Nor-Solidarity PROM analysis report

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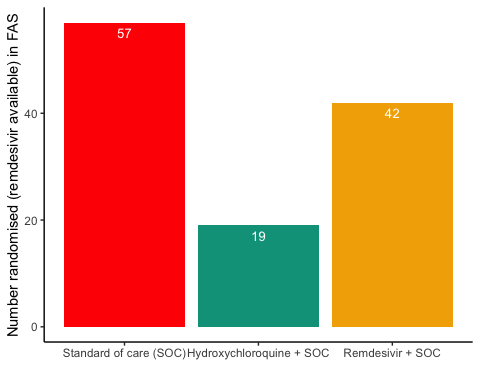
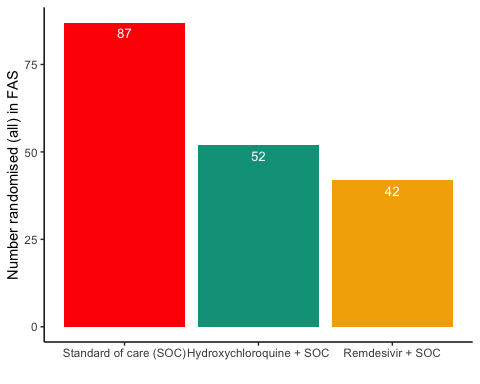
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# Introduction

This is the report for the patient reported outcome measures (PROMs) in the Nor-Solidarity trials. The data are based on an export from the Viedoc electronic data capture at “2021-01-04 00:30:34” system time stamped “ous\_20210104\_003034”. The results in this report is according to the true random allocation. There were 181 included patients. The EQ-5D and SF-36 data are gathered from the Norwegian Intensive Care and Pandemic Registry in an export dated 20 April 2021. There were 181 subjects with at least one PROM record.

# Inclusion status

## By treatment



# Demographics

Demographics, Remdesivir available

| Parameter | Remdesivir (N=42) | SOC ± HCQ (N=76) |
| --- | --- | --- |
| **Demographics** |  |  |
| Age (years) | 59.7 (16.5) | 58.4 (14.6) |
| Female, n (%) | 13 (31%) | 20 (26.3%) |
| Body Mass Index (kg/m2) | 28 (5) | 28 (4) |
| Body Mass Index (kg/m2) | 27 (25 - 32) | 28 (25 - 31) |
| Symptoms prior to admission (days) | 7.5 (6.1) | 7.6 (4) |
| P/F-ratio at admittance (kPa) | 38 (13) | 42 (14) |
| P/F-ratio < 40kPa, n (%) | 22 (52.4%) | 31 (40.8%) |
| Temperature (°C) | 37.2 (0.9) | 37.6 (1) |
| Respiratory rate (breaths/min) | 21.9 (5.3) | 22.4 (5.5) |
| Admitted to ward, n(%) | 39 (92.9%) | 71 (93.4%) |
| Admitted to ICU, n(%) | 3 (7.1%) | 5 (6.6%) |
| WHO Moderate disease state (4-5), n(%) | 41 (97.6%) | 71 (93.4%) |
| WHO Severe disease state (6-9), n(%) | 1 (2.4%) | 5 (6.6%) |
| WHO Severe disease state (6), n(%) | NA | 2 (2.6%) |
| WHO Severe disease state (5), n(%) | 27 (64.3%) | 39 (51.3%) |
| **Comorbidities** |  |  |
| Chronic cardiac disease, including congenital heart disease | 6 (14.6%) | 14 (18.4%) |
| Chronic pulmonary disease, n(%) | 4 (9.8%) | 3 (3.9%) |
| Ever smoking, n(%) | 16 (39%) | 34 (44.7%) |
| Hypertension, n(%) | 15 (36.6%) | 21 (27.6%) |
| Diabetes, n(%) | 9 (22%) | 12 (15.8%) |
| Obese (BMI > 30 kg/m2), n(%) | 11 (28.9%) | 17 (26.2%) |
| **Co-medications** |  |  |
| Steroids | 1 (2.4%) | 3 (4%) |
| Other immunomodulatory drugs | 1 (2.4%) | 1 (1.3%) |
| ACE inhibitor | 2 (4.9%) | 4 (5.3%) |
| AT-II blockers | 11 (26.8%) | 11 (14.7%) |
| **Hematology** |  |  |
| Hemoglobin (g/dL) | 13.2 (12.4 - 14.3) | 13.4 (12.7 - 14.3) |
| WBC (x109/L) | 6 (4.9 - 8.7) | 6.3 (4.8 - 9) |
| Neutrophils (x109/L) | 4.3 (2.7 - 6.8) | 4.7 (3 - 6.6) |
| Lymphocytes (x109/L) | 1.1 (0.9 - 1.5) | 1 (0.7 - 1.4) |
| Platelet counts (x10^9/L) | 206 (162 - 268) | 200.5 (159.2 - 267.2) |
| **Inflammatory markers** |  |  |
| CRP (mg/L) | 70 (39.8 - 139.2) | 82 (38.5 - 138.8) |
| Procalcitonin (µg/L) | 0.13 (0.1 - 0.2) | 0.12 (0.1 - 0.3) |
| Ferritin (µg/L) | 694.5 (343.2 - 1262.2) | 613 (317.8 - 1152.5) |
| **Other** |  |  |
| LDH (U/L) | 284 (234 - 400) | 267 (209 - 365) |
| D-dimer (mg/L FEU) | 0.76 (0.47 - 1.03) | 0.6 (0.41 - 0.95) |
| AST | 49 (34.5 - 77) | 39 (25.2 - 57) |
| ALT | 41 (22 - 69.2) | 35.5 (20.8 - 57.2) |
| eGFR (mL/min/1.73 m2) | 90.6 (77.2 - 106.2) | 89.4 (71 - 104.5) |
| **Viral count** |  |  |
| Viral count (log10 counts/1000 cells) | 1.6 (1.6) | 2.3 (1.8) |
| **Anti-SARS-CoV-2 Antibodies** |  |  |
| Sero converted (RBD ≥ 5) | 14 (42.4%) | 23 (42.6%) |
| Sero converted (Capsid ≥ 10) | 11 (33.3%) | 19 (35.2%) |
| **Supplementary baseline information** |  |  |
| Systolic Blood Pressure (mmHg) | 130 (20) | 122 (16) |
| Diastolic Blood Pressure (mmHg) | 76 (11) | 73 (11) |
| Mean Arterial Blood Pressure (mmHg) | 94 (12) | 89 (12) |
| SOFA score | 1.4 (1.3) | 1.7 (1.7) |
| Chronic kidney disease, n(%) | 1 (2.4%) | 4 (5.3%) |
| Autoimmune disease, n(%) | 0 (0%) | 2 (2.6%) |
| Cognitive impairment/dementia, n(%) | 2 (4.9%) | 0 (0%) |
| Neurological disorder, n(%) | 1 (2.4%) | 3 (3.9%) |
| Cancer, n(%) | 2 (4.9%) | 6 (7.9%) |
| Cirrhosis, n(%) | 0 (0%) | 0 (0%) |
| Asthma, n(%) | 2 (4.9%) | 8 (10.5%) |
| HIV, n(%) | 0 (0%) | 0 (0%) |
| Active TB, n(%) | 0 (0%) | 0 (0%) |
| Note, all percentages are given with observed values in the denominator, missing values discarded |  |  |

# Efficacy

## Primary endpoints

### Descriptives

| label | Statistic | Remdesivir | SOC ± HCQ |
| --- | --- | --- | --- |
| CAT Fatigue at 3 months | Mean (SD) | 2.6 (1.5) | 2.1 (1.6) |
| CAT Fatigue at 3 months | Median [IQR] | 2 [2 - 4] | 2 [1 - 3] |
| CAT Fatigue at 3 months | Missing / Non-Missing | 15 / 27 | 23 / 53 |
| CAT shortness of breath at 3 months | Mean (SD) | 3 (1.7) | 2.1 (1.8) |
| CAT shortness of breath at 3 months | Median [IQR] | 3.5 [2 - 4] | 2 [0 - 4] |
| CAT shortness of breath at 3 months | Missing / Non-Missing | 15 / 27 | 23 / 53 |
| CAT Coughing at 3 months | Mean (SD) | 1.8 (1.6) | 1.2 (1.5) |
| CAT Coughing at 3 months | Median [IQR] | 1 [1 - 3] | 1 [0 - 2] |
| CAT Coughing at 3 months | Missing / Non-Missing | 15 / 27 | 23 / 53 |

## Primary analysis

### Missingness pattern

## subjectid rantrt rantrt2 age\_calc sex oxygen rcwhocps survcens survtime  
## 45 1 1 1 1 1 1 1 1 1  
## 10 1 1 1 1 1 1 1 1 1  
## 1 1 1 1 1 1 1 1 1 1  
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## 11 1 1 1 1 1 1 1 1 1  
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## 8 1 1 1 1 1 1 1 1 1  
## 6 1 1 1 1 1 1 1 1 1  
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## 0 0 0 0 0 0 0 0 0  
## rcwhostate age\_cat age2\_cat sympdur sympdur\_cat crp\_cat fer\_cat hospdur  
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## 10 1 1 1 1 1 1 1 1  
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## 1 1 1 1 1 1 0 0 0  
## 1 1 1 1 0 0 1 1 1  
## 0 0 0 1 1 2 6 12  
## dphdisc vl\_cat copd1\_m1 copd2\_m1 copd3\_m1 copd5\_m1 copd7\_m1 copd8\_m1  
## 45 1 1 1 1 1 1 1 1  
## 10 1 1 1 1 1 1 1 1  
## 1 1 1 1 1 1 1 1 1  
## 1 1 1 1 1 1 1 1 1  
## 11 1 1 0 0 0 0 0 0  
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## 2 1 1 1 1 1 1 1 1  
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## 1 0 1 0 0 0 0 0 0  
## 1 1 0 1 1 1 1 1 1  
## 1 0 1 0 0 0 0 0 0  
## 1 1 0 1 1 1 1 1 1  
## 12 26 36 36 36 36 36 36  
## total\_m1 copd4\_m1 copd6\_m1 copd1\_m3 copd2\_m3 copd3\_m3 copd4\_m3 copd5\_m3  
## 45 1 1 1 1 1 1 1 1  
## 10 1 1 1 0 0 0 0 0  
## 1 1 1 0 1 1 1 1 1  
## 1 1 0 1 1 1 1 1 1  
## 11 0 0 0 1 1 1 1 1  
## 11 0 0 0 0 0 0 0 0  
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## 6 1 1 1 0 0 0 0 0  
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## 2 1 1 1 1 1 1 1 1  
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## 1 1 1 1 1 1 1 1 1  
## 36 37 37 38 38 38 38 38  
## copd6\_m3 copd7\_m3 copd8\_m3 total\_m3   
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## 1 1 1 1 1 1  
## 11 1 1 1 1 9  
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## 5 1 1 1 1 2  
## 1 0 0 0 0 11  
## 1 1 1 1 1 11  
## 1 0 0 0 0 20  
## 1 1 1 1 1 3  
## 1 1 1 1 1 12  
## 2 1 1 1 1 1  
## 1 0 0 0 0 19  
## 1 1 1 1 1 11  
## 1 0 0 0 0 21  
## 1 0 0 0 0 11  
## 1 0 0 0 0 22  
## 1 1 1 1 1 3  
## 38 38 38 38 728

We see that a majority of the observations are complete, and the majority of the missing data are missing primary endpoints. Of the baseline variables predefined to be used in the imputations, most missing values are on the hospital duration and discharge due to death. These will be imputed with proper values.

### Analyses

The primary analyses according to the Statistical Analysis Plan (SAP) is that the groups will be compared using t-test and the difference in means will be presented with 95% confidence intervals based on the t-distribution for the difference. We will implement it using the lm-function in R.

Missing data due to death will be imputed with worst outcome. Other missing data will be handled by multiple imputation with chained equations (MICE). The imputation will be based on a model with the following covariates:

* Age
* Sex
* Hospital duration
* Location after discharge (Home with or without requiring municipal assistance, recreation stay , municipal rehabilitation/nursing home, and local hospital)
* Baseline WHO Clinical progression scale
* Symptom duration before admission
* Viral load at baseline
* CRP at baseline
* Ferritin at baseline

Note that treatment is deliberately not part of the imputation model assuming this will provide conservative estimates of the treatment effect.

The following sensitivity analyses will be performed:

1. Equal to the primary analysis but excluding patients randomised to hydroxychloroquine

2. Equal to the primary analysis but excluding missing observations except due to death (complete case analysis)

3. Equal to the above but comparing using Mann-Whitney U test

Primary analysis with sensitivity analyses

| Variable | Analysis | Difference with 95% CI | P-value |
| --- | --- | --- | --- |
| CAT Fatigue at 3 months | Primary | -0.5 (95% CI -1.16 to 0.15) | 0.1293263 |
| CAT Fatigue at 3 months | HCQ excluded | -0.48 (95% CI -1.18 to 0.22) | 0.1791443 |
| CAT Fatigue at 3 months | Complete case | -0.55 (95% CI -1.29 to 0.18) | 0.1390022 |
| CAT Fatigue at 3 months | Mann-Whitney U test | NA | 0.1404365 |
| CAT shortness of breath at 3 months | Primary | -0.72 (95% CI -1.57 to 0.14) | 0.0986408 |
| CAT shortness of breath at 3 months | HCQ excluded | -0.76 (95% CI -1.69 to 0.17) | 0.1056208 |
| CAT shortness of breath at 3 months | Complete case | -0.94 (95% CI -1.77 to -0.11) | 0.0263098 |
| CAT shortness of breath at 3 months | Mann-Whitney U test | NA | 0.0302802 |
| CAT Coughing at 3 months | Primary | -0.45 (95% CI -1.19 to 0.29) | 0.2278158 |
| CAT Coughing at 3 months | HCQ excluded | -0.48 (95% CI -1.3 to 0.34) | 0.2413732 |
| CAT Coughing at 3 months | Complete case | -0.57 (95% CI -1.3 to 0.16) | 0.1237589 |
| CAT Coughing at 3 months | Mann-Whitney U test | NA | 0.0477244 |

### Subgroup analyses

Subgroup analyses will be performed according to the following subgroups: \*

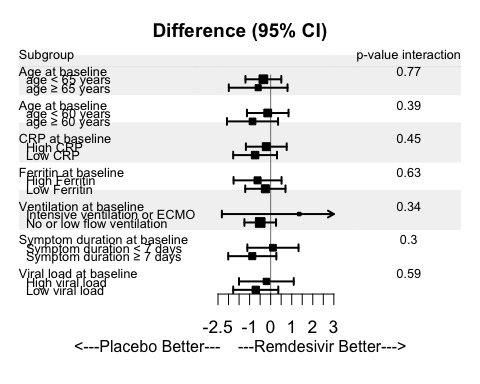
* Ventilation at baseline (No or low-flow oxygen vs intensive ventilation)
* Symptom duration at baseline (< 7 days vs ≥7 days)
* Age at baseline (< 60 vs ≥ 60 years)
* Age at baseline (< 65 vs ≥ 65 years)
* Viral load at baseline (< overall median vs ≥ overall median)
* CRP at baseline (< overall median vs ≥ overall median)
* Ferritin at baseline (< overall median vs ≥ overall median)

The subgroup analysis will be performed by an Analysis of Covariance model including a treatment / subgroup interaction term. Missing data will be handled using MICE as it was for the primary endpoint.

#### Coughing

Subgroup-analyses

| Variable | Subgroup | Category | Contrast | Difference with 95% CI | P-value | P-value interaction |
| --- | --- | --- | --- | --- | --- | --- |
| CAT Coughing at 3 months | Age at baseline | age < 60 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.14 (95% CI -1.13 to 0.85) | 0.7809879 | 0.3856816 |
| CAT Coughing at 3 months | Age at baseline | age ≥ 60 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.86 (95% CI -2.07 to 0.35) | 0.1609031 | 0.3856816 |
| CAT Coughing at 3 months | Age at baseline | age < 65 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.35 (95% CI -1.2 to 0.51) | 0.4243301 | 0.7656024 |
| CAT Coughing at 3 months | Age at baseline | age ≥ 65 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.59 (95% CI -1.99 to 0.8) | 0.3979904 | 0.7656024 |
| CAT Coughing at 3 months | CRP at baseline | High CRP | mean(SOC ± HCQ) - mean(Remdesivir) | -0.21 (95% CI -1.18 to 0.76) | 0.6741325 | 0.4510845 |
| CAT Coughing at 3 months | CRP at baseline | Low CRP | mean(SOC ± HCQ) - mean(Remdesivir) | -0.74 (95% CI -1.78 to 0.3) | 0.1631640 | 0.4510845 |
| CAT Coughing at 3 months | Ferritin at baseline | High Ferritin | mean(SOC ± HCQ) - mean(Remdesivir) | -0.62 (95% CI -1.76 to 0.52) | 0.2785192 | 0.6309667 |
| CAT Coughing at 3 months | Ferritin at baseline | Low Ferritin | mean(SOC ± HCQ) - mean(Remdesivir) | -0.25 (95% CI -1.21 to 0.7) | 0.6052117 | 0.6309667 |
| CAT Coughing at 3 months | Ventilation at baseline | Intensive ventilation or ECMO | mean(SOC ± HCQ) - mean(Remdesivir) | 1.36 (95% CI -2.32 to 5.04) | 0.4681595 | 0.3362262 |
| CAT Coughing at 3 months | Ventilation at baseline | No or low flow ventilation | mean(SOC ± HCQ) - mean(Remdesivir) | -0.5 (95% CI -1.25 to 0.26) | 0.1939031 | 0.3362262 |
| CAT Coughing at 3 months | Symptom duration at baseline | Symptom duration < 7 days | mean(SOC ± HCQ) - mean(Remdesivir) | 0.11 (95% CI -1.11 to 1.32) | 0.8592634 | 0.3003255 |
| CAT Coughing at 3 months | Symptom duration at baseline | Symptom duration ≥ 7 days | mean(SOC ± HCQ) - mean(Remdesivir) | -0.87 (95% CI -2.01 to 0.27) | 0.1307173 | 0.3003255 |
| CAT Coughing at 3 months | Viral load at baseline | High viral load | mean(SOC ± HCQ) - mean(Remdesivir) | -0.2 (95% CI -1.5 to 1.1) | 0.7527080 | 0.5880896 |
| CAT Coughing at 3 months | Viral load at baseline | Low viral load | mean(SOC ± HCQ) - mean(Remdesivir) | -0.71 (95% CI -1.78 to 0.36) | 0.1924397 | 0.5880896 |

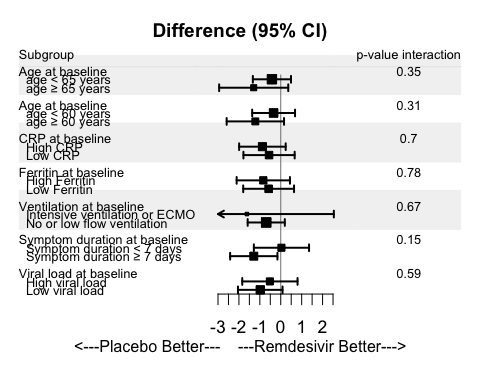


CAT Coughing

#### Shortness of breath

Subgroup-analyses

| Variable | Subgroup | Category | Contrast | Difference with 95% CI | P-value | P-value interaction |
| --- | --- | --- | --- | --- | --- | --- |
| CAT shortness of breath at 3 months | Age at baseline | age < 60 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.34 (95% CI -1.37 to 0.68) | 0.5128097 | 0.3116611 |
| CAT shortness of breath at 3 months | Age at baseline | age ≥ 60 years | mean(SOC ± HCQ) - mean(Remdesivir) | -1.21 (95% CI -2.59 to 0.16) | 0.0815547 | 0.3116611 |
| CAT shortness of breath at 3 months | Age at baseline | age < 65 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.42 (95% CI -1.33 to 0.49) | 0.3634640 | 0.3453776 |
| CAT shortness of breath at 3 months | Age at baseline | age ≥ 65 years | mean(SOC ± HCQ) - mean(Remdesivir) | -1.29 (95% CI -2.94 to 0.36) | 0.1220822 | 0.3453776 |
| CAT shortness of breath at 3 months | CRP at baseline | High CRP | mean(SOC ± HCQ) - mean(Remdesivir) | -0.88 (95% CI -1.99 to 0.24) | 0.1216799 | 0.7018713 |
| CAT shortness of breath at 3 months | CRP at baseline | Low CRP | mean(SOC ± HCQ) - mean(Remdesivir) | -0.56 (95% CI -1.78 to 0.67) | 0.3675655 | 0.7018713 |
| CAT shortness of breath at 3 months | Ferritin at baseline | High Ferritin | mean(SOC ± HCQ) - mean(Remdesivir) | -0.83 (95% CI -2.11 to 0.44) | 0.1949118 | 0.7816743 |
| CAT shortness of breath at 3 months | Ferritin at baseline | Low Ferritin | mean(SOC ± HCQ) - mean(Remdesivir) | -0.58 (95% CI -1.79 to 0.64) | 0.3474701 | 0.7816743 |
| CAT shortness of breath at 3 months | Ventilation at baseline | Intensive ventilation or ECMO | mean(SOC ± HCQ) - mean(Remdesivir) | -1.62 (95% CI -5.78 to 2.54) | 0.4449906 | 0.6747196 |
| CAT shortness of breath at 3 months | Ventilation at baseline | No or low flow ventilation | mean(SOC ± HCQ) - mean(Remdesivir) | -0.69 (95% CI -1.58 to 0.19) | 0.1237968 | 0.6747196 |
| CAT shortness of breath at 3 months | Symptom duration at baseline | Symptom duration < 7 days | mean(SOC ± HCQ) - mean(Remdesivir) | 0.03 (95% CI -1.29 to 1.35) | 0.9598967 | 0.1480432 |
| CAT shortness of breath at 3 months | Symptom duration at baseline | Symptom duration ≥ 7 days | mean(SOC ± HCQ) - mean(Remdesivir) | -1.29 (95% CI -2.42 to -0.16) | 0.0258754 | 0.1480432 |
| CAT shortness of breath at 3 months | Viral load at baseline | High viral load | mean(SOC ± HCQ) - mean(Remdesivir) | -0.52 (95% CI -1.84 to 0.8) | 0.4350495 | 0.5921090 |
| CAT shortness of breath at 3 months | Viral load at baseline | Low viral load | mean(SOC ± HCQ) - mean(Remdesivir) | -0.98 (95% CI -2.05 to 0.09) | 0.0713822 | 0.5921090 |

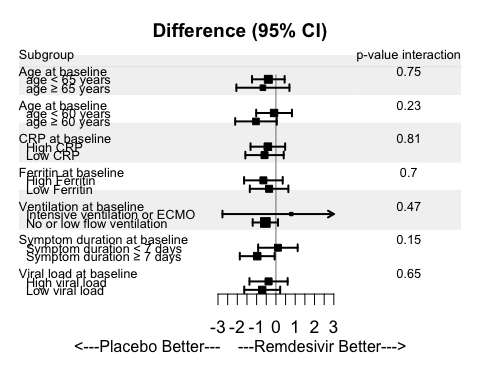


CAT Shortness of breath

#### Fatigue

Subgroup-analyses

| Variable | Subgroup | Category | Contrast | Difference with 95% CI | P-value | P-value interaction |
| --- | --- | --- | --- | --- | --- | --- |
| CAT Fatigue at 3 months | Age at baseline | age < 60 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.1 (95% CI -1.02 to 0.83) | 0.8389998 | 0.2313896 |
| CAT Fatigue at 3 months | Age at baseline | age ≥ 60 years | mean(SOC ± HCQ) - mean(Remdesivir) | -1.03 (95% CI -2.11 to 0.04) | 0.0598609 | 0.2313896 |
| CAT Fatigue at 3 months | Age at baseline | age < 65 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.39 (95% CI -1.24 to 0.45) | 0.3593967 | 0.7506646 |
| CAT Fatigue at 3 months | Age at baseline | age ≥ 65 years | mean(SOC ± HCQ) - mean(Remdesivir) | -0.67 (95% CI -2.05 to 0.7) | 0.3295805 | 0.7506646 |
| CAT Fatigue at 3 months | CRP at baseline | High CRP | mean(SOC ± HCQ) - mean(Remdesivir) | -0.42 (95% CI -1.32 to 0.48) | 0.3593559 | 0.8056262 |
| CAT Fatigue at 3 months | CRP at baseline | Low CRP | mean(SOC ± HCQ) - mean(Remdesivir) | -0.59 (95% CI -1.58 to 0.4) | 0.2429430 | 0.8056262 |
| CAT Fatigue at 3 months | Ferritin at baseline | High Ferritin | mean(SOC ± HCQ) - mean(Remdesivir) | -0.65 (95% CI -1.65 to 0.35) | 0.2012076 | 0.7033256 |
| CAT Fatigue at 3 months | Ferritin at baseline | Low Ferritin | mean(SOC ± HCQ) - mean(Remdesivir) | -0.35 (95% CI -1.35 to 0.64) | 0.4853618 | 0.7033256 |
| CAT Fatigue at 3 months | Ventilation at baseline | Intensive ventilation or ECMO | mean(SOC ± HCQ) - mean(Remdesivir) | 0.8 (95% CI -2.77 to 4.37) | 0.6603428 | 0.4671149 |
| CAT Fatigue at 3 months | Ventilation at baseline | No or low flow ventilation | mean(SOC ± HCQ) - mean(Remdesivir) | -0.55 (95% CI -1.2 to 0.11) | 0.1014543 | 0.4671149 |
| CAT Fatigue at 3 months | Symptom duration at baseline | Symptom duration < 7 days | mean(SOC ± HCQ) - mean(Remdesivir) | 0.1 (95% CI -0.92 to 1.13) | 0.8423932 | 0.1460407 |
| CAT Fatigue at 3 months | Symptom duration at baseline | Symptom duration ≥ 7 days | mean(SOC ± HCQ) - mean(Remdesivir) | -0.97 (95% CI -1.87 to -0.07) | 0.0351344 | 0.1460407 |
| CAT Fatigue at 3 months | Viral load at baseline | High viral load | mean(SOC ± HCQ) - mean(Remdesivir) | -0.38 (95% CI -1.37 to 0.61) | 0.4468876 | 0.6532330 |
| CAT Fatigue at 3 months | Viral load at baseline | Low viral load | mean(SOC ± HCQ) - mean(Remdesivir) | -0.71 (95% CI -1.64 to 0.22) | 0.1342634 | 0.6532330 |



CAT Fatigue

## Secondary endpoints

### Other CAT items including total

Secondary analyses with CAT Descriptives

| label | Statistic | Remdesivir | SOC ± HCQ |
| --- | --- | --- | --- |
| CAT Fatigue at 1 month | Mean (SD) | 2.7 (1.6) | 2.8 (1.3) |
| CAT Fatigue at 1 month | Median [IQR] | 3 [1.2 - 4] | 3 [2 - 4] |
| CAT Fatigue at 1 month | Missing / Non-Missing | 16 / 26 | 20 / 56 |
| CAT Shortness of breath at 1 month | Mean (SD) | 3 (1.8) | 2.9 (1.5) |
| CAT Shortness of breath at 1 month | Median [IQR] | 3.5 [1.2 - 5] | 3 [2 - 4] |
| CAT Shortness of breath at 1 month | Missing / Non-Missing | 16 / 26 | 21 / 55 |
| CAT Coughing at 1 month | Mean (SD) | 1.7 (1.7) | 1.5 (1.5) |
| CAT Coughing at 1 month | Median [IQR] | 1 [0.2 - 2.8] | 1 [0 - 2] |
| CAT Coughing at 1 month | Missing / Non-Missing | 16 / 26 | 20 / 56 |
| CAT total score at 1 month | Mean (SD) | 17 (11.3) | 15.8 (9.5) |
| CAT total score at 1 month | Median [IQR] | 19.3 [5.5 - 24] | 14 [10 - 20.2] |
| CAT total score at 1 month | Missing / Non-Missing | 16 / 26 | 20 / 56 |
| CAT total score at 3 months | Mean (SD) | 16.8 (11.4) | 11.4 (10.4) |
| CAT total score at 3 months | Median [IQR] | 13 [8.5 - 24] | 8 [4 - 15] |
| CAT total score at 3 months | Missing / Non-Missing | 15 / 27 | 23 / 53 |

Secondary analysis CAT

| Variable | Analysis | Difference with 95% CI | P-value |
| --- | --- | --- | --- |
| CAT Fatigue at 1 month | Primary | -0.01 (95% CI -0.62 to 0.6) | 0.9748967 |
| CAT Fatigue at 1 month | HCQ excluded | -0.15 (95% CI -0.79 to 0.48) | 0.6315279 |
| CAT Fatigue at 1 month | Complete case | 0.04 (95% CI -0.64 to 0.71) | 0.9131173 |
| CAT Fatigue at 1 month | Mann-Whitney U test | NA | 0.8102916 |
| CAT Shortness of breath at 1 month | Primary | -0.04 (95% CI -0.93 to 0.85) | 0.9247477 |
| CAT Shortness of breath at 1 month | HCQ excluded | -0.05 (95% CI -0.95 to 0.85) | 0.9166019 |
| CAT Shortness of breath at 1 month | Complete case | -0.07 (95% CI -0.84 to 0.7) | 0.8510029 |
| CAT Shortness of breath at 1 month | Mann-Whitney U test | NA | 0.7377754 |
| CAT Coughing at 1 month | Primary | -0.19 (95% CI -1.02 to 0.64) | 0.6472263 |
| CAT Coughing at 1 month | HCQ excluded | -0.2 (95% CI -1.1 to 0.7) | 0.6501814 |
| CAT Coughing at 1 month | Complete case | -0.23 (95% CI -0.97 to 0.51) | 0.5352789 |
| CAT Coughing at 1 month | Mann-Whitney U test | NA | 0.6259011 |
| CAT total score at 1 month | Primary | -0.89 (95% CI -5.62 to 3.84) | 0.7061425 |
| CAT total score at 1 month | HCQ excluded | -1.27 (95% CI -6.29 to 3.75) | 0.6103013 |
| CAT total score at 1 month | Complete case | -1.16 (95% CI -5.94 to 3.62) | 0.6297933 |
| CAT total score at 1 month | Mann-Whitney U test | NA | 0.6213823 |
| CAT total score at 3 months | Primary | -4.32 (95% CI -9.06 to 0.42) | 0.0729445 |
| CAT total score at 3 months | HCQ excluded | -4.34 (95% CI -9.47 to 0.79) | 0.0951702 |
| CAT total score at 3 months | Complete case | -5.34 (95% CI -10.4 to -0.29) | 0.0384964 |
| CAT total score at 3 months | Mann-Whitney U test | NA | 0.0191002 |

### EQ5D outcomes

Secondary analyses of EQ5D Descriptives

| label | Statistic | Remdesivir | SOC ± HCQ |
| --- | --- | --- | --- |
| EQ-5D-5L self-rated health | Mean (SD) | 46.1 (27.1) | 58.4 (28.1) |
| EQ-5D-5L self-rated health | Median [IQR] | 41 [31.5 - 70] | 67 [39 - 79] |
| EQ-5D-5L self-rated health | Missing / Non-Missing | 23 / 19 | 37 / 39 |
| EQ-5D-5L index value | Mean (SD) | 0.5 (0.4) | 0.7 (0.3) |
| EQ-5D-5L index value | Median [IQR] | 0.6 [0.3 - 0.8] | 0.8 [0.7 - 0.9] |
| EQ-5D-5L index value | Missing / Non-Missing | 23 / 19 | 39 / 37 |

EQ5D analyses with sensitivity analyses

| Variable | Analysis | Difference with 95% CI | P-value |
| --- | --- | --- | --- |
| EQ-5D-5L self-rated health | Primary | 3.554 (95% CI -7.418 to 14.526) | 0.5206785 |
| EQ-5D-5L self-rated health | HCQ excluded | 2.524 (95% CI -9.925 to 14.972) | 0.6858076 |
| EQ-5D-5L self-rated health | Complete case | 12.305 (95% CI -3.266 to 27.875) | 0.1190275 |
| EQ-5D-5L self-rated health | Mann-Whitney U test | NA | 0.1166975 |
| EQ-5D-5L index value | Primary | 0.058 (95% CI -0.069 to 0.185) | 0.3629968 |
| EQ-5D-5L index value | HCQ excluded | 0.054 (95% CI -0.088 to 0.195) | 0.4500177 |
| EQ-5D-5L index value | Complete case | 0.175 (95% CI -0.007 to 0.358) | 0.0591620 |
| EQ-5D-5L index value | Mann-Whitney U test | NA | 0.0592107 |

### SF-36 outcomes

Secondary analyses of S36 Descriptives

| label | Statistic | Remdesivir | SOC ± HCQ |
| --- | --- | --- | --- |
| SF-36 Physical functioning | Mean (SD) | 44.3 (30.3) | 57.1 (33.3) |
| SF-36 Physical functioning | Median [IQR] | 44.4 [25 - 60] | 60 [31.2 - 85] |
| SF-36 Physical functioning | Missing / Non-Missing | 21 / 21 | 34 / 42 |
| SF-36 Role limitations due to physical health problems | Mean (SD) | 23.8 (38.3) | 42.9 (42.5) |
| SF-36 Role limitations due to physical health problems | Median [IQR] | 0 [0 - 50] | 50 [0 - 93.8] |
| SF-36 Role limitations due to physical health problems | Missing / Non-Missing | 21 / 21 | 34 / 42 |
| SF-36 Role limitations due to emotional problems | Mean (SD) | 39.7 (46.7) | 52.4 (46.1) |
| SF-36 Role limitations due to emotional problems | Median [IQR] | 0 [0 - 100] | 66.7 [0 - 100] |
| SF-36 Role limitations due to emotional problems | Missing / Non-Missing | 21 / 21 | 34 / 42 |
| SF-36 Energy/fatigue | Mean (SD) | 34.5 (24) | 45.6 (29.6) |
| SF-36 Energy/fatigue | Median [IQR] | 40 [20 - 45] | 40 [25 - 73.8] |
| SF-36 Energy/fatigue | Missing / Non-Missing | 21 / 21 | 34 / 42 |
| SF-36 Emotional well-being | Mean (SD) | 56.6 (31.6) | 64.5 (29) |
| SF-36 Emotional well-being | Median [IQR] | 56 [40 - 84] | 72 [49 - 87] |
| SF-36 Emotional well-being | Missing / Non-Missing | 21 / 21 | 34 / 42 |
| SF-36 Social functioning | Mean (SD) | 48.2 (31.4) | 56.2 (32.7) |
| SF-36 Social functioning | Median [IQR] | 62.5 [25 - 75] | 62.5 [28.1 - 84.4] |
| SF-36 Social functioning | Missing / Non-Missing | 21 / 21 | 34 / 42 |
| SF-36 Bodily pain | Mean (SD) | 43.5 (31.8) | 54.7 (31.9) |
| SF-36 Bodily pain | Median [IQR] | 45 [22.5 - 67.5] | 45 [32.5 - 85.6] |
| SF-36 Bodily pain | Missing / Non-Missing | 21 / 21 | 34 / 42 |
| SF-36 General health perceptions | Mean (SD) | 38.8 (25.9) | 46.8 (27.3) |
| SF-36 General health perceptions | Median [IQR] | 40 [15 - 55] | 45 [30 - 68.8] |
| SF-36 General health perceptions | Missing / Non-Missing | 21 / 21 | 34 / 42 |
| SF-36 Perceived change in health from one year ago | Mean (SD) | 16.7 (19.9) | 23.2 (23) |
| SF-36 Perceived change in health from one year ago | Median [IQR] | 0 [0 - 25] | 25 [0 - 25] |
| SF-36 Perceived change in health from one year ago | Missing / Non-Missing | 21 / 21 | 34 / 42 |

sf36 analyses with sensitivity analyses

| Variable | Analysis | Difference with 95% CI | P-value |
| --- | --- | --- | --- |
| SF-36 Physical functioning | Primary | 6.89 (95% CI -6.93 to 20.71) | 0.3219202 |
| SF-36 Physical functioning | HCQ excluded | 6.63 (95% CI -7.34 to 20.6) | 0.3458720 |
| SF-36 Physical functioning | Complete case | 12.89 (95% CI -4.42 to 30.19) | 0.1416833 |
| SF-36 Physical functioning | Mann-Whitney U test | NA | 0.1337039 |
| SF-36 Role limitations due to physical health problems | Primary | 11.85 (95% CI -5.61 to 29.3) | 0.1802642 |
| SF-36 Role limitations due to physical health problems | HCQ excluded | 13.81 (95% CI -5.11 to 32.73) | 0.1490516 |
| SF-36 Role limitations due to physical health problems | Complete case | 19.05 (95% CI -2.96 to 41.06) | 0.0885774 |
| SF-36 Role limitations due to physical health problems | Mann-Whitney U test | NA | 0.0827690 |
| SF-36 Role limitations due to emotional problems | Primary | 6.37 (95% CI -12.95 to 25.69) | 0.5128135 |
| SF-36 Role limitations due to emotional problems | HCQ excluded | 10.35 (95% CI -10.41 to 31.1) | 0.3219880 |
| SF-36 Role limitations due to emotional problems | Complete case | 12.7 (95% CI -12.03 to 37.43) | 0.3084743 |
| SF-36 Role limitations due to emotional problems | Mann-Whitney U test | NA | 0.3174378 |
| SF-36 Energy/fatigue | Primary | 5.72 (95% CI -4.95 to 16.39) | 0.2895680 |
| SF-36 Energy/fatigue | HCQ excluded | 5.67 (95% CI -5.88 to 17.22) | 0.3300384 |
| SF-36 Energy/fatigue | Complete case | 11.07 (95% CI -3.83 to 25.97) | 0.1424294 |
| SF-36 Energy/fatigue | Mann-Whitney U test | NA | 0.2168128 |
| SF-36 Emotional well-being | Primary | 3.5 (95% CI -7.97 to 14.97) | 0.5450732 |
| SF-36 Emotional well-being | HCQ excluded | 3.81 (95% CI -7.96 to 15.59) | 0.5206464 |
| SF-36 Emotional well-being | Complete case | 7.9 (95% CI -8.07 to 23.88) | 0.3262336 |
| SF-36 Emotional well-being | Mann-Whitney U test | NA | 0.3344273 |
| SF-36 Social functioning | Primary | 3.06 (95% CI -9.88 to 15.99) | 0.6391699 |
| SF-36 Social functioning | HCQ excluded | 2.67 (95% CI -10.71 to 16.04) | 0.6922333 |
| SF-36 Social functioning | Complete case | 8.04 (95% CI -9.22 to 25.29) | 0.3554594 |
| SF-36 Social functioning | Mann-Whitney U test | NA | 0.3649537 |
| SF-36 Bodily pain | Primary | 3.72 (95% CI -11.59 to 19.02) | 0.6246817 |
| SF-36 Bodily pain | HCQ excluded | 4.21 (95% CI -12.4 to 20.81) | 0.6075951 |
| SF-36 Bodily pain | Complete case | 11.25 (95% CI -5.79 to 28.29) | 0.1915962 |
| SF-36 Bodily pain | Mann-Whitney U test | NA | 0.1944783 |
| SF-36 General health perceptions | Primary | 3.17 (95% CI -10.01 to 16.35) | 0.6270033 |
| SF-36 General health perceptions | HCQ excluded | 2.16 (95% CI -10.84 to 15.15) | 0.7376885 |
| SF-36 General health perceptions | Complete case | 7.98 (95% CI -6.37 to 22.33) | 0.2707627 |
| SF-36 General health perceptions | Mann-Whitney U test | NA | 0.3167105 |
| SF-36 Perceived change in health from one year ago | Primary | 3.5 (95% CI -5.75 to 12.75) | 0.4516024 |
| SF-36 Perceived change in health from one year ago | HCQ excluded | 3.23 (95% CI -6.8 to 13.26) | 0.5201279 |
| SF-36 Perceived change in health from one year ago | Complete case | 6.55 (95% CI -5.24 to 18.33) | 0.2708964 |
| SF-36 Perceived change in health from one year ago | Mann-Whitney U test | NA | 0.2995347 |

# Supplementary analyses

## HCG vs SoC

Supplementary analysis, HCQ vs SoC

| label | Statistic | Standard of care (SOC) | Hydroxychloroquine + SOC |
| --- | --- | --- | --- |
| CAT Fatigue at 3 months | Mean (SD) | 2.1 (1.6) | 2.1 (1.5) |
| CAT Fatigue at 3 months | Median [IQR] | 2 [1 - 3] | 2 [1.2 - 2.8] |
| CAT Fatigue at 3 months | Missing / Non-Missing | 18 / 39 | 5 / 14 |
| CAT shortness of breath at 3 months | Mean (SD) | 2 (1.8) | 2.3 (1.9) |
| CAT shortness of breath at 3 months | Median [IQR] | 2 [0 - 3.5] | 2 [1 - 3.8] |
| CAT shortness of breath at 3 months | Missing / Non-Missing | 18 / 39 | 5 / 14 |
| CAT Coughing at 3 months | Mean (SD) | 1.1 (1.5) | 1.4 (1.6) |
| CAT Coughing at 3 months | Median [IQR] | 1 [0 - 1.5] | 1 [0 - 2.8] |
| CAT Coughing at 3 months | Missing / Non-Missing | 18 / 39 | 5 / 14 |

| Variable | Analysis | Difference with 95% CI | P-value |
| --- | --- | --- | --- |
| CAT Fatigue at 3 months | SOC vs HCQ | -0.07 (95% CI -0.72 to 0.57) | 0.8272250 |
| CAT shortness of breath at 3 months | SOC vs HCQ | 0.12 (95% CI -0.68 to 0.93) | 0.7618051 |
| CAT Coughing at 3 months | SOC vs HCQ | 0.09 (95% CI -0.57 to 0.76) | 0.7830919 |

# Communications Medicine review

# Ref1 comment 2

Reviewer’s comment: “I have a major issue regarding the handling of missing data due to death. Imputing data with worst outcome seems highly biased, as it could possibly hide a potential efficacy or suggest a potential harm of treatment where none exists. I would suggest the authors use another imputation method to handle these data. Especially, adaptations of the MICE algorithms have been specially developed to handle MNAR data, such as NARFCS (see PMID: 29611205).”

While we disagree with the reviewer on this point, we will do the analysis using the suggested method (NARFCS). We use standard multiple imputation with chained equations as defined in the primary analysis, but put a shift on the imputed values for subjects who had missing data due to death. We used shift parameters of

Sensitivity estimands of the primary analysis using NARFCS with shift-parameter delta = 1

| Variable | Analysis | Difference with 95% CI | P-value |
| --- | --- | --- | --- |
| CAT Fatigue at 3 months | Primary | -0.47 (95% CI -1.34 to 0.39) | 0.2754646 |
| CAT Fatigue at 3 months | HCQ excluded | -0.45 (95% CI -1.36 to 0.47) | 0.3285170 |
| CAT Fatigue at 3 months | Complete case | -0.5 (95% CI -1.18 to 0.19) | 0.1534508 |
| CAT Fatigue at 3 months | Mann-Whitney U test | NA | 0.1551897 |
| CAT shortness of breath at 3 months | Primary | -1.06 (95% CI -2.29 to 0.17) | 0.0858694 |
| CAT shortness of breath at 3 months | HCQ excluded | -1.12 (95% CI -2.37 to 0.12) | 0.0741359 |
| CAT shortness of breath at 3 months | Complete case | -0.93 (95% CI -1.75 to -0.12) | 0.0255034 |
| CAT shortness of breath at 3 months | Mann-Whitney U test | NA | 0.0277806 |
| CAT Coughing at 3 months | Primary | -0.55 (95% CI -1.34 to 0.24) | 0.1636060 |
| CAT Coughing at 3 months | HCQ excluded | -0.62 (95% CI -1.46 to 0.23) | 0.1436024 |
| CAT Coughing at 3 months | Complete case | -0.48 (95% CI -1.04 to 0.08) | 0.0935969 |
| CAT Coughing at 3 months | Mann-Whitney U test | NA | 0.0455310 |

Sensitivity estimands of the primary analysis using NARFCS with shift-parameter delta = 2

| Variable | Analysis | Difference with 95% CI | P-value |
| --- | --- | --- | --- |
| CAT Fatigue at 3 months | Primary | -0.5 (95% CI -1.5 to 0.49) | 0.3173722 |
| CAT Fatigue at 3 months | HCQ excluded | -0.46 (95% CI -1.52 to 0.6) | 0.3915779 |
| CAT Fatigue at 3 months | Complete case | -0.5 (95% CI -1.18 to 0.19) | 0.1534508 |
| CAT Fatigue at 3 months | Mann-Whitney U test | NA | 0.1551897 |
| CAT shortness of breath at 3 months | Primary | -1.1 (95% CI -2.38 to 0.17) | 0.0876560 |
| CAT shortness of breath at 3 months | HCQ excluded | -1.13 (95% CI -2.48 to 0.21) | 0.0958232 |
| CAT shortness of breath at 3 months | Complete case | -0.93 (95% CI -1.75 to -0.12) | 0.0255034 |
| CAT shortness of breath at 3 months | Mann-Whitney U test | NA | 0.0277806 |
| CAT Coughing at 3 months | Primary | -0.57 (95% CI -1.47 to 0.32) | 0.2041312 |
| CAT Coughing at 3 months | HCQ excluded | -0.63 (95% CI -1.59 to 0.34) | 0.1969672 |
| CAT Coughing at 3 months | Complete case | -0.48 (95% CI -1.04 to 0.08) | 0.0935969 |
| CAT Coughing at 3 months | Mann-Whitney U test | NA | 0.0455310 |

Sensitivity estimands of the primary analysis using NARFCS with shift-parameter delta = 3

| Variable | Analysis | Difference with 95% CI | P-value |
| --- | --- | --- | --- |
| CAT Fatigue at 3 months | Primary | -0.53 (95% CI -1.73 to 0.68) | 0.3854181 |
| CAT Fatigue at 3 months | HCQ excluded | -0.47 (95% CI -1.76 to 0.82) | 0.4698754 |
| CAT Fatigue at 3 months | Complete case | -0.5 (95% CI -1.18 to 0.19) | 0.1534508 |
| CAT Fatigue at 3 months | Mann-Whitney U test | NA | 0.1551897 |
| CAT shortness of breath at 3 months | Primary | -1.11 (95% CI -2.64 to 0.43) | 0.1524950 |
| CAT shortness of breath at 3 months | HCQ excluded | -1.12 (95% CI -2.76 to 0.51) | 0.1735206 |
| CAT shortness of breath at 3 months | Complete case | -0.93 (95% CI -1.75 to -0.12) | 0.0255034 |
| CAT shortness of breath at 3 months | Mann-Whitney U test | NA | 0.0277806 |
| CAT Coughing at 3 months | Primary | -0.58 (95% CI -1.66 to 0.49) | 0.2793215 |
| CAT Coughing at 3 months | HCQ excluded | -0.63 (95% CI -1.77 to 0.52) | 0.2774310 |
| CAT Coughing at 3 months | Complete case | -0.48 (95% CI -1.04 to 0.08) | 0.0935969 |
| CAT Coughing at 3 months | Mann-Whitney U test | NA | 0.0455310 |

## Ref 1 comment 4

Comment: “A recent meta-analysis (PMID: 36828006) showed that remdesivir could reduce mortality in hospitalized patients depending on the oxygen support needed. Could the authors perform a supplementary subgroup analysis regarding this stratum?”

Added a sub-group analysis on 1) No ventilation at baseline: No or only low−flow oxygen or 2) Ventilation at baseline: High−flow or non−invasive ventilation, mechanical ventilation, ECMO See subgroup analysis

## Ref 2 Comment 2

Comment: - The trial is open label, which may pose problems of performance bias and measurement bias. This is mentionned in limitations. If the data is available, it would be interesting to know and compare co-interventions received in the two groups (I believe that Table 1 only reports cointerventions at baseline)

Add an overview of co-medication while hospitalised.

| cmtype | l5name | Remdesivir | SOC ± HCQ |
| --- | --- | --- | --- |
| Antibaterial drugs | amoxicillin | 2 (4.8%) | 2 (2.6%) |
| Antibaterial drugs | amoxicillin and beta-lactamase inhibitor | 0 (0.0%) | 4 (5.3%) |
| Antibaterial drugs | ampicillin | 0 (0.0%) | 1 (1.3%) |
| Antibaterial drugs | azithromycin | 0 (0.0%) | 1 (1.3%) |
| Antibaterial drugs | benzylpenicillin | 10 (23.8%) | 15 (19.7%) |
| Antibaterial drugs | cefotaxime | 6 (14.3%) | 19 (25%) |
| Antibaterial drugs | ceftriaxone | 1 (2.4%) | 1 (1.3%) |
| Antibaterial drugs | cefuroxime | 0 (0.0%) | 1 (1.3%) |
| Antibaterial drugs | ciprofloxacin | 0 (0.0%) | 3 (3.9%) |
| Antibaterial drugs | clindamycin | 0 (0.0%) | 1 (1.3%) |
| Antibaterial drugs | cloxacillin | 1 (2.4%) | 1 (1.3%) |
| Antibaterial drugs | doxycycline | 0 (0.0%) | 1 (1.3%) |
| Antibaterial drugs | erythromycin | 1 (2.4%) | 1 (1.3%) |
| Antibaterial drugs | fluconazole | 1 (2.4%) | 0 (0.0%) |
| Antibaterial drugs | gentamicin | 3 (7.1%) | 3 (3.9%) |
| Antibaterial drugs | linezolid | 0 (0.0%) | 1 (1.3%) |
| Antibaterial drugs | meropenem | 3 (7.1%) | 2 (2.6%) |
| Antibaterial drugs | metronidazole | 1 (2.4%) | 0 (0.0%) |
| Antibaterial drugs | phenoxymethylpenicillin | 1 (2.4%) | 2 (2.6%) |
| Antibaterial drugs | piperacillin and beta-lactamase inhibitor | 3 (7.1%) | 4 (5.3%) |
| Antibaterial drugs | sulfamethoxazole and trimethoprim | 0 (0.0%) | 1 (1.3%) |
| Antibaterial drugs | vancomycin | 0 (0.0%) | 2 (2.6%) |
| Antiviral (not included in the study medication) | micafungin | 1 (2.4%) | 0 (0.0%) |
| Anti-fungal drugs | clotrimazole | 0 (0.0%) | 1 (1.3%) |
| Anti-fungal drugs | fluconazole | 1 (2.4%) | 0 (0.0%) |
| Anti-fungal drugs | nystatin | 0 (0.0%) | 1 (1.3%) |
| Anti-fungal drugs | terbinafine | 0 (0.0%) | 1 (1.3%) |
| Other | acetylcysteine | 2 (4.8%) | 0 (0.0%) |
| Other | acetylsalicylic acid | 3 (7.1%) | 10 (13.2%) |
| Other | albumin | 1 (2.4%) | 0 (0.0%) |
| Other | alendronic acid | 0 (0.0%) | 1 (1.3%) |
| Other | alfacalcidol | 0 (0.0%) | 1 (1.3%) |
| Other | alfentanil | 1 (2.4%) | 1 (1.3%) |
| Other | alginic acid | 0 (0.0%) | 1 (1.3%) |
| Other | alimemazine | 1 (2.4%) | 3 (3.9%) |
| Other | allopurinol | 2 (4.8%) | 1 (1.3%) |
| Other | amitriptyline | 0 (0.0%) | 1 (1.3%) |
| Other | amlodipine | 1 (2.4%) | 1 (1.3%) |
| Other | anakinra | 1 (2.4%) | 4 (5.3%) |
| Other | antithrombin III | 1 (2.4%) | 0 (0.0%) |
| Other | apixaban | 2 (4.8%) | 2 (2.6%) |
| Other | atorvastatin | 1 (2.4%) | 6 (7.9%) |
| Other | betamethasone | 0 (0.0%) | 1 (1.3%) |
| Other | bisoprolol | 1 (2.4%) | 1 (1.3%) |
| Other | brimonidine | 1 (2.4%) | 0 (0.0%) |
| Other | bumetanide | 0 (0.0%) | 1 (1.3%) |
| Other | calcium lactate gluconate | 0 (0.0%) | 1 (1.3%) |
| Other | canagliflozin | 0 (0.0%) | 1 (1.3%) |
| Other | candesartan | 1 (2.4%) | 2 (2.6%) |
| Other | candesartan and diuretics | 0 (0.0%) | 1 (1.3%) |
| Other | carbohydrates | 1 (2.4%) | 1 (1.3%) |
| Other | carvedilol | 1 (2.4%) | 0 (0.0%) |
| Other | cetirizine | 1 (2.4%) | 3 (3.9%) |
| Other | chloramphenicol | 0 (0.0%) | 1 (1.3%) |
| Other | clopidogrel | 0 (0.0%) | 1 (1.3%) |
| Other | codeine and paracetamol | 0 (0.0%) | 1 (1.3%) |
| Other | combinations | 2 (4.8%) | 0 (0.0%) |
| Other | dalteparin | 10 (23.8%) | 21 (27.6%) |
| Other | desloratadine | 0 (0.0%) | 2 (2.6%) |
| Other | dexamethasone | 9 (21.4%) | 14 (18.4%) |
| Other | dexmedetomidine | 1 (2.4%) | 2 (2.6%) |
| Other | diclofenac | 0 (0.0%) | 1 (1.3%) |
| Other | electrolytes | 2 (4.8%) | 1 (1.3%) |
| Other | empagliflozin | 1 (2.4%) | 0 (0.0%) |
| Other | enoxaparin | 6 (14.3%) | 12 (15.8%) |
| Other | escitalopram | 1 (2.4%) | 3 (3.9%) |
| Other | esomeprazole | 2 (4.8%) | 5 (6.6%) |
| Other | ethylmorphine | 2 (4.8%) | 0 (0.0%) |
| Other | ezetimibe | 0 (0.0%) | 1 (1.3%) |
| Other | ferrous sulfate | 1 (2.4%) | 0 (0.0%) |
| Other | folic acid | 0 (0.0%) | 1 (1.3%) |
| Other | formoterol and beclometasone | 1 (2.4%) | 0 (0.0%) |
| Other | formoterol and budesonide | 1 (2.4%) | 0 (0.0%) |
| Other | furosemide | 4 (9.5%) | 3 (3.9%) |
| Other | glimepiride | 1 (2.4%) | 1 (1.3%) |
| Other | glyceryl trinitrate | 0 (0.0%) | 1 (1.3%) |
| Other | haloperidol | 0 (0.0%) | 1 (1.3%) |
| Other | heparin | 1 (2.4%) | 0 (0.0%) |
| Other | ibuprofen | 3 (7.1%) | 4 (5.3%) |
| Other | insulin (human) | 1 (2.4%) | 1 (1.3%) |
| Other | insulin aspart | 2 (4.8%) | 0 (0.0%) |
| Other | insulin degludec | 1 (2.4%) | 0 (0.0%) |
| Other | insulin lispro | 0 (0.0%) | 1 (1.3%) |
| Other | ipratropium bromide | 2 (4.8%) | 2 (2.6%) |
| Other | irbesartan | 1 (2.4%) | 0 (0.0%) |
| Other | ketamine | 0 (0.0%) | 1 (1.3%) |
| Other | ketobemidone | 1 (2.4%) | 0 (0.0%) |
| Other | lactulose | 2 (4.8%) | 2 (2.6%) |
| Other | lercanidipine | 0 (0.0%) | 2 (2.6%) |
| Other | levodopa and decarboxylase inhibitor | 0 (0.0%) | 1 (1.3%) |
| Other | levothyroxine sodium | 2 (4.8%) | 3 (3.9%) |
| Other | linagliptin | 1 (2.4%) | 0 (0.0%) |
| Other | losartan and diuretics | 3 (7.1%) | 1 (1.3%) |
| Other | macrogol, combinations | 0 (0.0%) | 1 (1.3%) |
| Other | melatonin | 0 (0.0%) | 4 (5.3%) |
| Other | mesalazine | 1 (2.4%) | 1 (1.3%) |
| Other | metformin | 5 (11.9%) | 7 (9.2%) |
| Other | methotrexate | 0 (0.0%) | 1 (1.3%) |
| Other | methylnaltrexone bromide | 1 (2.4%) | 1 (1.3%) |
| Other | metoclopramide | 6 (14.3%) | 6 (7.9%) |
| Other | metoprolol | 1 (2.4%) | 5 (6.6%) |
| Other | midazolam | 1 (2.4%) | 1 (1.3%) |
| Other | mirabegron | 0 (0.0%) | 1 (1.3%) |
| Other | mirtazapine | 0 (0.0%) | 1 (1.3%) |
| Other | montelukast | 0 (0.0%) | 1 (1.3%) |
| Other | morphine | 1 (2.4%) | 2 (2.6%) |
| Other | multienzymes (lipase, protease etc.) | 0 (0.0%) | 1 (1.3%) |
| Other | neostigmine, combinations | 0 (0.0%) | 1 (1.3%) |
| Other | nifedipine | 0 (0.0%) | 1 (1.3%) |
| Other | norepinephrine | 1 (2.4%) | 1 (1.3%) |
| Other | norethisterone and estrogen | 0 (0.0%) | 1 (1.3%) |
| Other | olanzapine | 0 (0.0%) | 1 (1.3%) |
| Other | ondansetron | 2 (4.8%) | 2 (2.6%) |
| Other | oxazepam | 0 (0.0%) | 5 (6.6%) |
| Other | oxycodone | 0 (0.0%) | 1 (1.3%) |
| Other | oxycodone and naloxone | 0 (0.0%) | 1 (1.3%) |
| Other | pantoprazole | 5 (11.9%) | 13 (17.1%) |
| Other | paracetamol | 9 (21.4%) | 17 (22.4%) |
| Other | phenylephrine | 1 (2.4%) | 0 (0.0%) |
| Other | piroxicam | 0 (0.0%) | 1 (1.3%) |
| Other | potassium chloride | 1 (2.4%) | 4 (5.3%) |
| Other | potassium citrate | 2 (4.8%) | 2 (2.6%) |
| Other | prednisolone | 1 (2.4%) | 5 (6.6%) |
| Other | propofol | 1 (2.4%) | 1 (1.3%) |
| Other | quetiapine | 1 (2.4%) | 0 (0.0%) |
| Other | ramipril | 1 (2.4%) | 1 (1.3%) |
| Other | rivaroxaban | 1 (2.4%) | 1 (1.3%) |
| Other | rocuronium bromide | 1 (2.4%) | 0 (0.0%) |
| Other | salbutamol | 5 (11.9%) | 3 (3.9%) |
| Other | salmeterol and fluticasone | 1 (2.4%) | 1 (1.3%) |
| Other | saxagliptin | 0 (0.0%) | 1 (1.3%) |
| Other | simvastatin | 4 (9.5%) | 3 (3.9%) |
| Other | sodium chloride | 3 (7.1%) | 3 (3.9%) |
| Other | sodium picosulfate | 1 (2.4%) | 3 (3.9%) |
| Other | spironolactone | 1 (2.4%) | 0 (0.0%) |
| Other | sumatriptan | 0 (0.0%) | 1 (1.3%) |
| Other | tamsulosin | 0 (0.0%) | 1 (1.3%) |
| Other | timolol | 1 (2.4%) | 0 (0.0%) |
| Other | timolol, combinations | 1 (2.4%) | 0 (0.0%) |
| Other | tiotropium bromide | 0 (0.0%) | 1 (1.3%) |
| Other | tramadol | 1 (2.4%) | 2 (2.6%) |
| Other | valsartan | 1 (2.4%) | 2 (2.6%) |
| Other | valsartan and amlodipine | 0 (0.0%) | 1 (1.3%) |
| Other | valsartan, amlodipine and hydrochlorothiazide | 1 (2.4%) | 2 (2.6%) |
| Other | vecuronium | 1 (2.4%) | 1 (1.3%) |
| Other | venlafaxine | 0 (0.0%) | 1 (1.3%) |
| Other | verapamil | 1 (2.4%) | 0 (0.0%) |
| Other | zolpidem | 0 (0.0%) | 2 (2.6%) |
| Other | zopiclone | 1 (2.4%) | 5 (6.6%) |
| Other | NA | 5 (11.9%) | 8 (10.5%) |
| NA | NA | 9 (21.4%) | 21 (27.6%) |

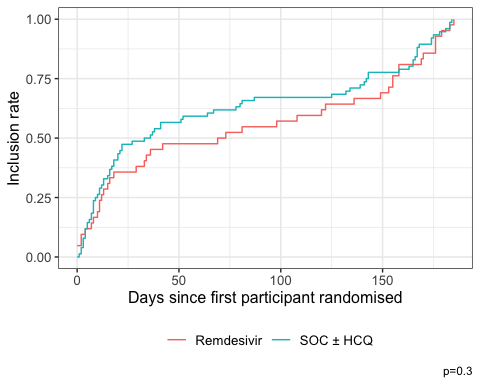
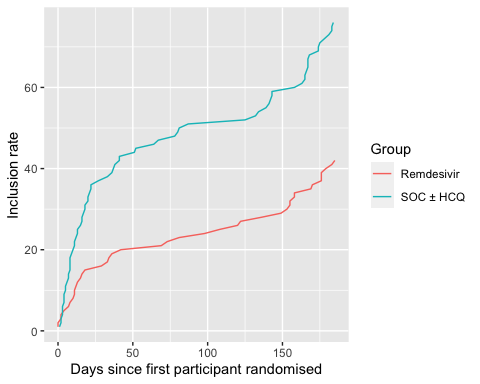
## Ref 2 Comment 3

* recruitment occured from March to October 2020, a period during which, there has been a lot a change in the way patients were cared for in terms of oxygenotherapy, cointerventions etc.) Because the trial is small, it is not excluded that there may be imabalance in terms of periods of inclusion. Can you check the balance in terms of period of inclusion in the two arms ?

Plot Kaplan-Meier plot of the inclusion

The slight difference seen is due to the 1:1:1 between HCQ:Remdesivir:SoC the first 40 days after remdesivir was available. This lead to a 2:1 randomisation between the two groups in this period. Between day 40 and the end the randomisation was 1:1 between Remdesivir and SoC.

## Don't know how to automatically pick scale for object of type <difftime>.  
## Defaulting to continuous.



## Ref 2 Comment 4

Analysis is on full analysis set. I suggest to add Intent to treat. It is also mandatory to report the number of patients randomized without at least one post-randomisation observation to understand how different was the sample was.

## `summarise()` has grouped output by 'ranavail\_rem', 'fas'. You can override  
## using the `.groups` argument.

## # A tibble: 8 × 4  
## # Groups: ranavail\_rem, fas [3]  
## ranavail\_rem fas rantrt n  
## <ord> <ord> <ord> <int>  
## 1 No Yes Standard of care (SOC) 30  
## 2 No Yes Hydroxychloroquine + SOC 33  
## 3 Yes No Standard of care (SOC) 1  
## 4 Yes No Hydroxychloroquine + SOC 2  
## 5 Yes No Remdesivir + SOC 1  
## 6 Yes Yes Standard of care (SOC) 57  
## 7 Yes Yes Hydroxychloroquine + SOC 19  
## 8 Yes Yes Remdesivir + SOC 42

So, 122 was randomised, and 4 were excluded from the full analysis set due to no post-randomisation observations.