Remdesivir for Severe COVID-19 versus a Cohort Receiving Standard of Care.

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Remdesivir for Severe COVID-19 versus a Cohort Receiving Standard of Care

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**Summary**

In this comparative analysis, remdesivir was associated with significantly lower mortality and higher recovery than standard-of-care treatment without remdesivir in patients with severe COVID-19. Ongoing studies will further determine the utility of remdesivir for the treatment of severe COVID-19.

**Trial registration details:** ClinicalTrials.gov NCT04292899 and EUPAS34303
Abstract

**Background:** We compared the efficacy of the antiviral agent, remdesivir, versus standard-of-care treatment in adults with severe COVID-19 using data from a phase 3 remdesivir trial and a retrospective cohort of patients with severe COVID-19 treated with standard-of-care.

**Methods:** GS-US-540-5773 is an ongoing phase 3, randomized, open-label trial comparing two courses of remdesivir (remdesivir-cohort). GS-US-540-5807 is an ongoing real-world, retrospective cohort study of clinical outcomes in patients receiving standard-of-care treatment (non-remdesivir-cohort). Inclusion criteria were similar between studies: patients had confirmed SARS-CoV-2 infection, were hospitalized, had oxygen saturation 94% or lower on room air or required supplemental oxygen, and had pulmonary infiltrates. Stabilized inverse probability of treatment weighted multivariable logistic regression was used to estimate the treatment effect of remdesivir versus standard-of-care. The primary endpoint was the proportion of patients with recovery on day 14, dichotomized from a 7-point clinical status ordinal scale. A key secondary endpoint was mortality.

**Results:** After the inverse probability of treatment weighting procedure 312 and 818 patients were counted in the remdesivir- and non-remdesivir-cohorts, respectively. At day 14, 74.4% of patients in the remdesivir-cohort had recovered versus 59.0% in the non-remdesivir-cohort (adjusted odds ratio 2.03: 95% confidence interval 1.34–3.08, p<0.001). At day 14, 7.6% of patients in the remdesivir-cohort had died versus 12.5% in the non-remdesivir-cohort (adjusted odds ratio 0.38, 95% confidence interval: 0.22–0.68, p=0.001).
Conclusions: In this comparative analysis, by day 14, remdesivir was associated with significantly greater recovery and 62% reduced odds of death versus standard-of-care treatment in patients with severe COVID-19.

Key words

SARS-CoV-2, severe COVID-19, remdesivir, antiviral treatment
Introduction

Coronavirus disease 2019 (COVID-19) is a major global public health and socioeconomic crisis, with over 4 million cases identified worldwide and more than 300,000 deaths (as of May 15, 2020) [1]. As a result, considerable international efforts are underway to find effective treatments involving multiple possible mechanisms. No therapy is fully approved for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Remdesivir, a prodrug of an adenosine analogue that inhibits viral RNA dependent RNA polymerase [2], was recently granted Emergency Use Authorization by the US Food and Drug Administration [3]. Remdesivir has in vitro activity against SARS-CoV-2 [4, 5], and early clinical data suggest promise as a treatment for COVID-19 [6-8]. Preliminary reported findings from the randomized National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial indicated benefits of a 10-day course of remdesivir versus placebo, including significantly faster (32%) recovery time and numerically lower mortality [8]. Additionally, an open-label, randomized clinical trial (GS-US-540-5773) comparing two remdesivir courses demonstrated that outcomes of 5-day and 10-day regimens of remdesivir were not significantly different and had acceptable safety [7]. While a randomized study in China failed to demonstrate statistically significant clinical benefit of remdesivir [9], the study was underpowered because of lack of enrollment and early study closure due to local disease control [10]. Although additional comparative trials are ongoing, data comparing remdesivir to standard-of-care remain limited.

We compared the efficacy of remdesivir, using data from the prospective GS-US-540-5773 randomized trial to a concurrent, retrospective cohort of patients with severe COVID-19 not treated with remdesivir using the stabilized inverse probability of treatment weighting (IPTW) method.
Methods

Study design

We compared interim data from two ongoing studies. First, a phase 3, randomized, open-label study comparing two doses of intravenous remdesivir in patients with severe COVID-19 (NCT04292899/GS-US-540-5773 [hereafter Study 5773]) was conducted at 45 sites in USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan [7]. The first patient visit for this study was March 9, 2020. The planned analysis cut-off date was April 10, 2020; an extension is ongoing. Patients were randomized 1:1 to receive: standard-of-care treatment (subject to clinical practice stipulated by individual sites) plus remdesivir 200mg on day 1, followed by remdesivir 100mg daily on days 2–5; or standard-of-care plus remdesivir 200mg on day 1, followed by remdesivir 100mg daily on days 2–10 (remdesivir-cohort). Since safety and efficacy were not significantly different between doses [7], data from both arms were combined for the present analysis. Study 5773 was approved by the institutional review board or independent ethics committee at each participating site and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization–Good Clinical Practice guidelines. All patients provided written informed consent.

The second study is a real-world, retrospective, longitudinal cohort study of clinical outcomes in adults with severe COVID-19 (EUPAS34303/GS-US-540-5807 [hereafter Study 5807]) conducted at 16 sites in USA, UK, Belgium, Singapore, and South Korea. The first hospitalization occurred on February 6, 2020 with an interim analysis cut-off of April 10, 2020. Patients received standard-of-care treatment according to local clinical practice at that time (non-remdesivir-cohort). This study was developed to align with Study 5773 in terms of study design, patient eligibility, and outcomes. Study 5807 complies with Good Pharmacoepidemiology Practice and Good Pharmacovigilance Practice.
Patients

Detailed methods for Study 5773 have been reported [7]. Briefly, hospitalized patients included in the interim analysis were at least 18 years of age with SARS-CoV-2 infection confirmed by polymerase chain reaction. Patients had oxygen saturation (SpO₂) of ≤94% on room air or required supplemental oxygen, and all had radiographic evidence of pulmonary infiltrates. Patients were excluded if they were receiving medications that may potentially treat COVID-19 (see Supplementary Digital Content 6) at entry but some received these treatments during the study. Patients on mechanical ventilation at screening were excluded; however, 13 patients who required ventilation between screening and the start of remdesivir treatment were included.

Study 5807 inclusion criteria were designed to align with those of Study 5773. Patients were 18 years of age or older with SARS-CoV-2 infection confirmed by polymerase chain reaction. Patients were hospitalized, with SpO₂ of ≤94% on room air or required supplemental oxygen, with radiographic evidence of pulmonary infiltrates, and did not receive remdesivir. Exclusion criteria were retroactively applied to Study 5807 to ensure the two study populations were comparable. These exclusions were: veno-arterial extracorporeal membrane oxygenation on day 1; alanine transferase or aspartate transferase greater than 5 times the upper limit of normal; creatinine clearance less than 50 mL/min using the Cockcroft-Gault formula at day 1; and being pregnant or breastfeeding. Patients were allowed to receive medications that may potentially treat COVID-19, excluding remdesivir.
Endpoints and assessments

Study 5773 individual study endpoints and assessments have been reported [7]. In Study 5807, the co-primary endpoints are clinical status assessed by a 7-point ordinal scale on day 14 (1 = death, 7 = discharged alive; Table 1) and all-cause mortality at day 28, which were not assessed in this interim analysis. Other endpoints, assessments, and data abstraction/management are detailed in Supplementary Digital Content 2.

Interim data from Study 5773 and Study 5807, reported herein, were compared in a pre-specified analysis, with a focus on efficacy alone. The primary endpoint in this planned interim analysis was recovery on day 14, based on the 7-point ordinal scale: improvement to a score of 5 to 7 for baseline of 2-4, 6 or 7 for baseline score of 5, and 7 for baseline score of 6 (Table 1; see Supplementary Digital Content 2 for rationale for selecting this endpoint). Secondary endpoints of the interim analysis include death at day 14; clinical improvement on day 14 (2-point improvement in score or discharged alive); and 1-point or more improvement in clinical status on day 14.

Safety analyses for Study 5773 have been described [7]. Safety data were not collected for Study 5807.

Statistical analysis

The planned sample size of Study 5773 was 400 patients [7]. As data for Study 5807 were collected concurrently with Study 5773 enrollment, and the remdesivir-cohort disease characteristics were unknown, we originally planned to identify up to 2,000 eligible patients in Study 5807 to have a sufficient sample for analyses based on propensity score. The full analysis set for the comparison included all eligible patients enrolled from study start to cut-off date in both studies, with their propensity scores within the common support region of both treatment cohorts. Included patients
from Study 5773 also had to receive at least one dose of remdesivir; additional exclusion criteria were retroactively applied to Study 5807 (as described above). Patients from Italian sites in Study 5773 were excluded, an a priori decision based on lack of comparative patients in Study 5807 and given differences in mortality outcomes seen in Italy compared to other sites (see Supplemental Digital Content 4 for rationale). In Study 5773 and Study 5807, day 1 was defined as randomization and hospital admission, respectively.

Since the two cohorts were from two different studies and were not randomized, imbalance in baseline characteristics may have existed that could confound the interpretation of a potential treatment effect of remdesivir. To approximate a randomized clinical trial and reduce selection bias, propensity score methods that aim to make treated and untreated groups as comparable as possible were used. The propensity score is defined as the probability of treatment assignment conditional on the observed baseline characteristics and was calculated using a logistic regression model with treatment assignment (remdesivir versus no remdesivir) as the dependent variable and the following observed baseline characteristics as the independent variables: age, gender, race, region (US, Ex-US), obesity, medical history (yes versus no for hypertension, cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and asthma), medications used to treat COVID-19, and baseline clinical status (7-point ordinal scale).

As the study objective was to estimate the treatment effect of remdesivir versus standard-of-care on the entire study population, a weighted analysis was adopted over a matched approach to minimize losses in sample size (and thus statistical power). Under the average treatment effect framework, the stabilized IPTW method was used after trimming the patients in either cohort whose propensity scores fell out of the common support region of the propensity score distribution. The sample created using IPTW assumes that the distribution of baseline characteristics is independent of treatment assignment in order to yield the average treatment effect [11]. Balance was verified by assessing various metrics including the absolute standardized differences of the independent
variables included in the model to estimate the propensity score. Hydroxychloroquine was widely used to treat COVID-19 in the US starting in March 2020. Since hydroxychloroquine use was discouraged in Study 5773, hydroxychloroquine use was not balanced between the two cohorts before weighting. The addition of hydroxychloroquine to the IPTW resulted in further imbalance in other prognostic factors, especially the baseline clinical status, which suggests that the treatment decision of hydroxychloroquine was made differently in the two cohorts. We performed the primary analysis excluding hydroxychloroquine from the propensity score and confirmed the robustness of the primary analysis with a sensitivity analysis including hydroxychloroquine in the propensity score.

The proportion of patients with recovery on day 14 was analyzed through a multivariable logistic regression model using IPTW weighted likelihood, including treatment group as the independent variable and all the baseline factors in the aforementioned propensity score calculation model as covariates. Moreover, stepwise model selection was performed with nonsignificant covariates removed from the final weighted logistic regression model. Hydroxychloroquine was included in both primary and sensitivity weighted logistic regression models.

Secondary endpoints were analyzed in the same way as the primary endpoint.

If an ongoing hospitalized patient (alive and not discharged) or a patient discharged or transferred to hospice or another facility had a missing clinical status at a visit, the last available post-baseline clinical status before the visit with a missing value was used for that visit. All other analyses were based on complete cases analysis. SAS® Version 9.4 (SAS Institute Inc., Cary, NC) was used.
Results

Study population

Of 397 patients who received remdesivir in Study 5773, 298 were included in this analysis (remdesivir-cohort), while 816 were included from Study 5807 (non-remdesivir-cohort) (Figure 1). After applying the IPTW method, as expected, modest changes in the apparent sample size were noted [12], and 312 and 818 patients were analyzed in the remdesivir- and non-remdesivir-cohorts, respectively. All outcomes are reported for this weighted analysis group [see Supplemental Digital Content 7 for further explanation of weighting methods].

Table 2 summarizes baseline demographics, disease characteristics, and concomitant medications for COVID-19 before and after applying IPTW. Baseline characteristics were balanced between the two cohorts after weighting for the factors included in the propensity score model described in the statistical analysis section (see Supplemental Digital Content 5). However, since hydroxychloroquine was not included in the propensity weighting (see statistical methods), imbalance was present even after weighting.

Recovery and improvement

At day 14, after IPTW, 74.4% of patients in the remdesivir-cohort versus 59.0% in the non-remdesivir-cohort reached the primary recovery endpoint (Figure 2A). In the weighted multivariable logistic regression model, the adjusted odds of recovery for the remdesivir-cohort was 2.03-fold higher than for the non-remdesivir-cohort (95% confidence interval: 1.34–3.08, p<0.001). Additionally, greater 14-day recovery was associated with younger age, female sex, higher baseline ordinal scale (less need for high-flow or invasive oxygen), not having hypertension and not receiving a biologic agent or hydroxychloroquine (Table 3). Results of the sensitivity analysis that included
hydroxychloroquine in the propensity score yielded similar results (odds ratio 1.68, 95% confidence interval 1.2-2.2, p=0.002), despite the further imbalance in other baseline prognostic factors (see Supplemental Digital Content 5, Figure B).

An improvement in clinical status of at least 2-points (or being discharged alive) at day 14 was seen in 71.9% and 58.8% of weighted patients in the remdesivir- and non-remdesivir-cohorts, respectively (adjusted odds ratio 1.64; 95% confidence interval: 1.10–2.43; p=0.01). A clinical status improvement of at least 1-point at day 14 was seen in 76.2% and 60.2% of weighted patients in the remdesivir- and non-remdesivir-cohorts, respectively (adjusted odds ratio 2.04; 95% confidence interval: 1.37–3.05; p<0.001).
Mortality

Up to day 14, the weighted mortality in the remdesivir-cohort versus the non-remdesivir-cohort was 7.6% versus 12.5%, respectively (Figure 2B). In the weighted multivariable logistic regression model, receipt of remdesivir was associated with a 62% lower adjusted odds of death (odds ratio 0.38, 95% confidence interval: 0.22–0.68, p=0.001). Additionally, lower mortality was associated with younger age, being white versus black/African American, higher baseline ordinal scale (less need for oxygen or invasive oxygen) and the absence of prior cardiovascular disease or chronic obstructive pulmonary disease. Results of the sensitivity analysis that included hydroxychloroquine in the propensity score yielded similar results (odds ratio of death 0.34, 95% confidence interval 0.19-0.62, p<0.001).

Discussion

There is an urgent need for effective treatments for severe COVID-19, which is associated with high mortality (estimates ranging from 8–28%) [13, 14]. Building on the promising in vitro and preclinical activity of remdesivir [4-6], and given that other placebo-controlled studies were planned or underway, Study 5773 was designed to provide severely ill patients with access to remdesivir and to determine the optimal treatment duration [7]. In the absence of a comparator arm, Study 5807 was designed to provide a synthetic control group by retrospectively collecting data from contemporaneously hospitalized patients with severe COVID-19, treated per local standard-of-care, using enrollment criteria similar to those of Study 5773. The comparison of remdesivir-treated patients with non-remdesivir-treated patients used robust statistical methodologies appropriate for non-randomized cohort studies.
In our analysis, after IPTW, 74.4% of patients in the remdesivir-cohort versus 59.0% in the non-remdesivir-cohort achieved the primary recovery endpoint at day 14, reflecting a two-fold higher adjusted odds of recovery. Significantly lower mortality was also observed in those treated with remdesivir compared with the non-remdesivir-cohort patients: 7.6% versus 12.5%, respectively, with 62% lower adjusted odds of all-cause death. This is the second study to demonstrate the potential benefit of remdesivir versus a comparator for SARS-CoV-2-infected patients with severe disease and the first to demonstrate a significant reduction in mortality. Consistent with our findings, preliminary data from the randomized NIAID Adaptive COVID-19 Treatment Trial also found that remdesivir had faster time to recovery versus placebo [8].

Our results are highly encouraging since studies of other antiviral agents have shown limited benefit, lacked a comparator, or observed significant toxicity [15-21]. In the one comparative study published to date, 199 patients with severe COVID-19 were randomized to receive lopinavir-ritonavir or standard care, with no significant benefit in recovery or mortality demonstrated [20].

The methodology used for our comparative study has several strengths that contribute to the robustness of the efficacy results. Data for remdesivir-treated patients came from Study 5773, a large, multicentre phase 3 trial, and information abstracted from Study 5807 included rigorously collected, detailed, patient-level data (including patient oxygenation status and support, vital signs, laboratory and radiology findings) that underwent thorough cleaning and review. Propensity score weighting balanced known factors associated with poor COVID-19 prognosis, and final models included all significant factors potentially associated with outcomes. Both studies ran in parallel, in an attempt to avoid confounding due to evolving or changing standards of care as the pandemic progressed. Finally, our population is broadly representative of the wider population with severe COVID-19 with respect to age, sex, and comorbidities, based on data from several other studies [6, 21-24].
There are also limitations of this analysis. Most importantly, the comparison was not randomized, and although all efforts were made to balance the cohorts for known factors associated with poor COVID-19 prognosis using IPTW and multivariable regression, there may be some factors that could not be well balanced as a result of inherent differences in care between centers. Imbalance was notable in the use of hydroxychloroquine, before and after IPTW (Table 2). The imbalance is not unexpected, as we did not include hydroxychloroquine in the propensity score model due to the reasons mentioned earlier. Instead, hydroxychloroquine was adjusted for in the final weighted logistic regression analysis; we found improved recovery was associated with remdesivir use after adjustments. We also performed a sensitivity analysis, including hydroxychloroquine in the propensity score calculation, which yielded better balance in hydroxychloroquine use, but imbalance in other important factors (see Supplemental Digital Content 5, Figure B). Adjustment for these factors yielded risk estimates for recovery and mortality that were concordant with those of the primary analysis. It is important to note that our comparative cohort analysis was not designed to evaluate the independent effect of hydroxychloroquine, which was associated with higher in-hospital mortality in a recent observational analysis [25].

Similarly, in either study, there may be confounding factors for COVID-19 prognosis, as yet unknown, such as the impact of other therapies that were unaccounted for and socioeconomic status. The open-label design of Study 5773 also introduces the possibility of bias between the two arms, although multivariable models showed no significant difference in outcomes between the 5 and 10-day remdesivir dosing durations. Since some patients in the remdesivir-cohort did receive other potential COVID-19 treatments, this was not a direct comparison of remdesivir versus standard care. However, use of other medications was adjusted for in the multivariable models to capture the independent effect of remdesivir. Finally, as clinicians caring for patients in the remdesivir cohort (study 5773) knew their patients were receiving an antiviral with potential activity against SARS-CoV-2, while clinicians in the non-remdesivir cohort (study 5807) did not have access to a potentially
active agent, clinicians in study 5807 may have used experimental agents that may have limited benefit and potentially be harmful.

Study 5773 and Study 5807 are ongoing. Analysis of the results of the comparative analysis with the full cohort, including Italian sites, is planned. Study 5807 ultimately aims to enroll up to 3,500 patients and 50 centers globally, providing a baseline for comparison against other potential future treatments.

In conclusion, remdesivir treatment was associated with significantly higher recovery rates and lower mortality than standard-of-care treatment without remdesivir in patients with severe COVID-19. The results are concordant with preliminary data from the NIAID randomized Adaptive COVID-19 Treatment Trial [8]. Ongoing studies and real-world data will further determine the optimal role of remdesivir for the treatment of COVID-19.
NOTES

Contributors

Susan A. Olender, Katherine K. Perez, Alan S. Go, Bindu Balani, Eboni G. Price-Haywood, Nirav S. Shah, Su Wang, Theresa L. Walunas, Shobha Swaminathan, Jihad Slim, BumSik Chin, Stéphane De Wit, Shamim M. Ali, Alex Soriano Viladomiu, Philip Robinson, Robert L. Gottlieb, Tak Yin Owen Tsang and Jose I Bernardino acquired the study data. I-Heng Lee, Hao Hu, Richard H. Haubrich, Anand P. Chokkalingam, Lanjia Lin, Lijie Zhong, B. Nebiyou Bekele, Robertino Mera-Giler, Chloé Phulpin, Holly Edgar, Joel Gallant, Helena Diaz-Cuervo, Lindsey E. Smith, Anu O. Osinusi, Diana M. Brainard conceived and designed the study and analyzed the data. All authors interpreted the data, were involved with drafting or critical revisions of the manuscript, and provided approval of the final manuscript for submission.

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We dedicate this work to those that are or have been ill with COVID-19 and the memory of health care workers who have given their lives in the care of these patients.

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Gilead Sciences makes available anonymized individual patient data upon request or as required by law or regulation with external researchers. Approval of such requests is at Gilead Sciences’s discretion and is dependent on the nature of the request, the merit of the research proposed, the
availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com. Data from GS-US-540-5807 can only be provided with each participating Institution’s prior written consent.

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Conflict of interests

References


Tables

Table 1: Ordinal scale of clinical status and definition of recovery

Recovery was defined as having a score of 5–7 points for patients with a baseline score of 2–4, or a score of 6–7 for patients with a baseline score of 5, or a score of 7 for patients with a baseline score of 6.

<table>
<thead>
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<th>Score</th>
<th>Status</th>
<th>Status score at baseline</th>
<th>Recovery score required at day 14</th>
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<tr>
<td>1</td>
<td>Death</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Hospitalized, on invasive mechanical ventilation or ECMO</td>
<td>2</td>
<td>5–7</td>
</tr>
<tr>
<td>3</td>
<td>Hospitalized, on non-invasive ventilation or high-flow oxygen devices</td>
<td>3</td>
<td>5–7</td>
</tr>
<tr>
<td>4</td>
<td>Hospitalized, requiring low-flow supplemental oxygen</td>
<td>4</td>
<td>5–7</td>
</tr>
<tr>
<td>5</td>
<td>Hospitalized, not requiring supplemental oxygen (i.e. breathing room air), but requiring ongoing medical care</td>
<td>5</td>
<td>6–7</td>
</tr>
<tr>
<td>6</td>
<td>Hospitalized, not requiring supplemental oxygen (i.e. breathing room air) or ongoing medical care</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>Not hospitalised</td>
<td>NA</td>
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ECMO, extracorporeal membrane oxygenation; NA, not applicable
Table 2. Demographics and baseline disease characteristics, before and after stabilized inverse probability of treatment weighting

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<th>Cohort before inverse probability weighting</th>
<th>Cohort after inverse probability weighting****</th>
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<td>Non-remdesivir-cohort (N=816)</td>
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<td>Age, %</td>
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**** Stabilized inverse probability of treatment weighting
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America (USA)</td>
<td>76</td>
<td>95</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>Europe*</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Asia*</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$), median (IQR)</td>
<td>29 (25, 34)</td>
<td>31 (27, 36)</td>
<td>31(26, 35)</td>
<td>31 (27, 35)</td>
</tr>
<tr>
<td>Most common coexisting conditions, ** %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>51</td>
<td>46</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>Cancer</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25</td>
<td>26</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>30</td>
<td>17</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Asthma</td>
<td>14</td>
<td>11</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Immunologic disease</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5</td>
<td>6</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>9</td>
<td>5</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Baseline clinical status on the 7-point scale, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 4</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>2 – on invasive mechanical ventilation or ECMO</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>3 – on non-invasive ventilation or high-flow oxygen</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>4 – on low-flow supplemental oxygen</td>
<td>63</td>
<td>60</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>5 – not on supplemental oxygen, requiring medical care</td>
<td>16</td>
<td>21</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>6 – no medical care needed</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Medications potentially active against SARS-CoV-2,** **%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>39</td>
<td>19</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Hydroxychloroquine group</td>
<td>17</td>
<td>75</td>
<td>15</td>
<td>72</td>
</tr>
<tr>
<td>HIV protease inhibitor</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Biologics</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Duration of symptoms before baseline, median (IQR), days</td>
<td>8 (5, 11)</td>
<td>7 (4, 8)</td>
<td>8 (6, 11)</td>
<td>7 (4, 8)</td>
</tr>
<tr>
<td>Initial AST (U/litre), median (IQR)</td>
<td>43 (31, 63)</td>
<td>43 (32, 62)</td>
<td>47 (34, 66)</td>
<td>41 (31, 60)</td>
</tr>
<tr>
<td>Initial ALT (U/litre), median (IQR)</td>
<td>33 (21, 57)</td>
<td>33 (22, 51)</td>
<td>36 (22, 65)</td>
<td>32 (21, 49)</td>
</tr>
<tr>
<td>Initial Estimated glomerular filtration rate by Cockcroft-Gault (mL/min, median (interquartile range))</td>
<td>104 (79, 140)</td>
<td>97 (73, 131)</td>
<td>112 (82, 145)</td>
<td>94 (72, 129)</td>
</tr>
</tbody>
</table>
*European countries included: Germany, Spain, Belgium, and United Kingdom; Asian countries included: Hong Kong, Republic of Korea, Singapore, and Taiwan.

**Conditions with more than 5% incidence are reported. Immunologic diseases included rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus.

***Hydroxychloroquine group included aminoquinolines, chloroquine, hydroxychloroquine, and hydroxychloroquine sulfate; biologics included interferons, investigational biologics, plasma, sarilumab, siltuximab, and tocilizumab.

****Patient numbers are modified based on inverse probability treatment weighting procedures. Percentages provided for the weighted groups may not add to 100% due to rounding. Variables included in the weighting include age, gender, race, region (US, Ex-US), obesity, medical history (yes versus no for hypertension, cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma and immunologic disease), medications used to treat COVID-19, and baseline clinical status (7-point ordinal scale).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECMO, extracorporeal membrane oxygenation
Table 3: Odds ratio of recovery and all-cause death at day 14 from weighted logistic regression model using all variables used for propensity scores (stepwise model selection)

<table>
<thead>
<tr>
<th>Variable (reference category)</th>
<th>Odds ratio of recovery at day 14</th>
<th>Odds ratio 95% confidence interval</th>
<th>P value</th>
<th>Odds ratio of death at day 14</th>
<th>Odds ratio 95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir treatment (no remdesivir)</td>
<td>2.03</td>
<td>1.34–3.08</td>
<td>&lt;0.001</td>
<td>0.38</td>
<td>0.22–0.68</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, years (65 or older)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>6.61</td>
<td>3.46–12.61</td>
<td>&lt;0.001</td>
<td>0.27</td>
<td>0.11–0.68</td>
<td>0.005</td>
</tr>
<tr>
<td>40–64</td>
<td>2.28</td>
<td>1.67–3.13</td>
<td>&lt;0.001</td>
<td>0.33</td>
<td>0.21–0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male (female)</td>
<td>0.67</td>
<td>0.49–0.91</td>
<td>0.01</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Race (White)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian race</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.92</td>
<td>0.89–4.15</td>
<td>0.10</td>
</tr>
<tr>
<td>Black or African</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.37</td>
<td>1.37–4.10</td>
<td>0.002</td>
</tr>
<tr>
<td>Other</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.77</td>
<td>0.99–3.16</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline Ordinal Scale (score of 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-invasive ventilation</td>
<td>0.02</td>
<td>0.01–0.05</td>
<td>&lt;0.001</td>
<td>9.39</td>
<td>4.30–20.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medications potentially active against SARS-CoV-2 (not received agent)*</td>
<td>3-high-flow oxygen</td>
<td>4-low-flow oxygen</td>
<td>5-high-flow oxygen</td>
<td>6-low-flow oxygen</td>
<td>7-high-flow oxygen</td>
<td>8-low-flow oxygen</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Received biologic agent</td>
<td>0.08</td>
<td>0.05–0.14</td>
<td>&lt;0.001</td>
<td>5.11</td>
<td>2.57–10.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Received hydroxychloroquine group</td>
<td>0.81</td>
<td>0.54–1.20</td>
<td>0.29</td>
<td>0.72</td>
<td>0.37–1.40</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Coexisting conditions (no condition present)

<table>
<thead>
<tr>
<th></th>
<th>3-high-flow oxygen</th>
<th>4-low-flow oxygen</th>
<th>5-high-flow oxygen</th>
<th>6-low-flow oxygen</th>
<th>7-high-flow oxygen</th>
<th>8-low-flow oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.23</td>
<td>1.40–3.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.06</td>
<td>1.63–5.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.70</td>
<td>0.51–0.95</td>
<td>0.02</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Hydroxychloroquine group included aminoquinolines, chloroquine, hydroxychloroquine, and hydroxychloroquine sulfate; biologics included interferons, investigational biologics, plasma, sarilumab, siltuximab, and tocilizumab.

NA, not applicable. After stepwise model selection, these variables were not significant and removed from the final weighted logistic regression model.
Figure legends

Figure 1. Study population

* Based on IPTW, the number of patients in remdesivir and non-remdesivir cohorts were modestly different from the original sample size (some patients weighted more, and some patients weighted less based on the patients’ propensity scores).

IPTW, stabilized inverse probability of treatment weighting method; OSA, ordinal scale assessment.

Figure 2. Proportion (95% confidence interval) of patients at day 14 in the remdesivir-cohort and non-remdesivir-cohort with: (A) recovery, based on the 7-point ordinal scale* and (B) mortality** (after stabilized inverse probability of treatment weighting).

*Recovery was defined as baseline score of 2-4 improved to 5-7, or baseline score of 5 improved to 6-7, or baseline score of 6 improved to 7. P-values, odds ratios between treatment groups and its 95% confidence interval were from the weighted logistic regression model with all baseline factors included in the model as covariates. After stepwise model selection insignificant baseline factors removed from the final model. The final model for day 14 included age, gender, baseline ordinal scale, hypertension, COVID-19 antiviral medications within the biologic and hydroxychloroquine groups.

**P-values, odds ratios between treatment groups and its 95% confidence interval were from the weighted logistic regression model with all baseline factors included in the model as covariates. After stepwise model selection insignificant baseline factors removed from the final model. The final model for day 14 included age, race, baseline ordinal scale, cardiovascular, and chronic obstructive pulmonary disease.
Non-remdesivir-cohort (Study GS-US-540-5807)

Data from 1268 patients were collected up to the cut-off date (4/10/2020)

332 patients were retroactively excluded to ensure the two study populations were comparable
- veno-arterial extracorporeal membrane oxygenation on day 1
- alanine transferase or aspartate transferase greater than 5 times the upper limit of normal
- creatinine clearance less than 50 L/min using the Cockcroft-Gault formula at day 1
- being pregnant or breastfeeding

816 patients were included in the final analysis set
- n=76: missing data
- n=36: propensity score out of the common support region (trimmed)

The weighted patient number was 312 after applying the IPTW weighting method*

Remdesivir-cohort (Study GS-US-540-5773)

Data from 397 patients were collected up to the cut-off date (4/10/2020)

77 patients enrolled from Italy were excluded to ensure the two study populations were comparable

298 patients were included in the final analysis set
- n=7: missing data
- n=15: propensity score out of the common support region (trimmed)

The weighted patient number was 312 after applying the IPTW weighting method*

928 patients were included in the propensity-score model

112 patients were removed due to:
- n=76: missing data
- n=36: propensity score out of the common support region (trimmed)

816 patients were included in the final analysis set

The weighted patient number was 818 after applying the IPTW weighting method*
**Adjusted odds ratio: 2.03**
(95% confidence interval: 1.34–3.08)
\[ p<0.001 \]

Patients with recovery at day 14 (%)

- Remdesivir-cohort (N=312)
  - 74.4% (n=232)

- Non-remdesivir-cohort (N=818)
  - 59.0% (n=483)

**Adjusted odds ratio: 0.38**
(95% confidence interval: 0.22–0.68)
\[ p=0.001 \]

Mortality at day 14 (%)

- Remdesivir-cohort (N=312)
  - 7.6% (n=24)

- Non-remdesivir-cohort (N=818)
  - 12.5% (n=102)