [N=562]	12 (8-18) [N=451]	12 (8-17) [N=524]
Pre-existing conditions, n/N (%) <sup>d</sup>			
Diabetes mellitus	135/564 (23.9)	94/455 (20.7)	115/527 (21.8)
Respiratory disease	112/564 (19.9)	91/455 (20.0)	98/527 (18.6)
Asthma/COPD	94/564 (16.7)	78/455 (17.1)	78/527 (14.8)
Other	25/564 (4.4)	18/455 (4.0)	27/527 (5.1)
Kidney disease	16/529 (3.0)	19/422 (4.5)	18/490 (3.7)
Severe cardiovascular disease	17/553 (3.1)	22/441 (5.0)	24/520 (4.6)
Immunosuppressive disease	19/564 (3.4)	16/455 (3.5)	15/527 (2.9)
Chronic immunosuppressive therapy	14/564 (2.5)	11/455 (2.4)	17/527 (3.2)
Time to enrolment, median (IQR)			
From hospital admission, days	1.6 (0.9 -3.0)	1.8 (1.0 – 3.5)	1.8 (0.9 – 3.7)
From ICU admission, hours	17.2 (9.9 – 22.4)	17.9 (12 – 23.5)	18.2 (10.7 – 23.9)
Acute respiratory support, n (%)			
None/supplemental oxygen only	0 (0.0)	0 (0.0)	1 (0.2)
High flow nasal cannula	125 (22.2)	121 (26.6)	130 (24.7)
Non-invasive ventilation only	227 (40.3)	173 (38.0)	202 (38.3)
Invasive mechanical ventilation	212 (37.6)	161 (35.4)	194 (36.8)
ECMO, n/N (%)	0/563 (0.0)	0/452 (0.0)	0/525 (0.0)
Vasopressor support, n (%)	121 (21.5)	72 (15.8)	88 (16.7)
Median (IQR) acute physiology and laboratory values <sup>e</sup>			
PaO <sub>2</sub> /FiO <sub>2</sub>	115 (87-148) [N=539]	118 (90-163) [N=436]	113 (89-148) [N=500]
C-reactive protein, µg/mL	117 (62-179) [N=488]	110 (60-178) [N=417]	114 (60-179) [N=457]
Creatinine, mg/dL	0.8 (0.6 - 0.9) [N=547]	0.8 (0.6 – 1.0) [N=449]	0.8 (0.6 – 1.0) [N=512]
Lactate, mmol/L	1.3 (1.0 – 1.8) [N=516]	1.3 (1.0 – 1.6) [N=424]	1.3 (1.0 – 1.7) [N=477]
Platelets, x10 <sup>9</sup> /L	253 (197 - 315) [N=531]	240 (184 - 311) [N=447]	253 (197 - 328) [N=488]
Bilirubin, mg/dL	0.5 (0.4 – 0.8) [N=515]	0.6 (0.4 – 0.8) [N=425]	0.5 (0.4 – 0.8) [N=491]

Footnotes for Tables S3 to S9 are at the bottom of Table S9

**Table S6: Baseline characteristics of patients in the anticoagulation domain**

Characteristic	Therapeutic anticoagulation N=499	Standard thromboprophylaxis N=511
Age in years, median (IQR)	62 (52 – 71) [N=498]	62 (53 – 70) [N=511]
Male sex, n/N (%)	355/498 (71.3)	348/511 (68.1)
Female sex, n/N (%)	143/498 (28.7)	163/511 (31.9)
Race/Ethnicity <sup>a</sup> , n/N (%)		
Asian	70/409 (17.1)	71/430 (16.5)
Black	16/409 (3.9)	6/430 (1.4)
Mixed	0/409 (0.0)	6/430 (1.4)
Other <sup>a</sup>	11/409 (2.7)	17/430 (4.0)
White	312/409 (76.3)	330/430 (76.7)
Confirmed SARS-CoV2 infection, n/N (%) <sup>b</sup>	434/499 (87.0)	462/511 (90.4)
Body mass index, kg/m <sup>2</sup> , median (IQR)	30.2 (26.7 – 35.6) [N=448]	30.1 (26.5 – 34.6) [N=446]
APACHE II score <sup>c</sup> , median (IQR)	14 (8-21) [N=485]	13 (9-20) [N=496]
Pre-existing conditions, n/N (%) <sup>d</sup>		
Diabetes mellitus	156/498 (31.3)	164/511 (32.1)
Respiratory disease	125/498 (25.1)	123/511 (24.1)
Asthma/COPD	105/498 (21.1)	107/511 (20.9)
Other	24/498 (4.8)	22/511 (4.3)
Kidney disease	47/466 (10.1)	43/464 (9.3)
Severe cardiovascular disease	33/488 (6.8)	35/504 (6.9)
Immunosuppressive disease	21/498 (4.2)	16/511 (3.1)
Chronic immunosuppressive therapy	26/498 (5.2)	20/511 (3.9)
Time to enrolment, median (IQR)		
From hospital admission, days	1.7 (1.0 – 3.0)	1.6 (0.9 – 3.0)
From ICU admission, hours	17.6 (10.2 – 23.2)	16.8 (9.2 – 23.5)
Acute respiratory support, n (%)		
None/supplemental oxygen only	1 (0.2)	0 (0.0)
High flow nasal cannula	130 (26.1)	139 (27.2)
Non-invasive ventilation only	224 (44.9)	209 (40.9)
Invasive mechanical ventilation	147 (29.5)	166 (32.5)
ECMO, n/N (%)	0/487 (0.0)	0/498 (0.0)
Vasopressor support, n (%)	93 (18.6)	95 (18.6)
Median (IQR) acute physiology and laboratory values <sup>e</sup>		
PaO <sub>2</sub> /FiO <sub>2</sub>	120 (90 - 166) [N=432]	122 (93 - 164) [N=438]
C-reactive protein, µg/mL	121 (67 - 183) [N=347]	120 (69 - 201) [N=374]
Creatinine, mg/dL	0.9 (0.7 - 1.1) [N=497]	0.8 (0.7 - 1.1) [N=506]
Lactate, mmol/L	1.3 (1.0 - 1.8) [N=413]	1.3 (1.0 - 1.7) [N=430]
Platelets, x10 <sup>9</sup> /L	248 (190 - 318) [N=491]	245 (181 - 311) [N=504]
Bilirubin, mg/dL	0.5 (0.4 - 0.8) [N=449]	0.5 (0.4 - 0.8) [N=469]

Footnotes for Tables S3 to S9 are at the bottom of Table S9

**Table S7: Baseline characteristics of patients in the antiviral domain**

Characteristic	Lopinavir/ritonavir N=256	Hydroxychloroquine N=50	Hydroxychloroquine & Lopinavir/ritonavir N=27	No Antiviral N=362
Age in years, median (IQR)	61 (53 – 71)	59 (49 – 64)	61 (54 – 68)	61 (53 – 72)
Male sex, n (%)	183 (71.5)	35 (70.0)	19 (70.4)	252 (69.6)
Female sex, n (%)	73 (28.5)	15 (30.0)	8 (29.6)	110 (30.4)
Race/Ethnicity <sup>a</sup> , n/N (%)				
Asian	26/148 (17.6)	5/32 (15.6)	1/9 (11.1)	28/219 (12.8)
Black	3/148 (2.0)	4/32 (12.5)	1/9 (11.1)	6/219 (2.7)
Mixed	4/148 (2.7)	2/32 (6.3)	0/9 (0.0)	3/219 (1.4)
Other <sup>a</sup>	6/148 (4.1)	2/32 (6.3)	0/9 (0.0)	11/219 (5.0)
White	109/148 (73.7)	19/32 (59.4)	7/9 (77.8)	171/219 (78.1)
Confirmed SARS-CoV2 infection, n/N (%) <sup>b</sup>	219/256 (85.6)	43/50 (86.0)	22/26 (84.6)	303/362 (83.7)
Body mass index, kg/m <sup>2</sup> , median (IQR)	29.5 (25.9 – 34.7) [N=244]	30.7 (25.6 – 35.5) [N=50]	29.4 (25.1 – 32.0) [N=25]	30.2 (26.8 – 35.5) [N=342]
APACHE II score <sup>c</sup> , median (IQR)	13 (8-19) [N=250]	13 (8-20) [N=50]	14 (10-21) [N=26]	13 (8-19) [N=354]
Pre-existing conditions, n/N (%) <sup>d</sup>				
Diabetes mellitus	91/256 (35.5)	15/50 (30.0)	10/26 (38.5)	123/362 (34.0)
Respiratory disease	62/256 (24.2)	9/50 (18.0)	6/26 (23.1)	91/362 (25.1)
Asthma/COPD	57/256 (22.3)	8/50 (16.0)	6/26 (23.1)	77/362 (21.3)
Other	7/256 (2.7)	2/50 (4.0)	0/26 (0.0)	19/362 (5.3)
Kidney disease	31/235 (13.2)	3/44 (6.8)	4/24 (16.7)	37/328 (11.3)
Severe cardiovascular disease	40/252 (15.9)	2/48 (4.2)	3/26 (11.5)	37/354 (10.5)
Immunosuppressive disease	15/256 (5.9)	0/50 (0.0)	1/26 (3.9)	15/362 (4.1)
Chronic immunosuppressive therapy	6/256 (2.3)	2/50 (4.0)	1/26 (3.9)	18/362 (5.0)
Time to enrolment, median (IQR)				
From hospital admission, days	1.1 (0.8 – 2.7)	1.0 (0.6 – 1.7)	1.1 (0.7 – 1.5)	1.1 (0.8 – 2.2)
From ICU admission, hours	13.1 (6.7 – 19.0)	12.6 (4.9 – 20.5)	14.1 (2.5 – 18.7)	13.7 (6.3 – 19.4)
Acute respiratory support, n (%)				
None/supplemental oxygen only	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)
High flow nasal cannula	72 (28.1)	8 (16.0)	3 (11.1)	100 (27.6)
Non-invasive ventilation only	111 (43.4)	16 (32.0)	11 (40.7)	144 (39.8)
Invasive mechanical ventilation	73 (28.5)	26 (52.0)	13 (48.2)	114 (31.5)
ECMO, n/N (%)	0/250 (0.0)	0/50 (0.0)	0/26 (0.0)	0/354 (0.0)
Vasopressor support, n (%)	47 (18.4)	13 (26.0)	5 (18.5)	71 (19.6)
Median (IQR) acute physiology and laboratory values <sup>e</sup>				
PaO <sub>2</sub> /FiO <sub>2</sub>	122 (89–174) [N=216]	115 (86 - 152) [N=46]	116 (91 - 152) [N=24]	118 (90 - 169) [N=316]
C-reactive protein, µg/mL	157 (83 - 223) [N=130]	161 (125 - 280) [N=8]	202 (73 - 380) [N=3]	158 (91 - 228) [N=193]
Creatinine, mg/dL	0.9 (0.7 - 1.2) [N=256]	1.0 (0.7 - 1.3) [N=50]	1.0 (0.7 - 1.5) [N=26]	0.9 (0.7 - 1.2) [N=361]
Lactate, mmol/L	1.3 (1.0 - 1.9) [N=218]	1.1 (1.0 - 1.5) [N=41]	1.1 (0.9 - 1.6) [N=20]	1.3 (1.0 - 1.8) [N=312]
Platelets, x10 <sup>9</sup> /L	245 (180 - 308) [N=255]	200 (165 - 273) [N=50]	236 (193 - 378) [N=26]	247 (188 - 311) [N=359]
Bilirubin, mg/dL	0.6 (0.4 - 0.8) [N=233]	0.6 (0.5 - 0.9) [N=49]	0.7 (0.5 – 1.0) [N=23]	0.6 (0.4 - 0.8) [N=346]

Footnotes for Tables S3 to S9 are at the bottom of Table S9

**Table S8: Baseline characteristics of patients in the corticosteroid domain**

Characteristic	Fixed-dose hydrocortisone N=137	Shock-dependent hydrocortisone N=147	No Corticosteroid N=101
Age in years, median (IQR)	60 (53 – 69)	60 (52 – 69)	62 (50 – 72)
Male sex, n/N (%)	98/137 (71.5)	105/147 (71.4)	73/101 (72.3)
Female sex, n/N (%)	39/137 (28.5)	42/147 (28.6)	28/101 (27.7)
Race/Ethnicity <sup>a</sup> , n/N (%)			
Asian	8/55 (14.6)	7/48 (14.6)	12/33 (36.4)
Black	3/55 (5.5)	2/48 (4.2)	3/33 (9.1)
Mixed	1/55 (1.8)	0/48 (0.0)	1/33 (3.0)
Other <sup>a</sup>	5/55 (9.1)	3/48 (6.3)	2/33 (6.1)
White	38/55 (69.1)	36/48 (75.0)	15/33 (45.5)
Confirmed SARS-CoV2 infection, n/N (%) <sup>b</sup>	108/133 (81.2)	90/128 (70.3)	78/100 (78.0)
Body mass index, kg/m <sup>2</sup> , median (IQR)	29.5 (25.3 – 34.4) [N=133]	29.3 (25.1 – 33.7) [N=146]	28.3 (24.7 – 32.5) [N=100]
APACHE II score <sup>c</sup> , median (IQR)	15.5 (10-21) [N=118]	16 (11-23) [N=129]	14 (11-21) [N=93]
Pre-existing conditions, n/N (%) <sup>d</sup>			
Diabetes mellitus	51/137 (37.2)	38/147 (25.9)	29/101 (28.7)
Respiratory disease	27/137 (19.7)	27/147 (18.4)	20/101 (19.8)
Asthma/COPD	21/137 (15.3)	24/147 (16.3)	16/101 (15.8)
Other	7/137 (5.1)	4/147 (2.7)	4/101 (4.0)
Kidney disease	13/128 (10.2)	11/130 (8.5)	8/93 (8.6)
Severe cardiovascular disease	9/136 (6.6)	13/142 (9.2)	6/100 (6.0)
Immunosuppressive disease	7/137 (5.1)	8/147 (5.4)	2/101 (2.0)
Chronic immunosuppressive therapy	8/137 (5.8)	7/147 (4.8)	6/101 (5.9)
Time to enrolment, median (IQR)			
From hospital admission, days	1.2 (0.8 – 2.8)	1.0 (0.7 – 2.8)	1.1 (0.7 – 2.0)
From ICU admission, hours	15.1 (7.5 – 19.8)	12.3 (5.4 – 18.8)	13.6 (8.1 – 17.9)
Acute respiratory support, n (%)			
None/supplemental oxygen only	0 (0.0)	1 (0.7)	0 (0.0)
High flow nasal cannula	17 (12.4)	23 (15.7)	16 (15.8)
Non-invasive ventilation only	33 (24.1)	49 (33.3)	32 (31.7)
Invasive mechanical ventilation	87 (63.5)	74 (50.3)	53 (52.5)
ECMO, n (%)	1 (0.7)	0 (0.0)	2 (2.0)
Vasopressor support, n (%)	56 (40.9)	47 (32.0)	30 (29.7)
Median (IQR) acute physiology and laboratory values <sup>e</sup>			
PaO <sub>2</sub> /FiO <sub>2</sub>	140 (98 - 200) [N=128]	136 (104 - 175) [N=138]	140 (97 - 180) [N=93]
C-reactive protein, µg/mL	178 (122 - 316) [N=16]	160 (127-288) [N=15]	158 (121 - 221) [N=9]
Creatinine, mg/dL	0.9 (0.7 - 1.2) [N=115]	0.9 (0.7 - 1.2) [N=128]	0.8 (0.6 - 1.2) [N=91]
Lactate, mmol/L	1.2 (0.9 - 1.5) [N=106]	1.2 (0.9 - 1.7) [N=112]	1.0 (0.8 - 1.4) [N=83]
Platelets, x10 <sup>9</sup> /L	236 (181 - 315) [N=115]	250 (176 - 335) [N=128]	243 (172 - 320) [N=91]
Bilirubin, mg/dL	0.6 (0.5 - 0.9) [N=111]	0.6 (0.5 - 0.8) [N=120]	0.6 (0.4 - 0.8) [N=86]

Footnotes for Tables S3 to S9 are at the bottom of Table S9

**Table S9: Baseline characteristics of survivors with and without known day 180 vital status**

Characteristic	Day 180 vital status known N=4107	Missing day 180 vital status N=684 <sup>f</sup>
Age in years, median (IQR)	59.6 (12.5) [N=4107]	57.4 (14.7) [N=683]
Male sex, n/N (%)	2791/4107 (68.0)	462/683 (67.6)
Female sex, n/N (%)	1316/4107 (32.0)	221/683 (32.4)
Race/Ethnicity <sup>a</sup> , n/N (%)		
Asian	435/3082 (14.1)	69/475 (14.5)
Black	130/3082 (4.2)	30/475 (6.3)
Mixed	56/3082 (1.8)	13/475 (2.7)
Other <sup>a</sup>	138/3082 (4.5)	21/475 (4.4)
White	2323/3082 (75.4)	342/475 (72.0)
Confirmed SARS-CoV2 infection, n/N (%) <sup>b</sup>	3542/4088 (86.6)	597/676 (88.3)
Body mass index, kg/m <sup>2</sup> , median (IQR)	32.0 (7.8) [N=3777]	31.9 (7.8) [N=540]
APACHE II score <sup>c</sup> , median (IQR)	13 (8-20) [N=4019]	11 (7-17) [N=654]
Pre-existing conditions, n/N (%) <sup>d</sup>		
Diabetes mellitus	1204/4107 (29.3)	200/681 (29.4)
Respiratory disease	944/4107 (23.0)	123/681 (18.1)
Asthma/COPD	797/4107 (19.4)	100/681 (14.7)
Other	192/4107 (4.7)	26/681 (3.8)
Kidney disease	319/3797 (8.4)	51/630 (8.1)
Severe cardiovascular disease	334/4031 (8.3)	42/672 (6.3)
Immunosuppressive disease	176/4107 (4.3)	14/681 (2.1)
Chronic immunosuppressive therapy	161/4107 (3.9)	14/681 (2.1)
Time to enrolment, median (IQR)		
From hospital admission, days	1.7 (0.9 – 3.5)	1.5 (0.9 – 2.9)
From ICU admission, hours	16.6 (8.8 – 22.4)	17.8 (10.7 – 22.9)
Acute respiratory support, n (%)		
None/supplemental oxygen only	7 (0.2)	0 (0.0)
High flow nasal cannula	1043 (25.4)	155 (22.7)
Non-invasive ventilation only	1517 (36.9)	331 (48.4)
Invasive mechanical ventilation	1540 (37.5)	206 (30.1)
ECMO, n/N (%)	1/4057 (0.0)	3/672 (0.5)
Vasopressor support, n (%)	912 (22.2)	93 (13.6)
Median (IQR) acute physiology and laboratory values <sup>e</sup>		
PaO <sub>2</sub> /FiO <sub>2</sub>	116 (89 - 157) [N=3878]	120 (90 - 160) [N=490]
C-reactive protein, µg/mL	120 (67 - 195) [N=3128]	92 (50 - 159) [N=457]
Creatinine, mg/dL	0.8 (0.7 - 1.1) [N=4046]	0.9 (0.7 - 1.2) [N=635]
Lactate, mmol/L	1.3 (1.0 - 1.7) [N=3717]	1.4 (1.1 - 1.9) [N=488]
Platelets, x10 <sup>9</sup> /L	246 (185 - 315) [N=4038]	238 (178 - 305) [N=588]
Bilirubin, mg/dL	0.5 (0.4 - 0.8) [N=3836]	0.5 (0.4 - 0.8) [N=607]

Percentages may not sum to 100 because of rounding. SD denotes standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.

<sup>a</sup> Self-reported via fixed categories. Data collection was not approved in Asia, Canada, and continental Europe. "Other" includes "other ethnic group" and those who declined to respond or were not asked by registration personnel.

<sup>b</sup> SARS-CoV2 infection was confirmed by respiratory tract polymerase chain reaction test.

<sup>c</sup> Measures the severity of illness based on age, medical history, and physiological variables. Scores range from 0 to 71; higher numbers represent greater risk of death. The median score of 12 is typical for patients with COVID-19 admitted to intensive care units (ICUs).



<sup>d</sup> Kidney disease was determined from the most recent stable serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 130 µmol/L or greater (1.5mg/dL) for males or 100 µmol/L or greater (1.1 mg/dL) for females not previously receiving dialysis. Cardiovascular disease was defined as New York Heart Association class IV symptoms. Immunosuppression was defined by the receipt of recent chemotherapy, radiation, high-dose or long-term steroid treatment, or presence of immunosuppressive disease.

<sup>e</sup> Laboratory results available when captured for clinical care. Although specific laboratory cut-offs may vary, ranges for the following variables are generally considered normal: P<sub>a</sub>O<sub>2</sub>/F<sub>i</sub>O<sub>2</sub> ratio ≥400; creatinine <1.2 mg/dL; platelets ≥150 x10<sup>9</sup>/L; and bilirubin <1.2 mg/dL.

<sup>f</sup> Of the 684 participants with missing day 180 vital status, 512 were randomized at sites not participating in follow up beyond day 90.

**Table S10: Sensitivity Analysis of Day 180 mortality in non-negative COVID-19 population**

	Adjusted Hazard Ratio (95% CrI)	Probability of Superiority of Intervention (%) <sup>a</sup>	Probability of Futility of Intervention (%) <sup>a</sup>
<b>Immune Modulation Domain</b>			
IL-6 receptor antagonists	0.73 (0.59 to 0.90)	99.7%	9.6%
Anakinra	0.96 (0.73 to 1.23)	61.5%	85.1%
Control	1 (referent)	-	-
<b>Immunoglobulin Domain</b>			
Convalescent plasma	0.98 (0.85 to 1.14)	58.9%	98.8%
Control	1 (referent)	-	-
<b>Antiplatelet Domain</b>			
Antiplatelet	0.85 (0.70 to 1.04)	94.5%	59.7%
Control	1 (referent)	-	-
<b>Anticoagulation Domain</b>			
Therapeutic anticoagulation	1.17 (0.94 to 1.44)	8.3%	99.9%
Thromboprophylaxis	1 (referent)	-	-
<b>Antiviral Domain</b>			
Lopinavir-ritonavir	1.09 (0.82 to 1.44)	27.0%	96.8%
Hydroxychloroquine	1.81 (1.16 to 2.78)	0.5%	99.9%
Combination antiviral therapy	1.99 (1.15 to 3.32)	0.6%	>99.9%
Control	1 (referent)	-	-
<b>Corticosteroid Domain</b>			
Fixed dose corticosteroids	1.01 (0.61 to 1.64)	48.4%	78.8%
Shock-dependent corticosteroids	0.98 (0.57 to 1.63)	52.5%	73.4%
Control	1 (referent)	-	-

CrI denotes credible interval.

<sup>a</sup> The probability of superiority and futility is computed from a Bayesian piecewise exponential model using the posterior distribution.

**Table S11: Sensitivity Analysis of Day 180 mortality with independent effects for interleukin-6 receptor antagonists and antiplatelet interventions**

	N	Day 180 mortality <sup>a</sup> , n/N (%)	Adjusted Hazard Ratio (95% CrI)	Probability of Superiority of Intervention (%) <sup>b</sup>	Probability of Futility of Intervention (%) <sup>b</sup>
<b>Immune Modulation Domain</b>					
Tocilizumab	948	298/831 (35.9)	0.76 (0.61 to 0.93)	99.6%	17.1%
Sarilumab	485	138/417 (33.1)	0.72 (0.56 to 0.91)	99.6%	10.9%
Anakinra	371	138/325 (42.5)	0.96 (0.74 to 1.24)	62.4%	86.0%
Control	406	140/350 (40.0)	1 (referent)	-	-
<b>Immunoglobulin Domain</b>					
Convalescent plasma	1078	370/944 (39.2)	0.99 (0.86 to 1.14)	54.2%	99.0%
Control	911	324/790 (41.0)	1 (referent)	-	-
<b>Antiplatelet Domain</b>					
Aspirin	564	143/472 (30.3)	0.83 (0.66 to 1.03)	95.9%	47.0%
P2Y12 inhibitor	455	131/399 (32.8)	0.88 (0.70 to 1.11)	84.9%	69.0%
Control	527	143/441 (32.4)	1 (referent)	-	-
<b>Anticoagulation Domain</b>					
Therapeutic anticoagulation	499	165/403 (40.9)	1.16 (0.93 to 1.41)	9.6%	99.8%
Thromboprophylaxis	511	147/418 (35.2)	1 (referent)	-	-
<b>Antiviral Domain</b>					
Lopinavir-ritonavir	256	81/226 (35.8)	1.07 (0.82 to 1.39)	31.1%	96.9%
Hydroxychloroquine	50	16/41 (39.0)	1.51 (0.96 to 2.29)	3.7%	99.6%
Combination antiviral therapy	27	13/26 (50.0)	1.63 (0.95 to 2.68)	3.8%	99.3%
Control	362	107/311 (34.4)	1 (referent)	-	-
<b>Corticosteroid Domain</b>					
Fixed dose corticosteroids	137	34/109 (31.2)	0.93 (0.59 to 1.45)	61.2%	68.2%
Shock-dependent corticosteroids	147	39/137 (28.5)	0.97 (0.61 to 1.55)	55.5%	72.9%
Control	101	27/79 (34.2)	1 (referent)	-	-

CrI denotes credible interval.

<sup>a</sup> Due to censoring, reported day 180 mortality rates are restricted to patients at sites participating in day 180 follow-up with known day 180 vital status.

<sup>b</sup> The probability of superiority and futility is computed from a Bayesian piecewise exponential model using the posterior distribution.

**Table S12: Sensitivity Analysis of Day 180 mortality within domain-specific populations**

	Adjusted Hazard Ratio (95% CrI)	Probability of Superiority of Intervention (%) <sup>a</sup>	Probability of Futility of Intervention (%) <sup>a</sup>
<b>Immune Modulation Domain</b>			
IL-6 Receptor Antagonists	0.72 (0.58 to 0.91)	99.7%	10.5%
Anakinra	0.92 (0.70 to 1.22)	72.4%	76.1%
Control	1 (referent)	-	-
<b>Immunoglobulin Domain</b>			
Convalescent plasma	0.99 (0.85 to 1.14)	57.0%	98.9%
Control	1 (referent)	-	-
<b>Antiplatelet Domain</b>			
Antiplatelet	0.91 (0.75 to 1.09)	84.0%	80.4%
Control	1 (referent)	-	-
<b>Anticoagulation Domain</b>			
Therapeutic anticoagulation	1.21 (0.99 to 1.49)	3.3%	>99.9%
Thromboprophylaxis	1 (referent)	-	-
<b>Antiviral Domain</b>			
Lopinavir-ritonavir	1.11 (0.86 to 1.44)	21.1%	98.3%
Hydroxychloroquine	1.60 (0.98 to 2.58)	2.9%	99.6%
Combination antiviral therapy	1.78 (1.03 to 3.09)	1.9%	99.7%
Control	1 (referent)	-	-
<b>Corticosteroid Domain</b>			
Fixed dose corticosteroids	1.00 (0.62 to 1.55)	50.1%	78.3%
Shock-dependent corticosteroids	1.06 (0.68 to 1.74)	39.7%	85.0%
Control	1 (referent)	-	-

CrI, denotes credible interval.

<sup>a</sup> The probability of superiority and futility is computed from a Bayesian piecewise exponential model using the posterior distribution.

**Table S13: Day 90 mortality**

	N	Day 90 mortality, n/N (%)	Odds Ratio (95% CrI)	Probability of Superiority of Intervention (%) <sup>a</sup>	Probability of Futility of Intervention (%) <sup>a</sup>
<b>Immune Modulation Domain</b>					
IL-6 receptor antagonists	1433	481/1409 (34.1)	0.71 (0.54 to 0.94)	99.1%	12.8%
Anakinra	371	150/365 (41.1)	1.06 (0.74 to 1.52)	38.2%	90.1%
Control	406	151/399 (37.8)	1 (referent)	-	-
<b>Immunoglobulin Domain</b>					
Convalescent plasma	1078	408/1067 (38.2)	0.97 (0.79 to 1.19)	60.2%	93.1%
Control	911	358/901 (39.7)	1 (referent)	-	-
<b>Antiplatelet Domain</b>					
Antiplatelet	1019	298/1001 (29.8)	0.83 (0.64 to 1.07)	92.3%	48.2%
Control	527	171/522 (32.8)	1 (referent)	-	-
<b>Anticoagulation Domain</b>					
Therapeutic anticoagulation	499	191/490 (39.0)	1.23 (0.92 to 1.63)	8.1%	99.7%
Thromboprophylaxis	511	181/504 (35.9)	1 (referent)	-	-
<b>Antiviral Domain</b>					
Lopinavir-ritonavir	256	93/253 (36.8)	1.29 (0.91 to 1.85)	7.8%	99.3%
Hydroxychloroquine	50	17/49 (34.7)	1.89 (1.06 to 3.37)	1.7%	99.7%
Combination antiviral therapy	27	13/26 (50.0)	2.45 (1.23 to 4.85)	0.6%	99.9%
Control	362	116/361 (32.1)	1 (referent)	-	-
<b>Corticosteroid Domain</b>					
Fixed dose corticosteroids	137	41/135 (30.4)	0.84 (0.48 to 1.54)	71.1%	52.0%
Shock-dependent corticosteroids	147	36/146 (24.7)	0.77 (0.43 to 1.40)	80.6%	39.3%
Control	101	34/97 (35.1)	1 (referent)	-	-
<b>Pre-specified combination %/interaction</b>					
Therapeutic anticoagulation/antiplatelet combination <sup>b</sup>	35	17/35 (48.6)	1.38 (0.76 to 2.49)	14.4%	NA
Therapeutic anticoagulation/antiplatelet interaction			1.36 (0.80 to 2.26)		

SD denotes standard deviation; NA, not available; CrI, credible interval.

<sup>a</sup> The probability of superiority and futility is computed from a Bayesian logistic regression model using the posterior distribution.

<sup>b</sup> The combination effect provides the effect of giving both therapeutic anticoagulation and antiplatelet interventions together in combination. This is estimated by multiplying the hazard ratio for antiplatelet, therapeutic anticoagulation and the interaction effect for antiplatelet and therapeutic anticoagulation.

**Table S14: Baseline characteristics of survivors with and without EQ-5D-5L utility scores**

Characteristic	EQ-5D-5L utility score available N=989	Missing EQ-5D-5L utility score N=1601
Age in years, median (IQR)	60 (51 - 67)	56 (47 - 63)
Male sex, n (%)	650 (65.7)	1064 (66.5)
Female sex, n (%)	339 (34.3)	537 (33.5)
Race/Ethnicity <sup>a</sup> , n/N (%)		
Asian	53/588 (9.0)	179/1331 (13.5)
Black	24/588 (4.1)	67/1331 (5.0)
Mixed	6/588 (1.0)	34/1331 (2.6)
Other <sup>a</sup>	25/588 (4.3)	76/1331 (5.7)
White	480/588 (81.6)	975/1331 (73.3)
Confirmed SARS-CoV2 infection, n/N (%) <sup>b</sup>	832/978 (85.1)	1397/1600 (87.3)
Body mass index, kg/m <sup>2</sup> , median (IQR)	30.9 (27.1 – 36.3) [N=926]	31.5 (27.2 – 36.7) [N=1460]
APACHE II score <sup>c</sup> , median (IQR)	12 (8-18) [N=954]	12 (7-18) [N=1578]
Pre-existing conditions, n/N (%) <sup>d</sup>		
Diabetes mellitus	273/989 (27.6)	429/1601 (26.8)
Respiratory disease	222/989 (22.5)	325/1601 (20.3)
Asthma/COPD	189/989 (19.1)	280/1601 (17.5)
Other	48/989 (4.9)	59/1601 (3.7)
Kidney disease	58/922 (6.3)	84/1479 (5.7)
Severe cardiovascular disease	58/973 (6.0)	95/1568 (6.1)
Immunosuppressive disease	42/989 (4.3)	38/1601 (2.4)
Chronic immunosuppressive therapy	41/989 (4.2)	34/1601 (2.1)
Time to enrolment, median (IQR)		
From hospital admission, days	1.6 (0.9 – 3.0)	1.6 (0.9 – 2.9)
From ICU admission, hours	16.1 (7.8 – 21.8)	16.5 (9.2 – 22.2)
Acute respiratory support, n (%)		
None/supplemental oxygen only	2 (0.2)	2 (0.1)
High flow nasal cannula	381 (38.5)	402 (25.1)
Non-invasive ventilation only	310 (31.3)	632 (39.5)
Invasive mechanical ventilation	296 (29.9)	565 (35.3)
ECMO, n/N (%)	0/974 (0.0)	1/1585 (0.1)
Vasopressor support, n (%)	183 (18.5)	304 (19.0)
Median (IQR) acute physiology and laboratory values <sup>e</sup>		
PaO <sub>2</sub> /FiO <sub>2</sub>	121 (92 - 165) [N=913]	121 (94 - 163) [N=1525]
C-reactive protein, µg/mL	118 (67 - 183) [N=702]	119 (65 - 189) [N=1261]
Creatinine, mg/dL	0.8 (0.7 - 1.0) [N=961]	0.8 (0.7 - 1.0) [N=1585]
Lactate, mmol/L	1.3 (1.0 - 1.7) [N=886]	1.2 (1.0 - 1.7) [N=1471]
Platelets, x10 <sup>9</sup> /L	253 (194 - 320) [N=959]	253 (198 - 326) [N=1585]
Bilirubin, mg/dL	0.5 (0.4 - 0.7) [N=884]	0.5 (0.4 - 0.8) [N=1532]

Percentages may not sum to 100 because of rounding. SD denotes standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.

<sup>a</sup> Self-reported via fixed categories. Data collection was not approved in Asia, Canada, and continental Europe. "Other" includes "other ethnic group" and those who declined to respond or were not asked by registration personnel.

<sup>b</sup> SARS-CoV2 infection was confirmed by respiratory tract polymerase chain reaction test.

<sup>c</sup> Measures the severity of illness based on age, medical history, and physiological variables. Scores range from 0 to 71; higher numbers represent greater risk of death. The median score of 12 is typical for patients with COVID-19 admitted to intensive care units (ICUs).

<sup>d</sup> Kidney disease was determined from the most recent stable serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 130  $\mu\text{mol/L}$  or greater (1.5mg/dL) for males or 100  $\mu\text{mol/L}$  or greater (1.1 mg/dL) for females not previously receiving dialysis. Cardiovascular disease was defined as New York Heart Association class IV symptoms. Immunosuppression was defined by the receipt of recent chemotherapy, radiation, high-dose or long-term steroid treatment, or presence of immunosuppressive disease.

<sup>e</sup> Laboratory results available when captured for clinical care. Although specific laboratory cut-offs may vary, ranges for the following variables are generally considered normal:  $\text{P}_a\text{O}_2/\text{F}_i\text{O}_2$  ratio  $\geq 400$ ; creatinine  $< 1.2$  mg/dL; platelets  $\geq 150 \times 10^9/\text{L}$ ; and bilirubin  $< 1.2$  mg/dL.

**Table S15: Baseline characteristics of survivors with and without WHODAS scores**

Characteristic	WHODAS score available N=720	Missing WHODAS score N=1867
Age in years, median (IQR)	59 (51 - 67)	57 (48 - 64)
Male sex, n (%)	482 (66.9)	1230 (65.9)
Female sex, n (%)	238 (33.1)	637 (34.1)
Race/Ethnicity <sup>a</sup> , n/N (%)		
Asian	37/391 (9.5)	195/1527 (12.8)
Black	19/391 (4.9)	72/1527 (4.7)
Mixed	5/391 (1.3)	35/1527 (2.3)
Other <sup>a</sup>	17/391 (4.4)	84/1527 (5.5)
White	313/391 (80.1)	1141/1527 (74.7)
Confirmed SARS-CoV2 infection, n/N (%) <sup>b</sup>	604/713 (84.7)	1623/1862 (87.2)
Body mass index, kg/m <sup>2</sup> , median (IQR)	30.8 (27.1 – 35.9) [N=671]	31.4 (27.2 – 36.8) [N=1712]
APACHE II score <sup>c</sup> , median (IQR)	11 (8-17) [N=695]	12 (8-18) [N=1834]
Pre-existing conditions, n/N (%) <sup>d</sup>		
Diabetes mellitus	210/720 (29.2)	496/1867 (26.6)
Respiratory disease	163/720 (22.6)	384/1867 (20.6)
Asthma/COPD	137/720 (19.0)	332/1867 (17.8)
Other	37/720 (5.1)	70/1867 (3.8)
Kidney disease	40/672 (6.0)	100/1726 (5.8)
Severe cardiovascular disease	39/706 (5.5)	113/1832 (6.2)
Immunosuppressive disease	24/720 (3.3)	33/1867 (1.8)
Chronic immunosuppressive therapy	29/720 (4.0)	46/1867 (2.5)
Time to enrolment, median (IQR)		
From hospital admission, days	1.5 (0.9 – 3.0)	1.6 (0.9 – 3.0)
From ICU admission, hours	16.1 (8.4 – 21.8)	16.5 (8.9 – 22.1)
Acute respiratory support, n (%)		
None/supplemental oxygen only	1 (0.1)	3 (0.2)
High flow nasal cannula	298 (41.4)	483 (25.9)
Non-invasive ventilation only	214 (29.7)	728 (39.0)
Invasive mechanical ventilation	207 (28.8)	653 (35.0)
ECMO, n/N (%)	0/711 (0.0)	1/1845 (0.1)
Vasopressor support, n (%)	134 (18.6)	352 (18.9)
Median (IQR) acute physiology and laboratory values <sup>e</sup>		
PaO <sub>2</sub> /FiO <sub>2</sub>	121 (91 - 165) [N=657]	121 (93 - 163) [N=1779]
C-reactive protein, µg/mL	117 (69 - 182) [N=480]	119 (64 - 189) [N=1481]
Creatinine, mg/dL	0.8 (0.7 - 1.0) [N=698]	0.8 (0.7 - 1.0) [N=1845]
Lactate, mmol/L	1.3 (1.0 - 1.8) [N=631]	1.2 (1.0 - 1.7) [N=1723]
Platelets, x10 <sup>9</sup> /L	257 (201 - 326) [N=699]	251 (194 - 321) [N=1842]
Bilirubin, mg/dL	0.5 (0.4 - 0.7) [N=634]	0.5 (0.4 - 0.8) [N=1779]

Percentages may not sum to 100 because of rounding. SD denotes standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.

<sup>a</sup> Self-reported via fixed categories. Data collection was not approved in Asia, Canada, and continental Europe. "Other" includes "other ethnic group" and those who declined to respond or were not asked by registration personnel.

<sup>b</sup> SARS-CoV2 infection was confirmed by respiratory tract polymerase chain reaction test.

<sup>c</sup> Measures the severity of illness based on age, medical history, and physiological variables. Scores range from 0 to 71; higher numbers represent greater risk of death. The median score of 12 is typical for patients with COVID-19 admitted to intensive care units (ICUs).

<sup>d</sup> Kidney disease was determined from the most recent stable serum creatinine level prior to this hospital admission, except in patients who were receiving dialysis. Abnormal kidney function was defined as a creatinine level of 130  $\mu\text{mol/L}$  or greater (1.5mg/dL) for males or 100  $\mu\text{mol/L}$  or greater (1.1 mg/dL) for females not previously receiving dialysis. Cardiovascular disease was defined as New York Heart Association class IV symptoms. Immunosuppression was defined by the receipt of recent chemotherapy, radiation, high-dose or long-term steroid treatment, or presence of immunosuppressive disease.

<sup>e</sup> Laboratory results available when captured for clinical care. Although specific laboratory cut-offs may vary, ranges for the following variables are generally considered normal:  $\text{P}_a\text{O}_2/\text{F}_i\text{O}_2$  ratio  $\geq 400$ ; creatinine  $< 1.2$  mg/dL; platelets  $\geq 150 \times 10^9/\text{L}$ ; and bilirubin  $< 1.2$  mg/dL.



Table S16: Day 180 EQ-5D-5L results

	EQ-5D-5L domain n/N (%)									
	Mobility		Self Care		Usual Activities		Pain/Discomfort		Anxiety/Depression	
	No Problems	Problems <sup>a</sup>	No Problems	Problems <sup>a</sup>	No Problems	Problems <sup>a</sup>	No Problems	Problems <sup>a</sup>	No Problems	Problems <sup>a</sup>
<b>Immune Modulation Domain</b>										
Tocilizumab	106/231 (45.9)	125/231 (54.1)	164/234 (70.1)	70/234 (29.9)	90/235 (38.3)	145/235 (61.7)	92/233 (39.5)	141/233 (60.5)	131/234 (56.0)	103/234 (44.0)
Sarilumab	22/75 (29.3)	53/75 (70.7)	44/76 (57.9)	32/76 (42.1)	24/76 (31.6)	52/76 (68.4)	27/76 (35.5)	49/76 (64.5)	30/76 (39.5)	46/76 (60.5)
Anakinra	40/80 (50.0)	40/80 (50.0)	61/80 (76.3)	19/80 (23.8)	32/78 (41.0)	46/78 (59.0)	33/80 (41.3)	47/80 (58.8)	46/80 (57.5)	34/80 (42.5)
Control	31/93 (33.3)	62/93 (66.7)	59/97 (60.8)	38/97 (39.2)	31/97 (32.0)	66/97 (68.0)	38/97 (39.2)	59/97 (60.8)	45/96 (46.9)	51/96 (53.1)
<b>Immunoglobulin Domain</b>										
Convalescent plasma	83/218 (38.1)	135/218 (61.9)	139/217 (64.1)	78/217 (35.9)	79/218 (36.2)	139/218 (63.8)	77/218 (35.3)	141/218 (64.7)	100/217 (46.1)	117/217 (53.9)
Control	64/176 (36.4)	112/176 (63.6)	113/177 (63.8)	64/177 (36.2)	58/177 (32.8)	119/177 (67.2)	63/176 (35.8)	113/176 (64.2)	79/176 (44.9)	97/176 (55.1)
<b>Antiplatelet Domain</b>										
Aspirin	27/83 (32.5)	56/83 (67.5)	55/84 (65.5)	29/84 (34.5)	32/84 (38.1)	52/84 (61.9)	39/84 (46.4)	45/84 (53.6)	36/83 (43.4)	47/83 (56.6)
P2Y12 inhibitor	41/82 (50.0)	41/82 (50.0)	63/83 (75.9)	20/83 (24.1)	35/82 (42.7)	47/82 (57.3)	33/83 (39.8)	50/83 (60.2)	45/83 (54.2)	38/83 (45.8)
Control	31/95 (32.6)	64/95 (67.4)	63/95 (66.3)	32/95 (33.7)	36/95 (37.9)	59/95 (62.1)	28/95 (29.5)	67/95 (70.5)	42/95 (44.2)	53/95 (55.8)
<b>Anticoagulation Domain</b>										
Therapeutic anticoagulation	53/118 (44.9)	65/118 (55.1)	79/120 (65.8)	41/120 (34.2)	51/120 (42.5)	69/120 (57.5)	49/119 (41.2)	70/119 (58.8)	62/119 (52.1)	57/119 (47.9)
Thromboprophylaxis	51/124 (41.1)	73/124 (58.9)	87/125 (69.6)	38/125 (30.4)	51/125 (40.8)	74/125 (59.2)	50/125 (40.0)	75/125 (60.0)	61/125 (48.8)	64/125 (51.2)
<b>Antiviral Domain</b>										
Lopinavir-ritonavir	29/76 (38.2)	47/76 (61.8)	47/81 (58.0)	34/81 (42.0)	32/82 (39.0)	50/82 (61.0)	29/82 (35.4)	53/82 (64.6)	35/81 (43.2)	46/81 (56.8)
Hydroxychloroquine	1/1 (100)	0/1 (0.0)	1/1 (100)	0/1 (0.0)	1/1 (100)	0/1 (0.0)	1/1 (100)	0/1 (0.0)	1/1 (100)	0/1 (0.0)
Combination antiviral therapy	1/2 (50.0)	1/2 (50.0)	2/2 (100)	0/2 (0.0)	1/2 (50.0)	1/2 (50.0)	0/2 (0.0)	2/2 (100)	0/2 (0.0)	2/2 (100)
Control	48/102 (47.1)	54/102 (52.9)	68/103 (66.0)	35/103 (34.0)	45/103 (43.7)	58/103 (56.3)	50/103 (48.5)	53/103 (51.5)	56/102 (54.9)	46/102 (45.1)
<b>Corticosteroid Domain</b>										
Fixed dose corticosteroids	16/27 (59.3)	11/27 (40.7)	23/27 (85.2)	4/27 (14.8)	17/27 (63.0)	10/27 (37.0)	14/27 (51.9)	13/27 (48.2)	17/27 (63.0)	10/27 (37.0)
Shock-dependent corticosteroids	19/35 (54.3)	16/35 (45.7)	29/36 (80.6)	7/36 (19.4)	21/36 (58.3)	15/36 (41.7)	15/36 (41.7)	21/36 (58.3)	26/35 (74.3)	9/35 (25.7)
Control	10/21 (47.6)	11/21 (52.4)	14/21 (66.7)	7/21 (33.3)	9/21 (42.9)	12/21 (57.1)	14/21 (66.7)	7/21 (33.3)	12/21 (57.1)	9/21 (42.9)

<sup>a</sup> Patients reporting problems includes patients reporting mild problems, moderate problems, severe problems or extreme problems

Table S17: Day 180 EQ VAS results

	n	EQ VAS	
		Mean (SD)	Median (IQR)
<b>Immune Modulation Domain</b>			
Tocilizumab	235	69.1 (22.6)	75 (50 – 86)
Sarilumab	76	63.4 (25.5)	70 (50 – 81)
Anakinra	75	70.9 (21.3)	75 (70 – 80)
Control	97	68.5 (20.7)	75 (60 – 85)
<b>Immunoglobulin Domain</b>			
Convalescent plasma	218	65.0 (23.7)	70 (50 – 82)
Control	177	65.4 (23.0)	70 (50 – 80)
<b>Antiplatelet Domain</b>			
Aspirin	84	65.7 (22.3)	70 (50 – 85)
P2Y12 inhibitor	83	71.3 (20.1)	75 (50 – 90)
Control	96	66.1 (21.0)	70 (50 – 80)
<b>Anticoagulation Domain</b>			
Therapeutic anticoagulation	119	71.8 (20.0)	78 (60 – 85)
Thromboprophylaxis	124	68.6 (20.6)	75 (50 – 80)
<b>Antiviral Domain</b>			
Lopinavir-ritonavir	82	67.7 (23.1)	73 (50 – 90)
Hydroxychloroquine	1	NA	70 (70 – 70)
Combination antiviral therapy	2	NA	100 (100 – 100)
Control	103	72.2 (20.8)	75 (60 - 90)
<b>Corticosteroid Domain</b>			
Fixed dose corticosteroids	27	76.9 (17.4)	80 (70 – 90)
Shock-dependent corticosteroids	36	74.0 (22.2)	80 (70 – 90)
Control	21	69.0 (22.5)	75 (60 – 85)

SD denotes standard deviation; IQR, interquartile range

**Table S18: Day 180 Disability Categories**

	WHODAS category n/N (%)				
	No Disability	Mild Disability	Moderate Disability	Severe Disability	Complete Disability
<b>Immune Modulation Domain</b>					
Tocilizumab	49/159 (30.8)	46/159 (28.9)	38/159 (23.9)	25/159 (15.7)	1/159 (0.6)
Sarilumab	12/44 (27.3)	14/44 (31.8)	8/44 (18.2)	10/44 (22.7)	0/44 (0.0)
Anakinra	19/58 (32.8)	17/58 (29.3)	14/58 (24.1)	8/58 (13.8)	0/58 (0.0)
Control	12/58 (20.7)	18/58 (31.0)	17/58 (29.3)	9/58 (15.5)	2/58 (3.4)
<b>Immunoglobulin Domain</b>					
Convalescent plasma	40/152 (26.3)	48/152 (31.6)	35/152 (23.0)	25/152 (16.4)	4/152 (2.6)
Control	29/115 (25.2)	47/115 (40.9)	20/115 (17.4)	19/115 (16.5)	0/115 (0.0)
<b>Antiplatelet Domain</b>					
Aspirin	15/60 (25.0)	18/60 (30.0)	15/60 (25.0)	12/60 (20.0)	0/60 (0.0)
P2Y12 inhibitor	22/62 (35.5)	24/62 (38.7)	9/62 (14.5)	7/62 (11.3)	0/62 (0.0)
Control	19/70 (27.1)	23/70 (32.9)	16/70 (22.9)	11/70 (15.7)	1/70 (1.4)
<b>Anticoagulation Domain</b>					
Therapeutic anticoagulation	27/82 (32.9)	28/82 (34.1)	19/82 (23.2)	7/82 (8.5)	1/82 (1.2)
Thromboprophylaxis	27/92 (29.3)	34/92 (37)	20/92 (21.7)	10/92 (10.9)	1/92 (1.1)
<b>Antiviral Domain</b>					
Lopinavir-ritonavir	18/61 (29.5)	12/61 (19.7)	19/61 (31.1)	11/61 (18.0)	1/61 (1.6)
Hydroxychloroquine	1/1 (100)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Combination antiviral therapy	0/2 (0.0)	2/2 (100)	0/2 (0.0)	0/2 (0.0)	0/2 (0.0)
Control	28/74 (37.8)	17/74 (23.0)	18/74 (24.3)	11/74 (14.9)	0/74 (0.0)
<b>Corticosteroid Domain</b>					
Fixed dose corticosteroids	12/24 (50.0)	6/24 (25.0)	4/24 (16.7)	2/24 (8.3)	0/24 (0.0)
Shock-dependent corticosteroids	13/31 (41.9)	12/31 (38.7)	5/31 (16.1)	1/31 (3.2)	0/31 (0.0)
Control	6/19 (31.6)	6/19 (31.6)	3/19 (15.8)	4/19 (21.1)	0/19 (0.0)

**Table S19: Day 180 Disability**

	N (survivors at day 180)	WHODAS score, median (IQR) [N]	Adjusted Odds Ratio <sup>a</sup> (95% CrI)	Probability of Superiority of Intervention (%) <sup>b</sup>
<b>Immune Modulation Domain</b>				
IL-6 receptor antagonists	812	14.6 (3.2-36.4) [N=203]	0.67 (0.39 to 1.15)	92.6%
Anakinra	187	16.7 (2.1-35.4) [N=58]	0.62 (0.30 to 1.26)	90.8%
Control	210	21.8 (8.3-30.8) [N=58]	1 (referent)	-
<b>Immunoglobulin Domain</b>				
Convalescent plasma	574	17.4 (4.2-41.1) [N=152]	1.14 (0.72 to 1.77)	28.6%
Control	466	12.5 (4.4-31.2) [N=115]	1 (referent)	-
<b>Antiplatelet Domain</b>				
Antiplatelet	597	12.5 (2.1-30.8) [N=122]	0.78 (0.46 to 1.33)	81.6%
Control	298	14.6 (4.2-38.5) [N=70]	1 (referent)	-
<b>Anticoagulation Domain</b>				
Therapeutic anticoagulation	238	10.4 (2.1-31.2) [N=82]	1.07 (0.61 to 1.86)	41.2%
Thromboprophylaxis	271	13.6 (4.2-29.3) [N=92]	1 (referent)	-
<b>Antiviral Domain</b>				
Lopinavir-ritonavir	145	25 (4.2-38.6) [N=61]	1.56 (0.84 to 2.93)	8.3%
Hydroxychloroquine	25	0 (0-0) [N=1]	NA	NA
Combination antiviral therapy	13	15.1 (13.2-16.9) [N=2]	NA	NA
Control	204	12.5 (0-28.4) [N=74]	1 (referent)	-
<b>Corticosteroid Domain</b>				
Fixed dose corticosteroids	74	5.2 (2.1-20.3) [N=24]	0.75 (0.29 to 2.00)	72.3%
Shock-dependent corticosteroids	98	8.3 (2.1-19.8) [N=31]	0.85 (0.35 to 2.07)	63.9%
Control	52	10.4 (3.2-32.3) [N=19]	1 (referent)	-

IQR denotes interquartile range; CrI, credible interval.

<sup>a</sup> Odds ratio parameters are for the analysis of WHODAS disability category. An OR<1 indicates reduced disability.

<sup>b</sup> The probability of superiority is computed from the posterior distribution of a Bayesian mixture model.

**Table S20: Sensitivity Analysis of EQ-5D-5L utility score without imputation**

	Adjusted Mean Difference (95% CrI)	Probability of Superiority of Intervention (%) <sup>a</sup>
<b>Immune Modulation Domain</b>		
IL-6 Receptor Antagonists	0.04 (-0.03 to 0.12)	87.2%
Anakinra	0.07 (-0.03 to 0.18)	92.2%
Control	0 (referent)	-
<b>Immunoglobulin Domain</b>		
Convalescent plasma	-0.03 (-0.09 to 0.03)	18.4%
Control	0 (referent)	-
<b>Antiplatelet Domain</b>		
Antiplatelet	0.08 (0.00 to 0.16)	98.0%
Control	0 (referent)	-
<b>Anticoagulation Domain</b>		
Therapeutic anticoagulation	0.01 (-0.07 to 0.09)	60.6%
Thromboprophylaxis	0 (referent)	-
<b>Antiviral Domain</b>		
Lopinavir-ritonavir	-0.10 (-0.19 to -0.01)	1.3%
Hydroxychloroquine	NA	NA
Combination antiviral therapy	NA	NA
Control	0 (referent)	-
<b>Corticosteroid Domain</b>		
Fixed dose corticosteroids	-0.01 (-0.17 to 0.16)	46.3%
Shock-dependent corticosteroids	-0.02 (-0.17 to 0.14)	42.5%
Control	0 (referent)	-

CrI denotes credible interval.

<sup>a</sup> The probability of superiority is computed from the posterior distribution of a Bayesian mixture model.

**Table S21: Sensitivity Analysis of WHODAS disability category without imputation**

	Adjusted Odds Ratio <sup>a</sup> (95% CrI)	Probability of Superiority of Intervention (%) <sup>b</sup>
<b>Immune Modulation Domain</b>		
IL-6 Receptor Antagonists	0.69 (0.40 to 1.19)	91.1%
Anakinra	0.62 (0.30 to 1.26)	90.5%
Control	1 (referent)	-
<b>Immunoglobulin Domain</b>		
Convalescent plasma	1.14 (0.72 to 1.78)	27.9%
Control	1 (referent)	-
<b>Antiplatelet Domain</b>		
Antiplatelet	0.78 (0.45 to 1.35)	81.2%
Control	1 (referent)	-
<b>Anticoagulation Domain</b>		
Therapeutic anticoagulation	1.05 (0.60 to 1.83)	43.0%
Thromboprophylaxis	1 (referent)	-
<b>Antiviral Domain</b>		
Lopinavir-ritonavir	1.56 (0.84 to 2.93)	8.2%
Hydroxychloroquine	NA	NA
Combination antiviral therapy	NA	NA
Control	1 (referent)	-
<b>Corticosteroid Domain</b>		
Fixed dose corticosteroids	0.77 (0.29 to 2.03)	69.4%
Shock-dependent corticosteroids	0.88 (0.35 to 2.18)	60.9%
Control	1 (referent)	-

CrI denotes credible interval.

<sup>a</sup> Odds ratio parameters are for the analysis of WHODAS disability category. An OR<1 indicates reduced disability.

<sup>b</sup> The probability of superiority is computed from the posterior distribution of a Bayesian mixture model.

**Table S22: Day 180 mortality in patients mechanically ventilated at baseline**

	N	Day 180 mortality <sup>a</sup> , n/N (%)	Hazard Ratio (95% CrI)	Probability of Superiority of Intervention (%) <sup>b</sup>	Probability of Futility of Intervention (%) <sup>b</sup>
<b>Immune Modulation Domain</b>					
IL-6 receptor antagonists	467	188/437 (43.0)	0.70 (0.51 to 1.00)	97.5%	15.9%
Anakinra	137	70/128 (54.7)	0.93 (0.62 to 1.41)	63.9%	69.1%
Control	123	58/115 (50.4)	1 (referent)	-	-
<b>Immunoglobulin Domain</b>					
Convalescent plasma	357	159/333 (47.8)	0.93 (0.74 to 1.17)	72.5%	83.8%
Control	291	145/276 (52.5)	1 (referent)	-	-
<b>Antiplatelet Domain</b>					
Antiplatelet	373	126/317 (39.7)	0.93 (0.70 to 1.28)	69.2%	77.0%
Control	194	62/155 (40.0)	1 (referent)	-	-
<b>Anticoagulation Domain</b>					
Therapeutic anticoagulation	147	69/132 (52.3)	1.30 (0.91 to 1.84)	7.0%	99.4%
Thromboprophylaxis	166	63/148 (42.6)	1 (referent)	-	-
<b>Antiviral Domain</b>					
Lopinavir-ritonavir	73	36/70 (51.4)	1.20 (0.79 to 1.78)	20.0%	96.0%
Hydroxychloroquine	26	7/19 (36.8)	1.10 (0.59 to 1.96)	37.7%	82.0%
Combination antiviral therapy	13	7/12 (58.3)	1.31 (0.63 to 2.70)	23.0%	89.2%
Control	114	46/102 (45.1)	1 (referent)	-	-
<b>Corticosteroid Domain</b>					
Fixed dose corticosteroids	87	20/67 (29.9)	1.08 (0.58 to 2.03)	40.7%	78.9%
Shock-dependent corticosteroids	74	21/72 (29.2)	1.04 (0.55 to 2.02)	44.5%	75.6%
Control	53	10/41 (24.4)	1 (referent)	-	-

CrI denotes credible interval.

<sup>a</sup> Due to censoring, reported day 180 mortality rates are restricted to patients at sites participating in day 180 follow-up with known day 180 vital status.

<sup>b</sup> The probability of superiority and futility is computed from a Bayesian piecewise exponential model using the posterior distribution.

**Table S23: Day 180 mortality in patients not mechanically ventilated at baseline**

	N	Day 180 mortality <sup>a</sup> , n/N (%)	Hazard Ratio (95% CrI)	Probability of Superiority of Intervention (%) <sup>b</sup>	Probability of Futility of Intervention (%) <sup>b</sup>
<b>Immune Modulation Domain</b>					
IL-6 receptor antagonists	966	248/811 (30.6)	0.76 (0.59 to 0.98)	98.2%	22.4%
Anakinra	234	68/197 (34.5)	0.93 (0.67 to 1.28)	67.8%	72.7%
Control	283	82/235 (34.9)	1 (referent)	-	-
<b>Immunoglobulin Domain</b>					
Convalescent plasma	721	211/611 (34.5)	1.03 (0.86 to 1.24)	37.0%	98.8%
Control	620	179/514 (34.8)	1 (referent)	-	-
<b>Antiplatelet Domain</b>					
Antiplatelet	646	148/554 (26.7)	0.80 (0.62 to 1.05)	94.7%	38.3%
Control	333	81/286 (28.3)	1 (referent)	-	-
<b>Anticoagulation Domain</b>					
Therapeutic anticoagulation	352	96/271 (35.4)	1.12 (0.86 to 1.46)	19.7%	98.6%
Thromboprophylaxis	345	84/270 (31.1)	1 (referent)	-	-
<b>Antiviral Domain</b>					
Lopinavir-ritonavir	183	45/156 (28.9)	1.02 (0.74 to 1.41)	45.0%	89.0%
Hydroxychloroquine	24	9/22 (40.9)	1.85 (1.01 to 3.28)	2.3%	99.3%
Combination antiviral therapy	14	6/14 (42.9)	1.89 (0.93 to 3.70)	3.8%	98.7%
Control	248	61/209 (29.2)	1 (referent)	-	-
<b>Corticosteroid Domain</b>					
Fixed dose corticosteroids	50	14/42 (33.3)	0.93 (0.48 to 1.74)	60.1%	63.0%
Shock-dependent corticosteroids	73	18/65 (27.7)	0.94 (0.49 to 1.70)	57.7%	65.3%
Control	48	17/38 (44.7)	1 (referent)	-	-

CrI denotes credible interval.

<sup>a</sup> Due to censoring, reported day 180 mortality rates are restricted to patients at sites participating in day 180 follow-up with known day 180 vital status.

<sup>b</sup> The probability of superiority and futility is computed from a Bayesian piecewise exponential model using the posterior distribution.



Table S24: Day 180 mortality in immune deficient patients <sup>a</sup>

	N	Day 180 mortality <sup>b</sup> , n/N (%)	Hazard Ratio (95% CrI)	Probability of Superiority of Intervention (%) <sup>c</sup>	Probability of Futility of Intervention (%) <sup>c</sup>
<b>Immune Modulation Domain</b>					
IL-6 receptor antagonists	36	16/31 (51.6)	0.94 (0.43 to 2.19)	55.8%	61.4%
Anakinra	6	3/5 (60.0)	1.38 (0.41 to 4.13)	29.5%	79.5%
Control	18	8/17 (47.1)	1 (referent)	-	-
<b>Immunoglobulin Domain</b>					
Convalescent plasma	67	30/64 (46.9)	0.67 (0.41 to 1.13)	93.4%	20.3%
Control	61	33/53 (62.3)	1 (referent)	-	-
<b>Antiplatelet Domain</b>					
Antiplatelet	43	28/41 (68.3)	1.63 (0.82 to 3.42)	7.6%	97.3%
Control	23	11/22 (50.0)	1 (referent)	-	-
<b>Anticoagulation Domain</b>					
Therapeutic anticoagulation	31	20/28 (71.4)	2.33 (1.11 to 5.20)	1.2%	99.7%
Thromboprophylaxis	25	8/24 (33.3)	1 (referent)	-	-
<b>Antiviral Domain</b>					
Lopinavir-ritonavir	15	7/15 (46.7)	1.05 (0.43 to 2.46)	45.7%	69.5%
Hydroxychloroquine	2	2/2 (100)	3.17 (0.75 to 12.30)	5.8%	96.7%
Combination antiviral therapy	1	1/1 (100)	3.29 (0.63 to 17.15)	8.3%	94.7%
Control	24	13/22 (59.1)	1 (referent)	-	-
<b>Corticosteroid Domain</b>					
Fixed dose corticosteroids	12	3/10 (30.0)	0.55 (0.15 to 1.89)	83.4%	25.2%
Shock-dependent corticosteroids	12	5/12 (41.7)	0.91 (0.26 to 3.25)	55.4%	55.9%
Control	6	3/5 (60.0)	1 (referent)	-	-

CrI denotes credible interval.

<sup>a</sup> Immune deficient patients include the combination of patients receiving immunosuppressive therapy prior to this hospital admission (including chemotherapy within 4 weeks of admission, radiation, high-dose or long-term steroid treatment) and immunosuppressive disease (including acquired immunodeficiency syndrome, acute leukemia, lymphoma, metastatic cancer, myeloma, or any other disease that is sufficiently advanced to suppress resistance to infection but excluding malignancy which has been in remission for 5 years or more)

<sup>b</sup> Due to censoring, reported day 180 mortality rates are restricted to patients at sites participating in day 180 follow-up with known day 180 vital status.

<sup>c</sup> The probability of superiority and futility is computed from a Bayesian piecewise exponential model using the posterior distribution.

**Table S25: Day 180 mortality in non-immune deficient patients**

	N	Day 180 mortality <sup>a</sup> , n/N (%)	Hazard Ratio (95% CrI)	Probability of Superiority of Intervention (%) <sup>b</sup>	Probability of Futility of Intervention (%) <sup>b</sup>
<b>Immune Modulation Domain</b>					
IL-6 receptor antagonists	1395	420/1217 (34.5)	0.72 (0.59 to 0.90)	99.9%	9.4%
Anakinra	365	135/320 (42.2)	0.92 (0.71 to 1.20)	71.0%	78.3%
Control	388	132/333 (39.6)	1 (referent)	-	-
<b>Immunoglobulin Domain</b>					
Convalescent plasma	1011	340/880 (38.6)	1.02 (0.88 to 1.18)	41.6%	99.5%
Control	850	291/737 (39.5)	1 (referent)	-	-
<b>Antiplatelet Domain</b>					
Antiplatelet	976	246/830 (29.6)	0.82 (0.67 to 1.00)	97.5%	41.7%
Control	504	132/419 (31.5)	1 (referent)	-	-
<b>Anticoagulation Domain</b>					
Therapeutic anticoagulation	467	145/375 (38.7)	1.08 (0.86 to 1.34)	26.2%	98.8%
Thromboprophylaxis	486	139/394 (35.3)	1 (referent)	-	-
<b>Antiviral Domain</b>					
Lopinavir-ritonavir	241	74/211 (35.1)	1.08 (0.83 to 1.40)	29.1%	97.1%
Hydroxychloroquine	48	14/39 (35.9)	1.46 (0.94 to 2.29)	4.7%	99.3%
Combination antiviral therapy	25	12/25 (48.0)	1.58 (0.94 to 2.71)	4.6%	99.1%
Control	338	94/289 (32.5)	1 (referent)	-	-
<b>Corticosteroid Domain</b>					
Fixed dose corticosteroids	125	31/99 (31.3)	0.98 (0.61 to 1.56)	54.1%	73.9%
Shock-dependent corticosteroids	135	34/125 (27.2)	0.95 (0.59 to 1.52)	58.7%	69.5%
Control	95	24/74 (32.4)	1 (referent)	-	-

CrI denotes credible interval.

<sup>a</sup> Due to censoring, reported day 180 mortality rates are restricted to patients at sites participating in day 180 follow-up with known day 180 vital status.

<sup>b</sup> The probability of superiority and futility is computed from a Bayesian piecewise exponential model using the posterior distribution.

### 3. Supplemental Results Figures

Figure S1: Forest plot of Day 180 mortality hazard ratios in unblinded ITT population

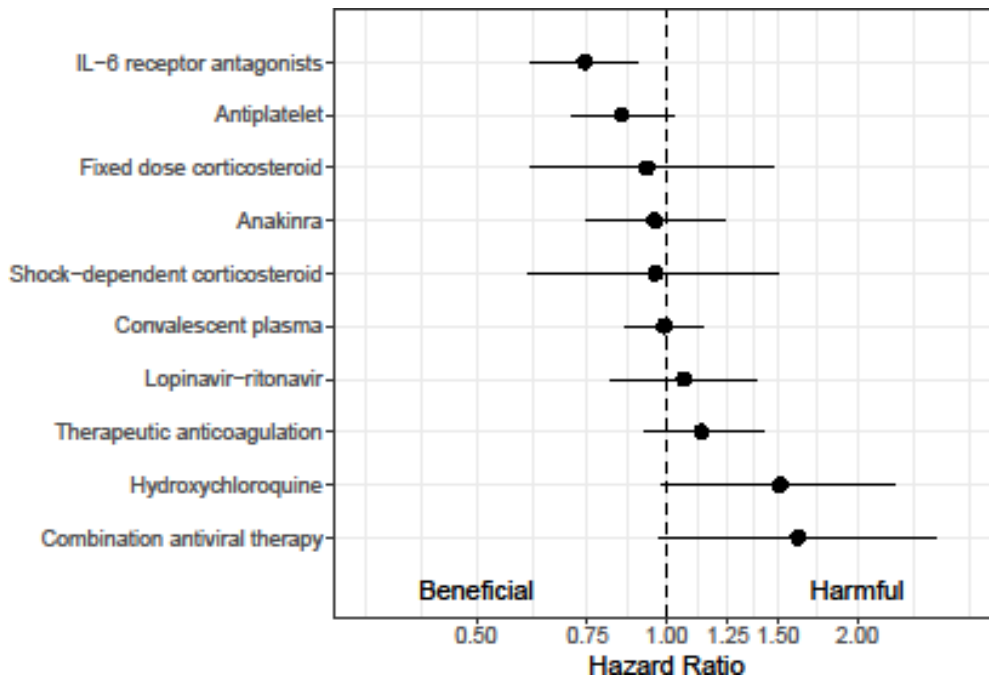


Figure S2: Forest plot of Day 180 mortality hazard ratios in sensitivity analyses

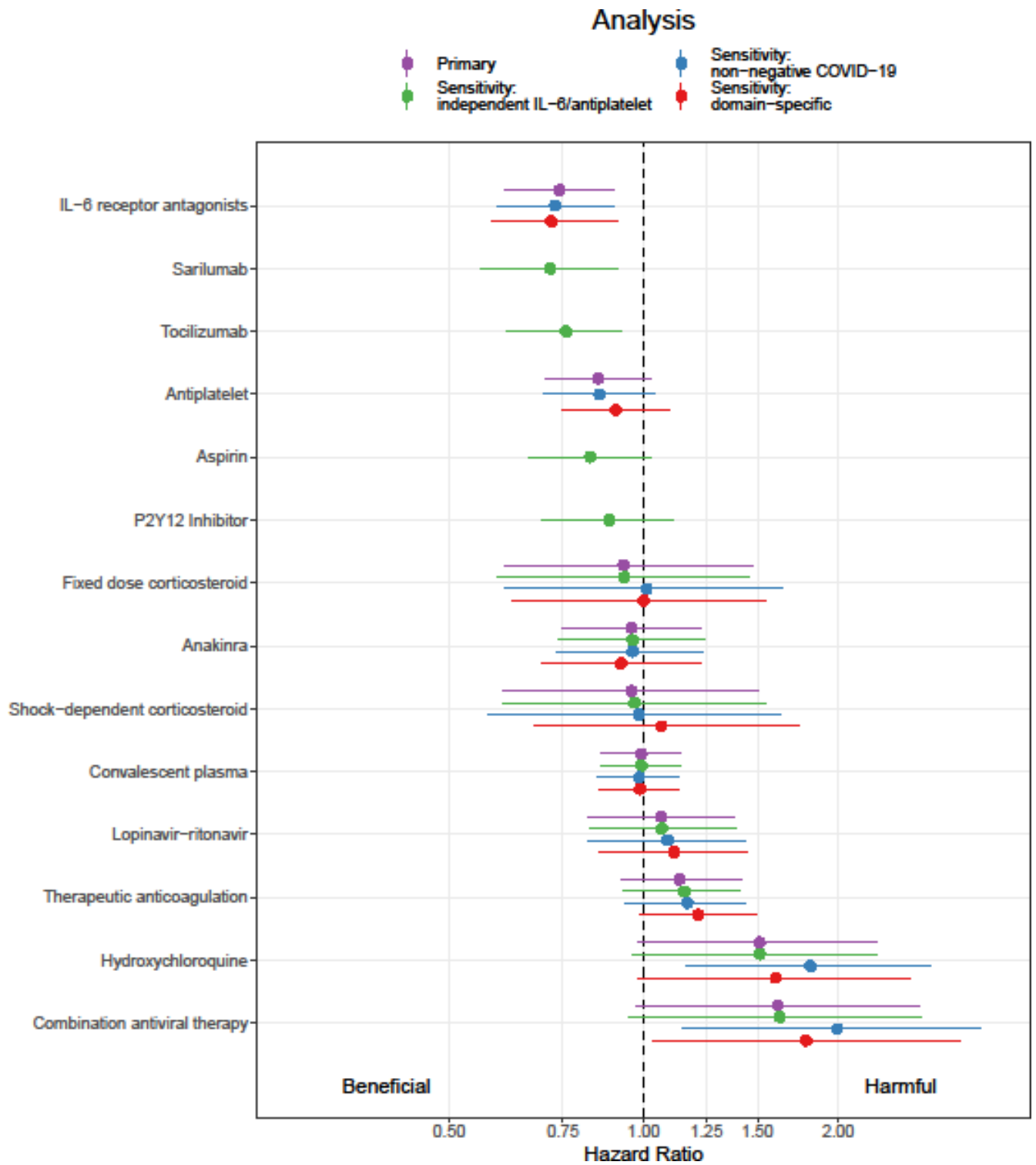
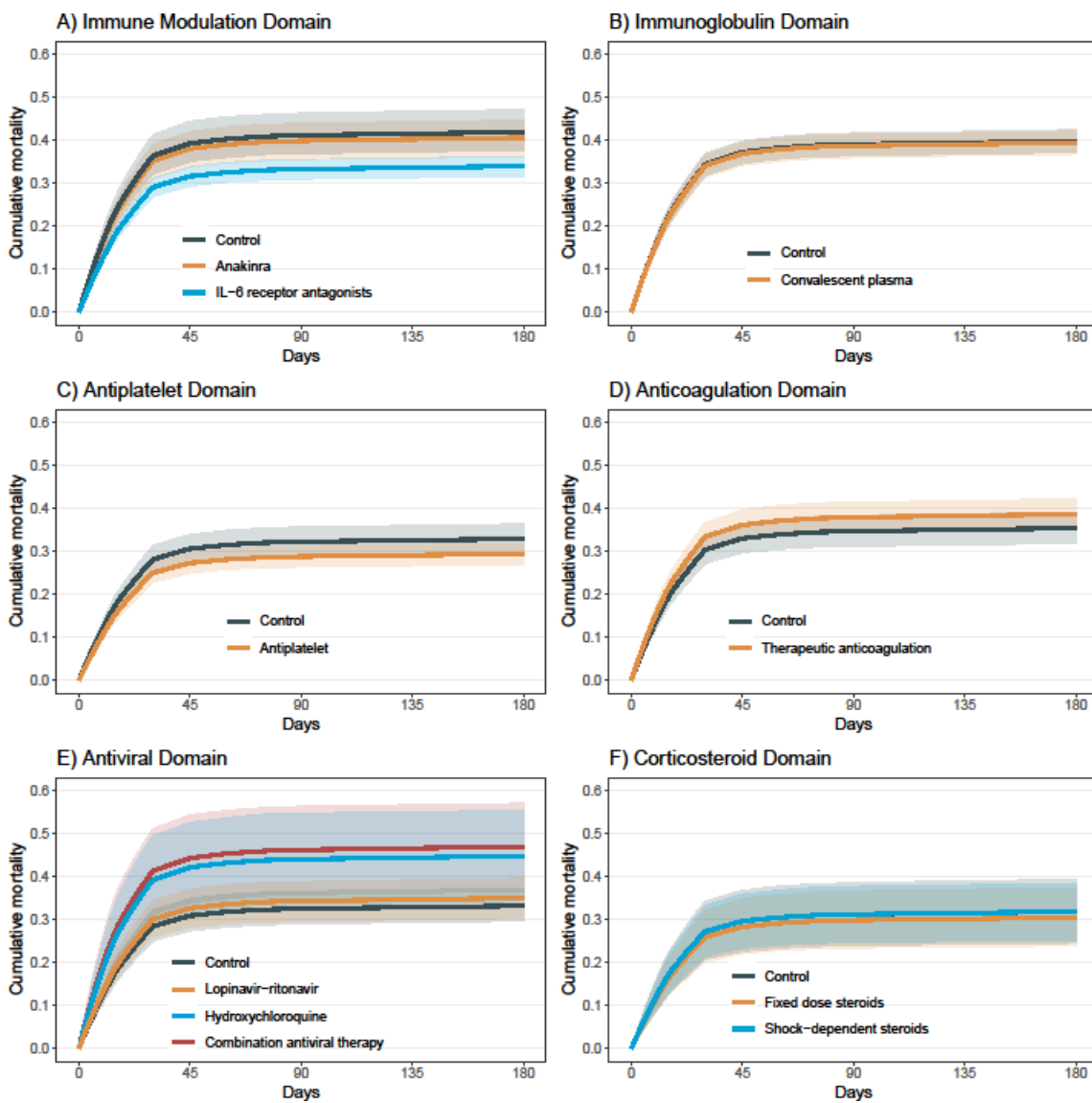
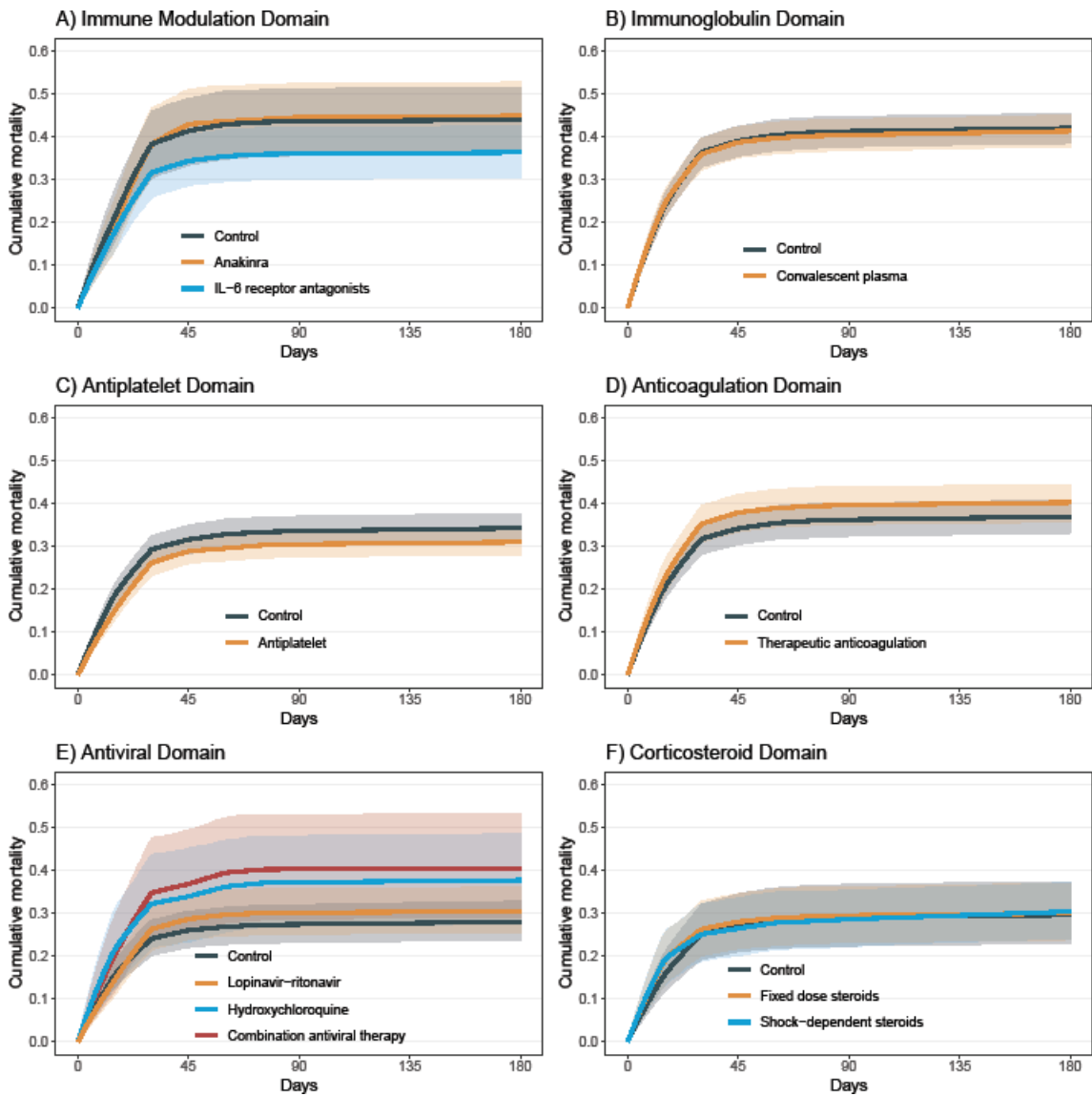


Figure S3: Fitted Kaplan-Meier curves for mortality through Day 180 with proportional hazard ratios, adjusting for covariates.



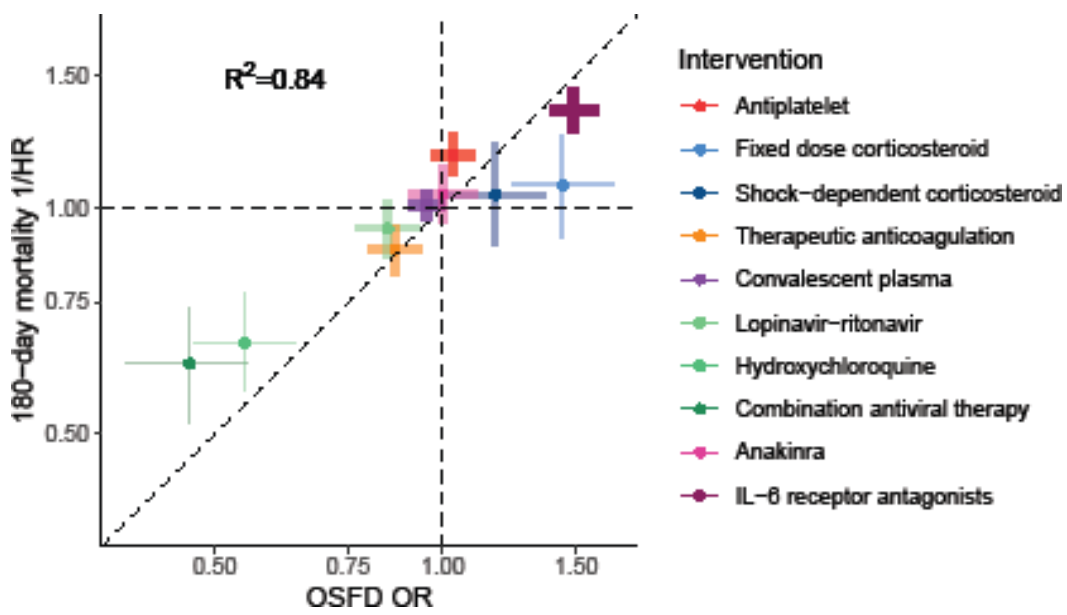
Shaded area represents the 95% credible interval of the fitted survival curves.

Figure S4: Fitted Kaplan-Meier curves for mortality through Day 180 with time-varying hazards, adjusting for covariates.



Shaded area represents the 95% credible interval of the fitted survival curves.

Figure S5: Association between OSFD odds ratios and the reciprocal of day 180 mortality hazard ratios



Each point represents the posterior median for an intervention. The solid line segments display the 50% CrI for each intervention on the respective endpoint. The horizontal/vertical dashed lines represent no effect on each outcome. The diagonal dashed reference line is provided as a visual reference to assess the association between treatment effects.

Figure S6: Forest plot of Day 90 mortality odds ratios in unblinded ITT population

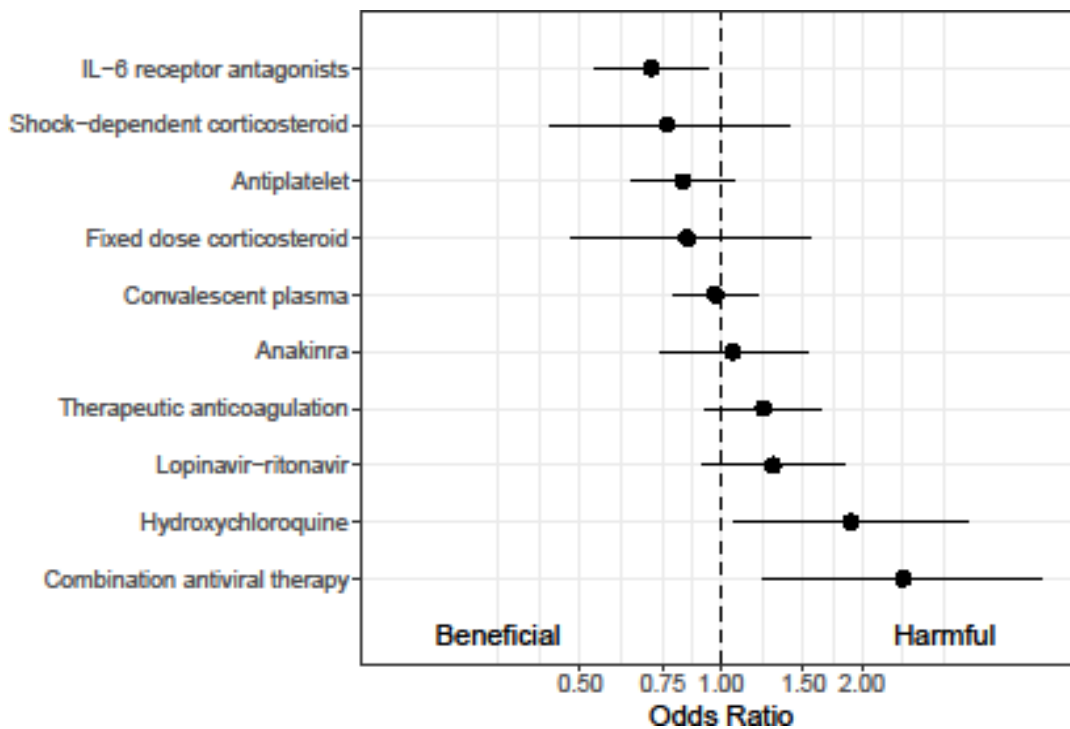


Figure S7: Forest plot of expected effect on EQ-5D-5L utility score in all patients (assuming patients who died within 180 days have a utility score of 0)

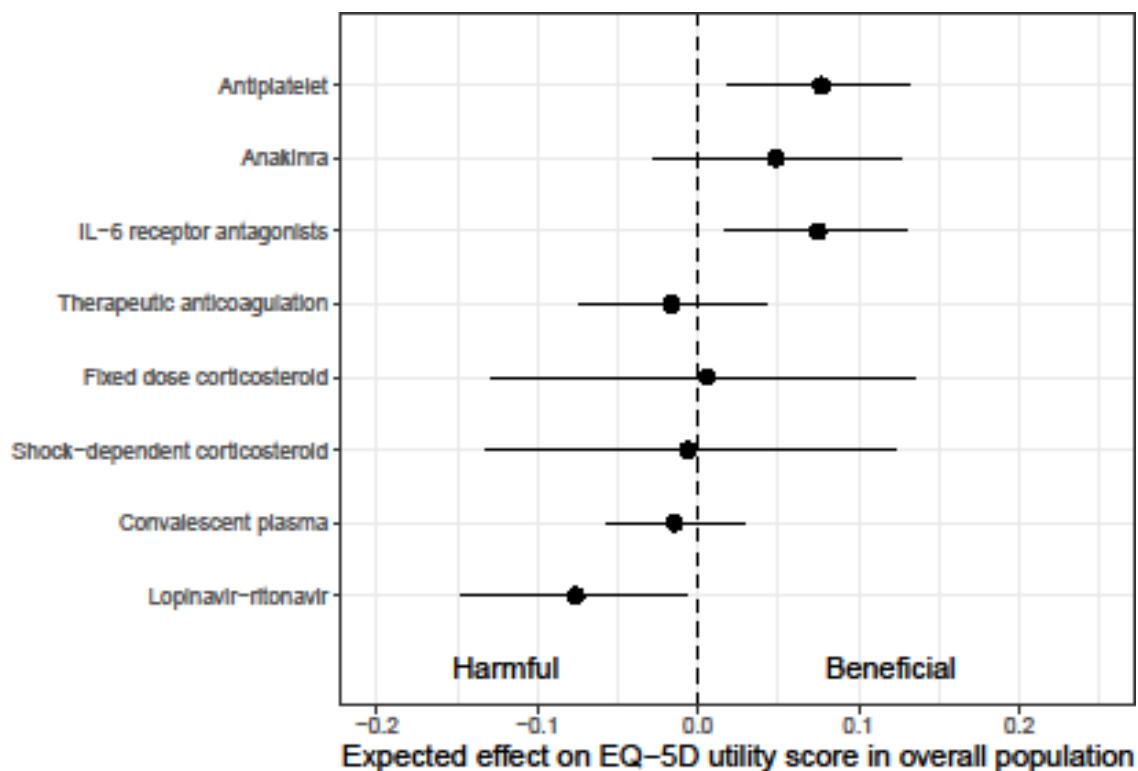


Figure S8: Forest plot of the odds ratio on WHODAS disability category in survivors in unblinded ITT analysis

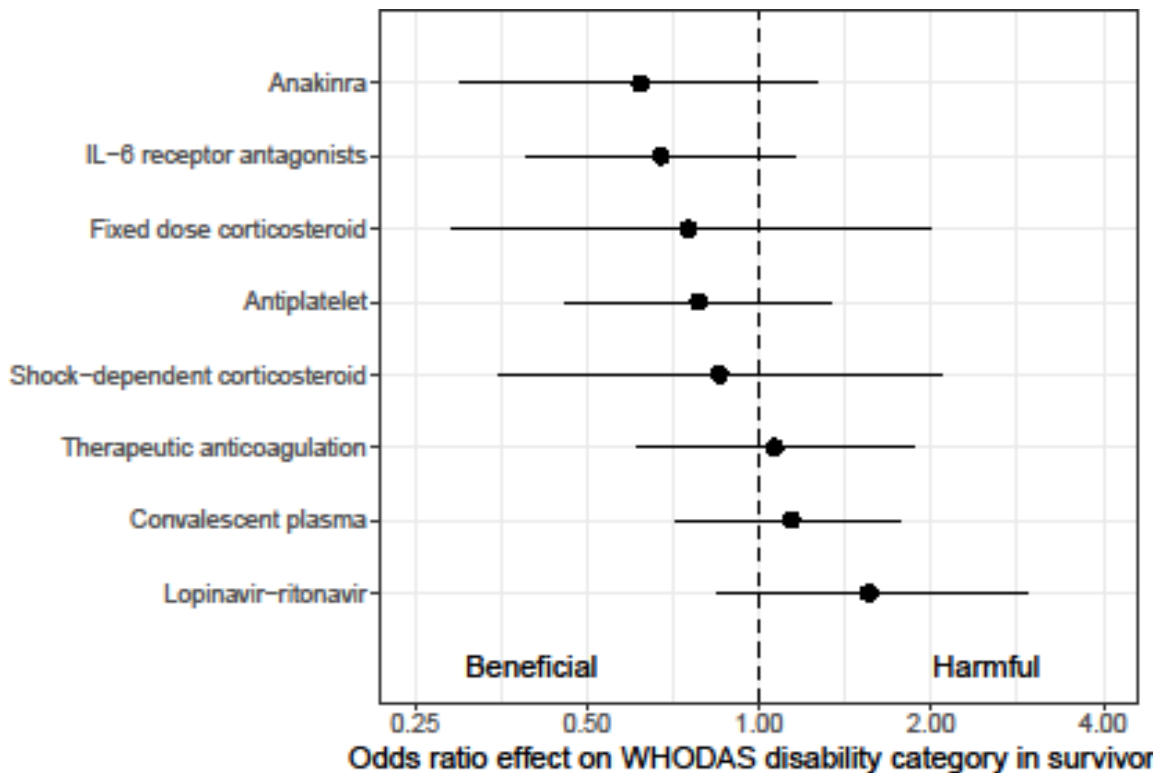




Figure S9: Forest plot of Day 180 mortality hazard ratios in unblinded ITT population comparing mechanical ventilation status at baseline

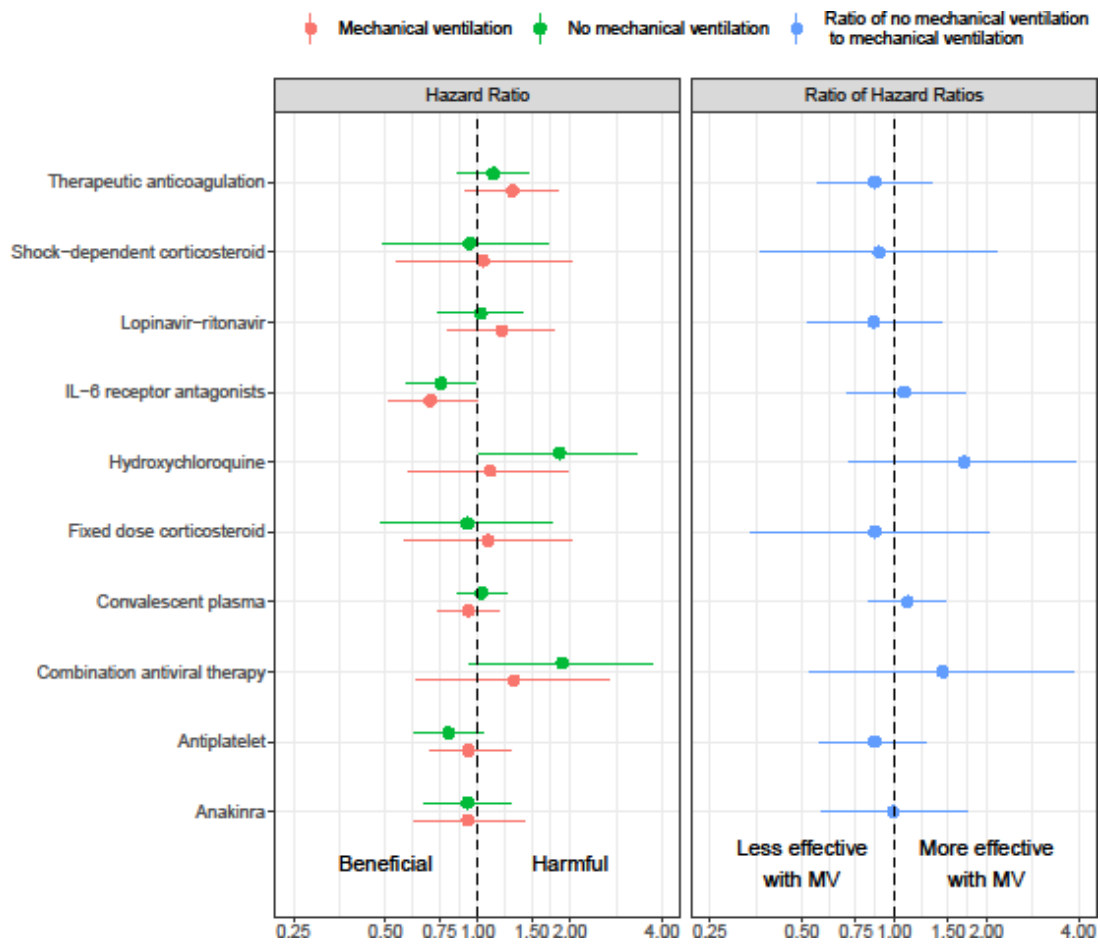
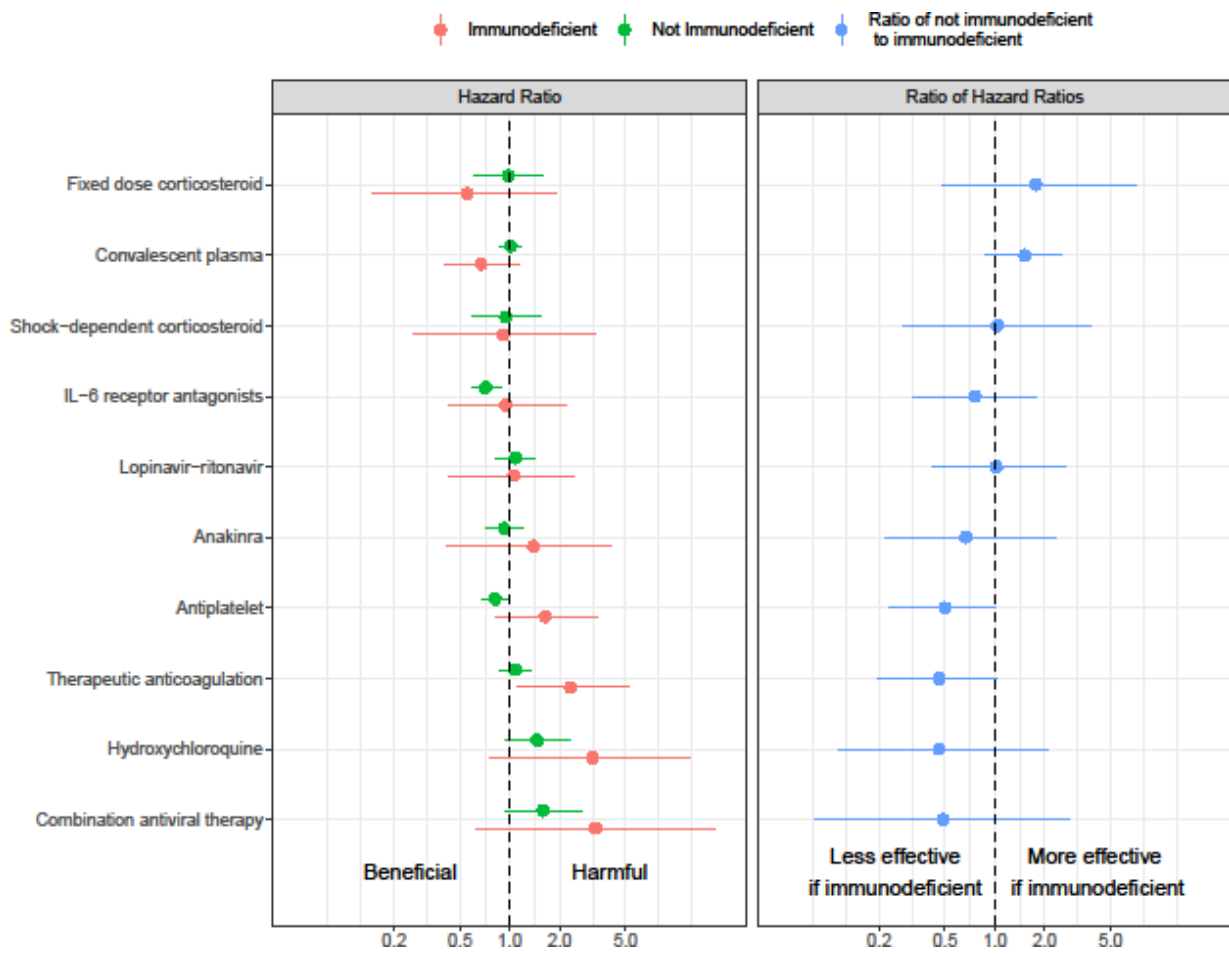


Figure S10: Forest plot of Day 180 mortality hazard ratios in unblinded ITT population comparing immune deficient status at baseline



## 4. Model Evaluation Report

# REMAP-CAP Long Term Outcomes Model Evaluation Report

Prepared by the ITSC Analysis Committee

November 17, 2022

### 4.1 Overview

This report describes sensitivity analyses and model evaluation of the primary model for the Long-Term Outcomes analysis of REMAP-CAP. The primary analysis model is a Bayesian piecewise exponential model of Day 180 mortality that estimates proportional hazard ratios for each intervention. The primary analysis model adjusts for baseline covariates including age, sex, site nested within country, and time period of enrollment. The full model specification is detailed in the Long-Term Outcomes SAP. This report evaluates specific assumptions made in the primary analysis model.

#### 4.1.1 Proportional hazards assumption

We evaluate the proportional hazards assumption in two ways:

1. First, for each domain, we perform a hypothesis test of the proportional hazards assumption for a Cox regression based on the Schoenfeld weighted residuals versus transformed time. For each intervention within each domain, we report the p-value of the hypothesis test, where a p-value  $<0.05$  would indicate a statistically significant deviation from proportionality for an intervention.
2. Second, we fit a Bayesian piecewise exponential model with a non-proportional hazard ratio. This sensitivity analysis is identical to the primary analysis except for estimating time-varying hazard ratios for each intervention. Time-varying hazards and hazard ratios are estimated for each 15-day period up to day 90 and then the 90-day period up to day 180 (corresponding to the original intervals used for the hazard rates in the primary analysis). Fitted survival curves are displayed to provide a visual inspection of whether the proportional hazards assumptions hold.

### 5.1.1.1 Hypothesis tests of proportional hazards

For each domain, we fit a Cox model and assess the proportional hazards assumption of each intervention using the R function `cox.zph`. This function performs a hypothesis test of whether the hazard ratio for that intervention is proportional. For all interventions, the p-value exceeds 0.05 and we fail to detect a violation of proportional hazards.

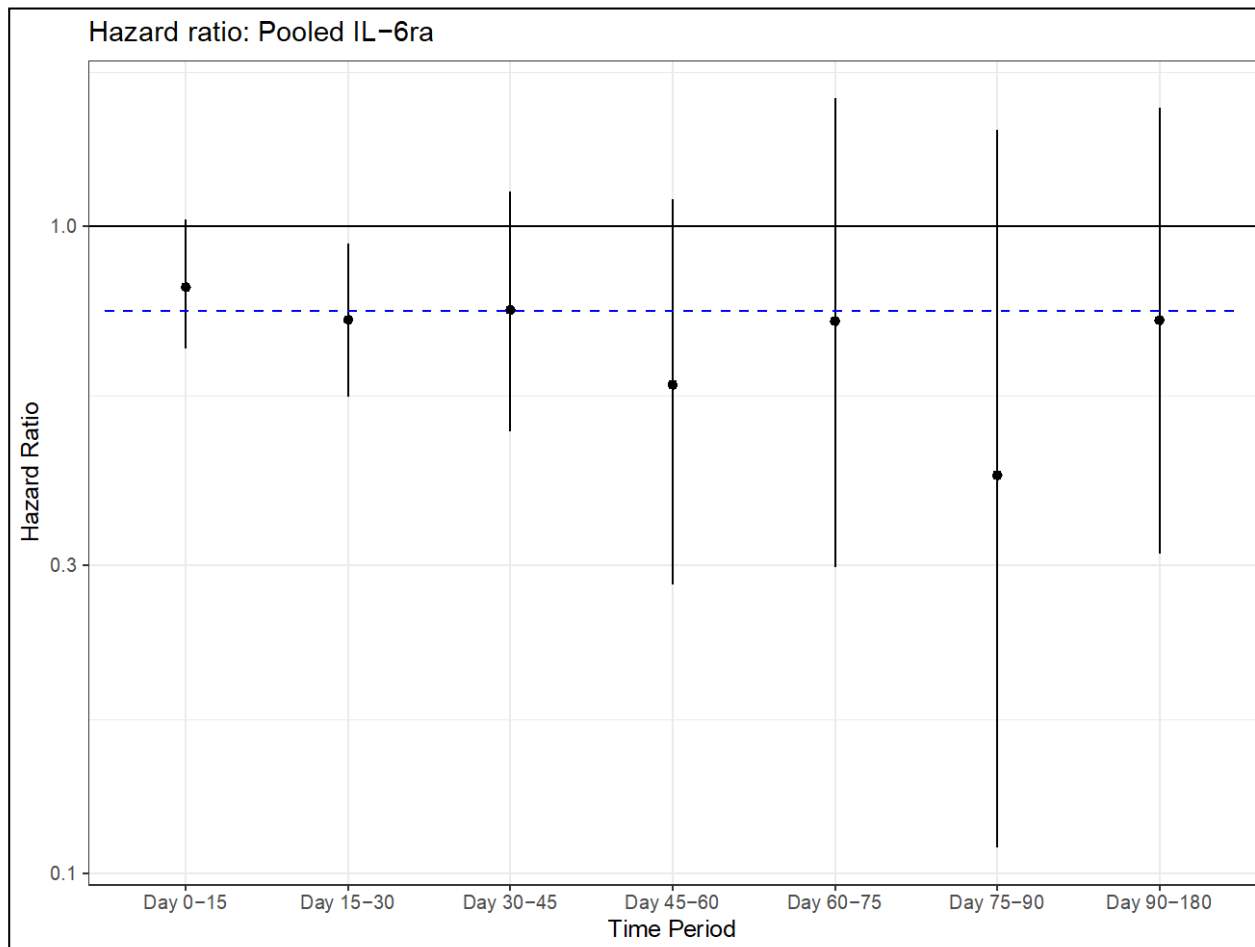
Table S5.1: Results of hypothesis test of proportional hazards for each intervention

Intervention	Chi-square test statistic	Degrees of freedom	p-value
Interferon-beta-1a	2.916	1	0.088
Anakinra	2.837	1	0.092
IL-6 receptor antagonists	2.319	1	0.128
Fixed dose steroids	0.269	1	0.604
Shock-dependent steroids	0.675	1	0.411
Lopinavir-ritonavir	1.629	1	0.202
Hydroxychloroquine	0.030	1	0.862
Combination antiviral therapy	0.092	1	0.762
Convalescent plasma	0.906	1	0.341
Delayed convalescent plasma	1.418	1	0.234
Therapeutic anticoagulation	0.758	1	0.384
Antiplatelet	0.025	1	0.875

### 5.1.1.2 Visualization of proportional hazards assumptions

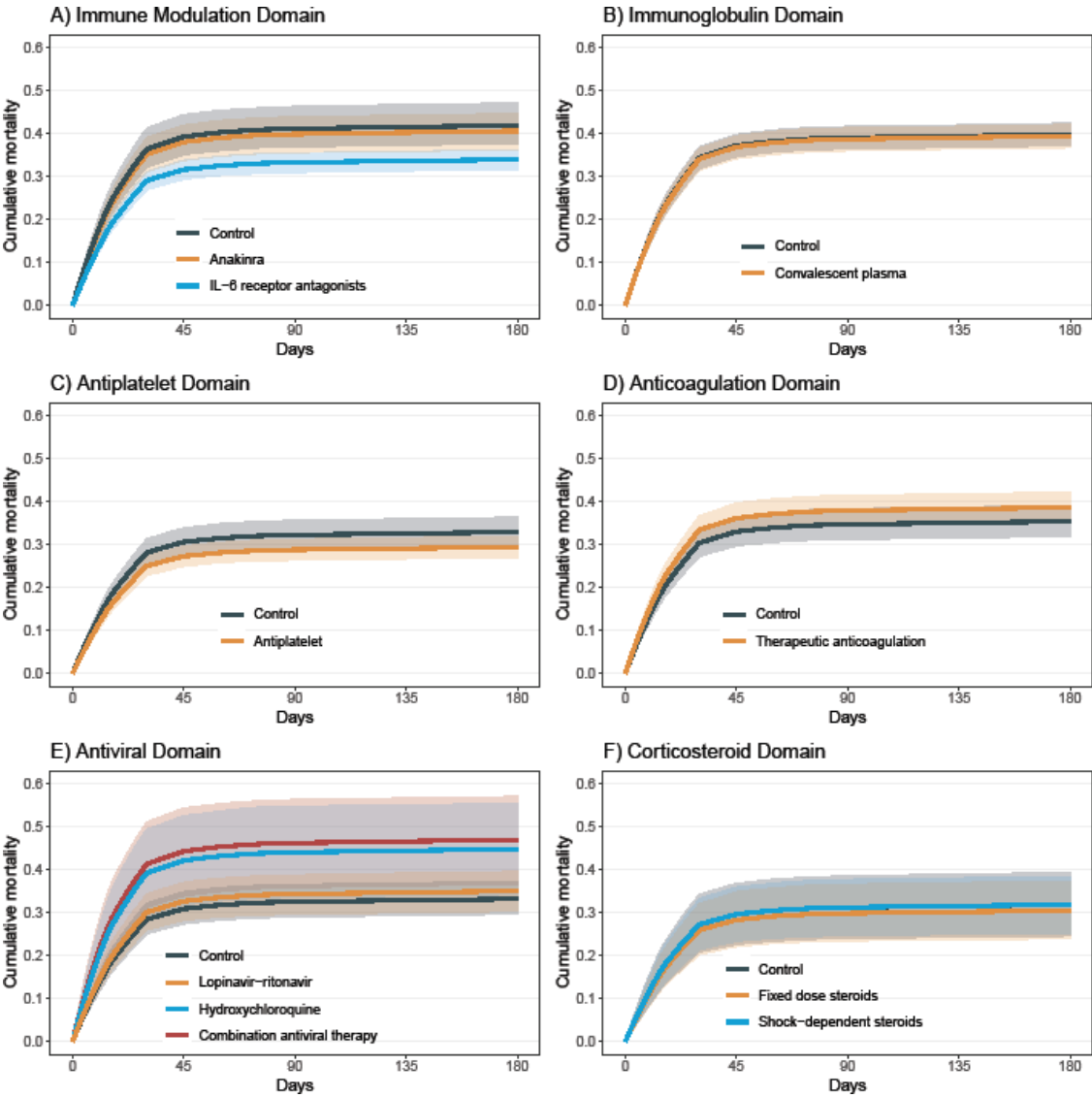
Next, we perform a sensitivity analysis of the primary analysis where we allow hazard ratio to differ over time. In this analysis, time-varying hazards and hazard ratios are estimated for each 15-day period up to day 90 and then the 90-day period up to day 180 (corresponding to the original intervals used for the hazard rates in the primary analysis). As an example, we display the estimated hazard ratios for the pooled IL-6ra intervention from the immune modulation domain. In this figure (S5.1), we plot the IL-6ra hazard ratio and 95% credible interval for each interval; the hazard ratio from the primary analysis model (assumed constant over time) is displayed as a horizontal dashed line with blue shading representing the 95% credible interval. Because most events are observed in earlier time periods, the 95% credible intervals are narrower in earlier periods compared to the later periods. In general, it appears that the time-varying hazard ratios are relatively constant over time and consistent with the proportional hazard ratio.

Figure S5.1: Estimated hazard ratios from time-varying sensitivity model for pooled IL-6ra

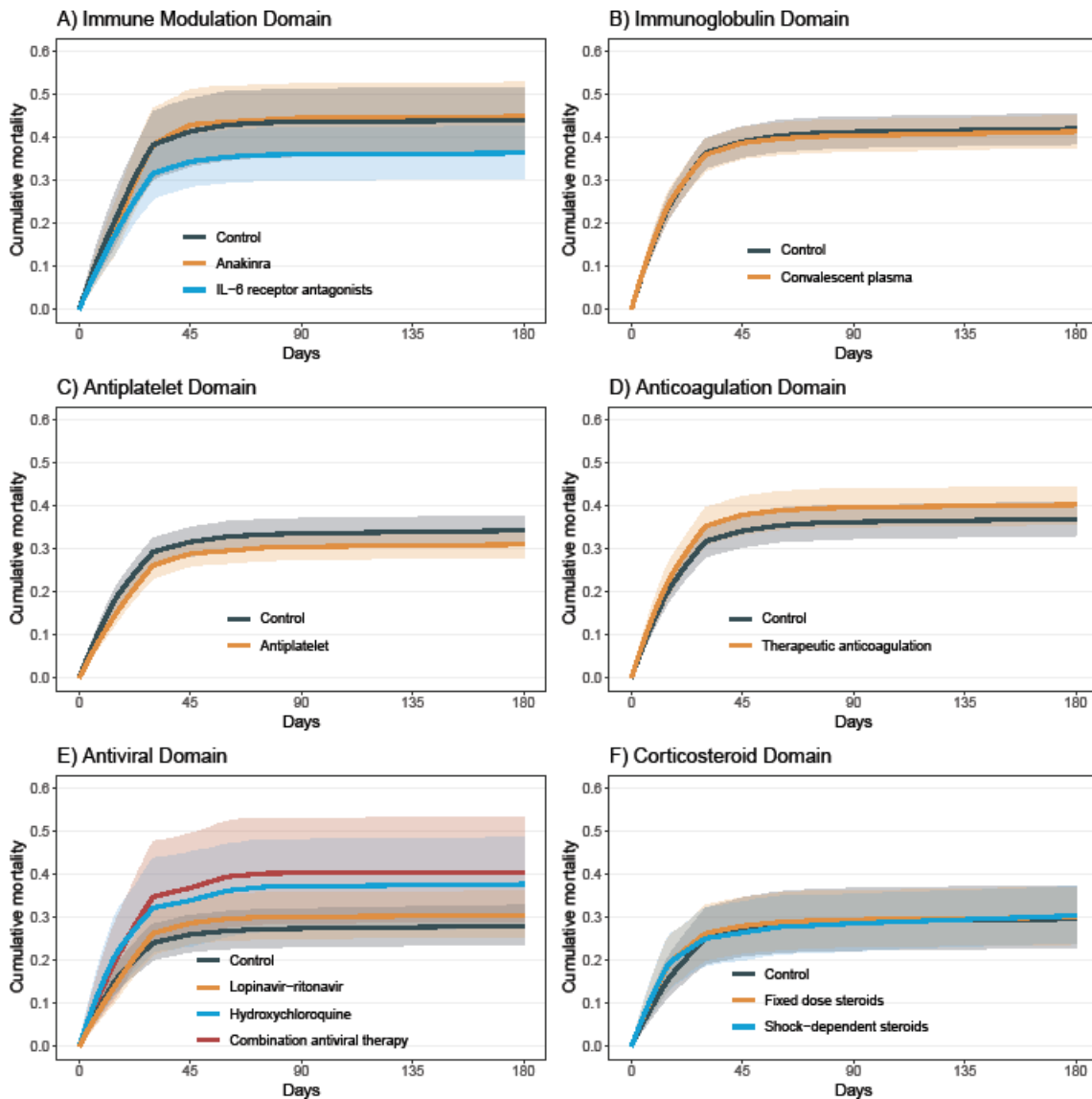


As a diagnostic visualization tool of the proportional odds assumption, we provide estimated mortality curves for each intervention based on the primary model and the time-varying hazard sensitivity analysis. We display a set of estimated mortality curves from each model. The first set of figures (S5.2) summarizes the fitted mortality curves for each intervention under the pre-specified primary analysis model assuming a proportional hazards ratio. The second figure (S5.3) displays the fitted mortality curves from the model with time-varying hazard ratios. In the primary analysis, the assumption of a constant hazard ratio implies that the difference between the estimated mortality curves must increase proportionally over time. This means that, given proportional hazards, the estimated mortality curves cannot cross or separate and then come back together. In the time-varying hazard ratio model, the hazard ratio is allowed to vary by time interval. If the estimated hazard ratio varied over time, the curves would reveal this through non-proportional behavior where the curves cross or the distance between curves is not proportional over time. In general, the estimated mortality curves from the sensitivity analysis appear to be largely proportional. There are some minor deviations from proportionality observed. For example, Lopinavir-ritonavir and Control cross at approximately 20 days and the Steroid arms appear to have higher mortality than Control until approximately day 30. However, despite these minor deviations, the overall takeaways about the effect of interventions appear to hold when the proportionality assumption is removed.

Figure S5.2: Fitted survival curves from primary analysis model



**Figure S5.3: Fitted survival curves from sensitivity analysis with time-varying hazard ratios**



## 4.2 Prior distributions / Piecewise constant hazards

In this section, we evaluate the impact of two assumptions made in the primary model: 1) the prior distributions specified in the primary analysis model, and 2) the parametric assumption that survival times are piecewise exponential. To address both of these assumptions, we have performed frequentist Cox models with similar covariate adjustments to the primary analysis. These Cox models are fit within the frequentist framework, so no prior distributions are specified, and the results will be similar to a Bayesian model with non-informative prior distributions. Additionally, the Cox model makes no assumption on the underlying distribution of survival times, so this analysis will evaluate robustness of the results to the assumption of piecewise constant hazards in the primary model.

The Cox model summarized in this section adjusts for the same covariates as the Bayesian analysis. For site and time effects, we have incorporated each as a random intercept term in the model which is similar to

the hierarchical prior that is pre-specified in the primary model. In Table S5.2 below, we present the hazard ratios and 95% credible/confidence intervals for each intervention for the primary analysis (column 1) and the Cox model sensitivity analysis (column 2). We also compare the hazard ratios for each intervention in a forest plot.

The hazard ratios and uncertainty intervals from the Cox model are very similar to the primary analysis results. Removing the prior distributions and incorporating a more flexible model of time did not appear to impact the resulting hazard ratio for each intervention. The largest difference across the two models is the hazard ratio estimated for the combination antiviral intervention which is 1.61 (0.97 to 2.67) in the primary analysis and 2.94 (1.10 to 7.90) in the Cox model. The Bayesian analysis incorporates a prior distribution on the interaction term for lopinavir-ritonavir and hydroxychloroquine that 1) pulls the interaction term towards zero and 2) borrows information from the lopinavir-ritonavir and hydroxychloroquine interventions when estimating the combination effect. The Bayesian model structure results in an estimated hazard ratio that is smaller and less variable than the Cox model estimate. However, the overall conclusion of the two models is the same in that it appears that combination antiviral therapy is harmful.



Table S5.2: Comparison of results from primary analysis and equivalent frequentist Cox model

Intervention	Primary analysis hazard ratio (95% CrI)	Frequentist Cox model hazard ratio (95% CI)
Pooled IL-6ra	0.74 (0.61, 0.90)	0.75 (0.61, 0.92)
Pooled antiplatelet	0.85 (0.71, 1.03)	0.82 (0.67, 0.99)
Fixed duration hydrocortisone	0.93 (0.61, 1.47)	0.96 (0.60, 1.53)
Anakinra	0.96 (0.75, 1.23)	0.95 (0.74, 1.23)
Shock-dependent hydrocortisone	0.96 (0.61, 1.50)	0.97 (0.61, 1.56)
Convalescent plasma	0.99 (0.86, 1.14)	0.99 (0.86, 1.14)
Lopinavir/ritonavir	1.06 (0.82, 1.38)	1.00 (0.76, 1.32)
Therapeutic anticoagulation	1.13 (0.93, 1.42)	1.12 (0.90, 1.39)
Hydroxychloroquine	1.51 (0.98, 2.29)	1.46 (0.85, 2.51)
Antiviral combination therapy	1.61 (0.97, 2.67)	2.95 (1.10, 7.90)

Figure S5.4: Forest plot of Day 180 mortality hazard ratios estimated from the primary analysis and frequentist Cox model.

