Clinical improvement, outcomes, antiviral activity, and costs associated with early treatment with remdesivir for patients with COVID-19

Carlos K.H. Wong[1,2] PhD, Kristy T.K. Lau[1] MSc, Ivan C.H. Au[2] BSc, Xi Xiong[1] MSc, Eric H. Y. Lau[3,4] PhD, Benjamin J. Cowling[3,4] PhD

1 Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

2 Department of Family Medicine and Primary Care, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

3 WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

4 Laboratory of Data Discovery for Health Limited, Hong Kong Science Park, New Territories, Hong Kong SAR, China

Corresponding author:

Carlos K.H. Wong, Department of Pharmacology and Pharmacy, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

Tel: +852 28315055; Email: carlosho@hku.hk

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

© The Author(s) 2021. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

Summary

Among hospitalised patients with moderate COVID-19, early initiation of remdesivir was associated with significantly shorter time to clinical improvement, low viral load and positive IgG antibody, a shorter length of hospital stay, and a significantly lower risk of in-hospital death.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Abstract

Background: Evidence remains inconclusive on any significant benefits of remdesivir in mild-to-moderate COVID-19 patients. This study explored the disease progression, various clinical outcomes, changes in viral load, and costs associated with early remdesivir treatment among COVID-19 patients.

Methods: A territory-wide retrospective cohort of 10,419 patients with COVID-19 hospitalized from 21st January 2020 to 31st January 2021 in Hong Kong were identified. Early remdesivir users were matched with controls using propensity-score matching in a ratio of up to 1:4. Study outcomes were time to clinical improvement on the WHO clinical progression scale of at least 1 score; hospital discharge; recovery; viral clearance; low viral load; positive IgG antibody; in-hospital death; and composite outcomes of in-hospital death, requiring invasive ventilation or intensive care.

Results: After multiple imputation and propensity-score matching, the median follow-up was 14 days for both remdesivir (n=352) and control (n=1,347) groups. Time to clinical improvement was significantly shorter in the remdesivir group than that of control (hazard ratio (HR)=1.14, 95%CI 1.01-1.29, p=0.038), as well as for achieving low viral load (HR=1.51, 95%CI 1.24-1.83, p<0.001) and positive IgG antibody (HR=1.50, 95%CI 1.31-1.70, p<0.001). Early remdesivir treatment was associated with a lower risk of in-hospital death (HR=0.58, 95%CI 0.34-0.99, p=0.045), in addition to a significantly shorter length of hospital stay (difference -2.56 days, 95%CI -4.86 to -0.26, p=0.029), without increasing the risks of composite outcomes for clinical deterioration.

Conclusions: Early remdesivir treatment could be extended to hospitalized patients presenting with moderate COVID-19 and not requiring oxygen therapy on admission.

Keywords: COVID-19; remdesivir; clinical improvement; antiviral activity; cost

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Introduction

By May 2021, the antiviral agent remdesivir remains the only drug approved by the US Food and Drug Administration as a treatment option for Coronavirus Disease 2019 (COVID-19), which has been recommended for patients with moderate disease requiring low-flow supplemental oxygen, given its demonstrated benefits in reducing mortality and time to recovery [1-4]. While some systematic reviews have suggested potential benefits of remdesivir in facilitating recovery and clinical improvement, lowering the odds of mortality and progression to mechanical ventilation or extracorporeal membrane oxygenation (ECMO), shortening the time to hospital discharge and length of stay (LOS); others have shown no significant differences versus placebo/standard care [5-11].

Consistent with the mechanism of remdesivir in inhibiting viral replication at the early stage of COVID-19, several studies have identified potentially better outcomes when this antiviral was introduced early prior to the development of host hyperinflammatory response, for example, within the first ten days of symptom onset, or the first three days of hospital admission [10,12-17]. Besides, accumulating evidence has suggested similar or more desirable outcomes with 5-day versus 10-day course of remdesivir treatment in COVID-19 patients, accompanied by lower drug cost and utilization of the limited healthcare resources [7,8,13,18]. However, questions remain concerning the treatment efficacy in selected patient subgroups, when used in combination with other medications, virological dynamics, and long-term safety of remdesivir [15,17]. This population-based observational study aims to explore the disease progression, various clinical outcomes, changes in viral load, and direct medical costs associated with early initiation of 5-day remdesivir treatment in COVID-19 patients.

Methods

Data source and study population

Individual patient data from a territory-wide retrospective cohort of all hospitalised patients with laboratory-confirmed COVID-19 in Hong Kong, China were analysed, covering the period from 21st January 2020 to 31st January 2021. All patients with positive reverse transcription polymerase chain reaction (RT-PCR) results were admitted to local public hospitals. Our cohort was fully representative of the region, with a wide spectrum of disease severity including asymptomatic, non-severe, severe, and critically ill cases.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

In the latest Hong Kong Hospital Authority interim drug treatment handbook for COVID-19, interferon-beta-1b has been recommended as backbone therapy [19]. Early administration of subcutaneous interferon-beta-1b (250mcg on alternate day for a maximum of 7 doses up to 14 days) provided clinical benefits to mild-to-moderate patients [20]. Intravenous remdesivir (200mg on the first day and 100mg once daily on subsequent days), an approved treatment for COVID-19 patients in Hong Kong since July 2020, is a potential antiviral drug option for high-risk patients with mild-to-moderate COVID-19, and a suggested therapeutic for those with severe and critical diseases [19].

Treatment exposure and follow-up period

Patients receiving early treatment with remdesivir were defined as those who had initiated remdesivir intravenously within the first two days of admission. Treatment exposure period was set at two days to mitigate selection bias due to heterogeneity of treatment initiation days between patients, and immortal time bias due to the time difference between admission and treatment initiation [21-23]. Patients who had initiated remdesivir after two days of admission or those who did not receive any remdesivir during hospitalisation would serve as the control group. Patients were observed from the day of admission until in-hospital death, hospital discharge, treatment crossover (i.e. control patients were censored at the initiation of remdesivir), or the censoring date of 30th April 2021, whichever came first. Accordingly, this study focused on comparing the outcomes of early remdesivir use (exposed) versus no remdesivir use at all (control).

Outcome definition

WHO clinical progression scale provides a measure of disease severity with scores from 0 (non-infected) to 10 (dead) for COVID-19 clinical status assessment [3]. Study outcomes were time to clinical improvement on the WHO clinical progression scale of at least 1 score; hospital discharge (score ≤3); recovery without the need for oxygen therapy (score ≤4); viral clearance (first negative PCR result); low viral load (cycle threshold (Ct) value ≥35 cycles); positive antibody against COVID-19 (first detection of IgG antibody); composite outcome of in-hospital death or invasive mechanical ventilation (score ≥7); composite outcome of in-hospital death or invasive mechanical ventilation (score ≥7) or admission to the intensive care unit (ICU); composite outcome of in-hospital death, invasive mechanical ventilation, vasopressors, dialysis, or ECMO (score ≥9); and in-hospital death (score 10).

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Time from admission to discharge among survivors was measured. The criteria for hospital discharge were (i) two consecutive negative clinical specimens 24 hours apart (ii) positive antibody against COVID-19, and (iii) clinically stable as determined by attending medical staff. Mean WHO clinical progression scale score, clinical severity status, and cumulative direct medical costs on day (day-0), seven days (day-7), 15 days (day-15), 30 days (day-30), 60 days (day-60) and 90 days (day-90) after admission were reported. Unit costs of remdesivir per vial, hospitalisation at general ward or ICU, emergency department visit, polymerase chain reaction tests, tracheostomy, dialysis, and ECMO were referenced to official price list [24] and Hong Kong Government Gazette [25] (Supplementary Table 1).

Data analysis

Descriptive statistics of baseline characteristics between the remdesivir and control groups before and after propensity-score matching (described below) were presented as count and proportion for categorical variables, and mean and standard deviation (SD) for continuous variables. Missing laboratory data on admission were imputed 20 times using other parameters such as sex, age, pandemic waves, living regions, attended hospitals, emergency department admission, clinical presentation (symptomatic or asymptomatic), clinical severity defined by the WHO clinical progression scale [3], progression risk defined by the 4C mortality score [26], pre-existing comorbidities, use of long-term medications, and concomitant use of interferon-beta-1b within two days of admission using multiple imputation by chained equations (MICE) [27]. To minimize residual confounding biases due to imbalance in baseline characteristics, a logistic regression model was performed to estimate the propensity score for each patient in treatment group through the covariates used in multiple imputation, and baseline readings of white blood cell, neutrophil count, lymphocyte count, platelet count, lactate dehydrogenase (LDH), creatine kinase, total bilirubin, C-reactive protein (CRP), and Ct value. The set of covariates in each group had data completion rates of >90% (Supplementary Table 2). Remdesivir users were then matched with controls using the propensity-score matching up to 4 controls for every remdesivir user, using the caliper width of 0.05. Standardized mean difference (SMD) assessed balance of baseline covariates between treatment groups, with SMDs ≤0.2 implying sufficient balance after propensity-score matching [28].

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Hazard ratios (HR) of event outcomes were estimated using Cox regression models. Differences in WHO clinical progression scale scores between treatment groups on admission and follow-up days were tested using linear regression. Differences in cumulative direct medical costs between groups on admission and follow-up days were tested using generalised linear model with gamma distribution and log-link. Among survivors, time from hospital admission to discharge was compared between groups by linear regression.

Sensitivity analyses were conducted on 1) the removal of hospital discharge as a censoring criterion, hence all patients were observed until the last follow-up or study end date; 2) restriction of the follow-up period to 30 days since admission; 3) restriction of the follow-up period to 90 days; and 4) including only remdesivir users who had completed the 5-day standard regimen. Effects of early remdesivir treatment on study outcomes were also examined in several patient subgroups, namely by age (≤65 and >65 years), sex, WHO scores on admission (score 4 and scores 5-6), receipt of other therapeutics for COVID-19 during hospitalisation (interferon-beta-1b and dexamethasone), ICU admission, and pre-existing comorbidities (hypertension and diabetes).

All data analyses were performed using Stata Version 16 (StataCorp LP, College Station, TX). All significance tests were two- tailed. P values <0.05 were taken to indicate statistical significance.

Results

Patient cohort

Among 10,459 patients diagnosed with COVID-19 infection between 21st January 2020 and 31st January 2021 in Hong Kong, 10,419 patients were hospitalised, of whom 411 had received early remdesivir treatment, while 10,008 patients received remdesivir after the first two days of admission (n=450) or had not received any remdesivir (n=9,558). After multiple imputation and propensity-score matching, the median follow-up was 14 days for both remdesivir (n=352) and control (n=1,347) groups, and the total person-days of follow up were 7,218 and 26,457, respectively.

Baseline characteristics of patients in the two groups are presented in Table 1. Hypertension and diabetes were the two most common comorbidities of hospitalised patients, which was

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

also evident in other clinical trials and observational studies of remdesivir [12,16,18,29-31]. Among patients who were clinically symptomatic, the mean duration from symptom onset to hospital admission was 3.7 (SD 3.0) and 3.9 (SD 3.9) days in remdesivir and control groups, respectively. Except for CRP reading on admission, all baseline characteristics were balanced between groups with SMDs ≤0.2 after multiple imputation and propensity-score matching, including the 4C mortality score for in-hospital death prediction [26]. Density plot of propensity scores in the two groups indicated a high amount of overlap (Supplementary Figure 1).

The median duration of remdesivir treatment was five days with a cumulative dosage of 600mg, while the median time from admission to treatment initiation was one day in the remdesivir group. 154 (11.4%) patients in the control group were administered remdesivir after a median of five days since admission, whose follow-up was censored at treatment crossover.

Clinical improvement, hospital discharge, and recovery

Clinical severity status, derived from scores on the WHO clinical progression scale, of the two groups on admission and follow-up days were depicted in Figure 1. Patients on early remdesivir treatment had significantly lower scores since day-30 (p=0.020) after admission compared to control (Figure 2a). Time to clinical improvement by at least 1 score on the WHO clinical progression scale (median: 13 vs 14 days; HR=1.14, 95%CI 1.01-1.29, p=0.038) was significantly shorter in the remdesivir group than that of matched control (Table 2 and Figure 3). The same trend could be observed across the subgroup and sensitivity analyses (Supplementary Tables 3 and 4). Among survivors, early remdesivir treatment was associated with a significantly shorter LOS (-2.56 days, 95%CI -4.86 to -0.26, p=0.029). However, time to hospital discharge (HR=1.06, 95%CI 0.93-1.20, p=0.372) or recovery (HR=1.16, 95%CI 0.87-1.57, p=0.314) was not significantly different between the two groups.

Viral clearance, low viral load, and positive antibody

Early remdesivir treatment was associated with a significantly greater increase in Ct value on day-7 (p=0.042) compared to control (Figure 2b). Time to low viral load (median: 9 vs 10 days; HR=1.51, 95%CI 1.24-1.83, p<0.001) and positive IgG antibody (median: 6 vs 7 days; HR=1.50, 95%CI 1.31-1.70, p<0.001) were significantly shorter among early remdesivir users than matched controls (Table 2 and Figure 3). These significant results persisted or

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

indicated trends towards benefit in all subgroup and sensitivity analyses (Supplementary Tables 3 and 4). However, time to viral clearance was not significantly different between the two groups (HR=1.06, 95%CI 0.87-1.30, p=0.552).

Costs

Mean direct medical costs incurred by patients of the two groups over the follow-up period were displayed in Figure 2c. Remdesivir users incurred significantly higher cumulative costs from admission to day-60 than their control counterparts, yet converged on day-90 (US$32,183 vs US$27,056, p=0.096).

In-hospital death and composite outcomes of serious complications

Early remdesivir treatment was associated with a marginally lower risk of in-hospital death (median: 33 vs 15 days; HR=0.58, 95%CI 0.34-0.99, p=0.045) compared to control (Table 2 and Figure 3). Such observation mostly persisted across the subgroup and sensitivity analyses (Supplementary Tables 3 and 4). However, there were no significant differences in the risks of composite outcomes inclusive of in-hospital death, invasive mechanical ventilation, ICU admission, vasopressors, dialysis, or ECMO between the two groups (Table 2 and Supplementary Figure 2).

Discussion

In this population-based cohort of COVID-19 patients hospitalised with mainly moderate disease and not requiring any oxygen therapy, early administration of 5-day remdesivir treatment was associated with significantly shorter time to clinical improvement, low viral load and positive IgG antibody, a shorter hospital LOS, and a lower risk of in-hospital death than control. Notably, these beneficial effects were also observed in subgroup and sensitivity analyses, supporting their robustness over varying follow-up periods, across different patient characteristics and drug combinations for COVID-19.

In a randomised clinical trial with over 80% of COVID-19 patients hospitalised with moderate disease and not requiring any supplemental oxygen, remdesivir was similarly introduced after a median of two days since admission, and the 5-day course was associated with better clinical status on a 7-point ordinal scale at days 11 and 14 of follow-up compared to standard care [18]. Our results

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

indicated that such pattern was also evident from day-30 to day-90 using the WHO clinical progression scale, with remdesivir-treated patients obtaining significantly lower scores than their control counterparts. In the previous study, time to clinical improvement with remdesivir treatment was not significantly different from that of standard care [18]; yet our results suggested otherwise, and such faster progression to clinical improvement might be relevant in certain resource-limited healthcare settings. In addition to confirming the modest benefit of early remdesivir treatment in shortening the hospital LOS in this patient subgroup, the lower risk of mortality associated with this antiviral therapy managed to reach statistical significance in our cohort [2,8,10,14,18].

The current literature has mostly examined clinical outcomes associated with remdesivir treatment in COVID-19 patients requiring supplemental oxygen but not mechanical ventilation or ECMO at baseline. Either significant benefits or no considerable differences from placebo/standard care have been reported with remdesivir treatment on the time to clinical improvement or recovery, initiation or duration of respiratory support, mortality, hospital LOS and discharge [12,16,29-32]. Most importantly, remdesivir treatment has generally been associated with a lower incidence or risk of serious adverse events than the control group, including respiratory failure in COVID-19 [7,8,12,15,18]. In this study, early remdesivir treatment in COVID-19 patients with moderate disease was not associated with any increased risks of clinical deterioration as illustrated by the composite outcomes of serious complications. Therefore, our results could lend support to extending this antiviral therapy to COVID-19 patients with WHO score 4 in situations where drug supply and healthcare resources are available, or following prioritisation to those with score 5, as proposed by a review article on the role of remdesivir in hospitalised COVID-19 patients stratified by baseline severity, suggesting some potential benefits among those breathing ambient air [2].

While *in vitro* and *in vivo* studies have demonstrated antiviral activity of remdesivir with reduced viral load, especially in the lungs, evidence is still lacking in translating such observation to the clinical setting [33,34]. A few studies did identify reduced viral load over follow-up or measure viral clearance at day 7, yet no significant benefits of remdesivir in producing a larger reduction or a more rapid decline could be determined compared to control [11,15,16,30]. Limited evidence also recognised that remdesivir might not have a significant impact on IgG antibody levels or neutralisation potency [35]. Meanwhile, our study established significant benefits of attaining low viral load and positive IgG antibody more rapidly, in addition to a trend towards faster viral clearance, among patients with

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

moderate COVID-19 on early remdesivir treatment than those who were not. These are in line with findings that antibody response may help prevent disease progression, as well as promoting viral clearance or even shortening the duration of viral shedding [36,37]. As our remdesivir and control groups had comparable Ct values at baseline, earlier antibody response among remdesivir-treated patients could not be explained by a higher viral load [37]. Further research is needed to delineate any effects of remdesivir on the virological dynamics of COVID-19.

Corresponding to the increased cost for drug acquisition, the cumulative direct medical costs incurred by remdesivir-treated patients were significantly higher than those receiving standard care. Interestingly, the higher cumulative direct medical cost of remdesivir group was no longer significantly different from that of control on day-90 in this cohort. This may imply that over a longer follow-up period, remdesivir treatment could offer clinical benefits to patients with moderate COVID-19, without imposing a significantly higher burden on medical expenses. Assuming a survival benefit with remdesivir, an updated report has concluded that it may be cost-effective among patients with moderate-to-severe COVID-19, as the drug cost could be offset by its effect on limiting clinical deterioration, on top of associated increases in quality-adjusted life years [38].

Using a population-based cohort of patients with mainly moderate COVID-19, this study could add substantial evidence to exploring the early use of remdesivir in hospitalised COVID-19 patients not requiring any oxygen therapy on admission. Besides, the WHO clinical progression scale was adopted to facilitate the comparison of results with other studies. Nevertheless, some key limitations of this study should be addressed. Firstly, while propensity-score matching had been performed as an attempt to balance the baseline characteristics of treatment groups, our findings could be affected by residual or unmeasured confounding biases. Further studies with larger sample sizes are needed. Secondly, the vast majority of patients presented with moderate COVID-19 at baseline, albeit comprising non-selective and consecutive cases from public hospitals in Hong Kong, which was similar to the distribution of clinical severity among reported cases in China [39]. Therefore, our results might not be applicable to patient populations with a different spectrum of disease severity. Lastly, heterogeneity across studies will likely persist with the evolving, local clinical guidelines of COVID-19 management in different geographical regions and different time periods of the pandemic; thus, our findings might not be generalisable to other healthcare settings, not to mention our relatively stringent criteria for hospital discharge. This calls for a cautious interpretation of our cost results,

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

and additional studies to evaluate the cost-effectiveness of early remdesivir treatment in specific patient populations.

This population-based cohort study of patients with mainly moderate COVID-19 demonstrated that early initiation of 5-day remdesivir treatment within two days of admission was associated with significantly shorter time to clinical improvement, low viral load and positive IgG antibody, a shorter hospital LOS, and a lower risk of in-hospital death compared to not using the antiviral drug. Accordingly, early remdesivir treatment could be extended to patients presenting with moderate disease but not requiring oxygen therapy on admission, all without increasing the risks of requiring invasive ventilation or intensive care.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Notes:

Author contributions

C.K.H.W. reviewed the literature, designed statistical analysis, conducted analyses, wrote the manuscript; K.T.K.L. reviewed the literature, contributed to the interpretation of the analysis, and wrote the manuscript. C.H.A. conducted analyses. X.X. and E.H.Y.L. contributed to the interpretation of the analysis. B.J.C. contributed to the interpretation of the analysis, critically reviewed and revised the manuscript. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgements

We thank the Hong Kong Hospital Authority for the data provision, and Professor Gabriel Leung for guidance and advice.

Ethical approval and informed consent

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster (Reference No. UW 20-493). Given the extraordinary nature of the COVID-19 pandemic, individual patient informed consent was not required for this retrospective cohort study using anonymised data.

Data sharing statement

The data that support the findings of this study were provided by the Hong Kong Hospital Authority. Restrictions apply to the availability of these data, which were used under license for this study.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Transparency statement

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Funding

We received financial support from the Health and Medical Research Fund, The Food and Health Bureau, The Government of the Hong Kong Special Administrative Region, China (grant no. COVID190210). The funders did not have any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Role of the funding source

The funders did not have any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Potential conflicts

BJC consults for Roche, AstraZeneca, Sanofi Pasteur, GSK and Moderna (consulting fees paid to them). BJC reports support paid to their institution from HMRF, RGC, NIH, CDC, NIAID, ITC, Wellcome, and WHO; and is supported by the AIR@innoHK program of the Innovation and Technology Commission of the Hong Kong SAR Government, all outside the submitted work. C.K.H.W. reports support paid to their institution from the general Research Fund, Research Grant Council, Government of the Hong Kong Special Administrative Region, China; and EuroQol Group Research Foundation, outside the submitted work. E.H.Y.L. reports support paid to their institution from the Health and Medical Research Fund, Food and Health Bureau; General Research Fund, Research Grant Council, and Government of the Hong Kong Special Administrative Region, China, outside the submitted work. The authors report no other potential conflicts of interest.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

References

1. Bhimraj A, Morgan R, Shumaker A, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Published 2021. Accessed 26/05/2021.
2. Davis MR, McCreary EK, Pogue JM. That Escalated Quickly: Remdesivir's Place in Therapy for COVID-19. *Infectious Diseases and Therapy.* 2020;9(3):525-536.
3. Marshall JC, Murthy S, Diaz J, et al. A minimal common outcome measure set for COVID-19 clinical research. *The Lancet Infectious Diseases.* 2020;20(8):e192-e197.
4. National Institutes of Health. Therapeutic Management of Adults With COVID-19. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/. Published 2021. Accessed 26/05/2021.
5. Al-Abdouh A, Bizanti A, Barbarawi M, et al. Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. *Contemporary Clinical Trials.* 2021;101:106272.
6. Bansal V, Mahapure KS, Bhurwal A, et al. Mortality Benefit of Remdesivir in COVID-19: A Systematic Review and Meta-Analysis. *Frontiers in Medicine.* 2021;7(1124).
7. Elsawah HK, Elsokary MA, Abdallah MS, ElShafie AH. Efficacy and safety of remdesivir in hospitalized Covid-19 patients: Systematic review and meta-analysis including network meta-analysis. *Reviews in Medical Virology.* 2020:e2187.
8. Kaka AS, MacDonald R, Greer N, et al. Major Update: Remdesivir for Adults With COVID-19. *Annals of Internal Medicine.* 2021;174(5):663-672.
9. Piscoya A, Ng-Sueng LF, Parra del Riego A, et al. Efficacy and harms of remdesivir for the treatment of COVID-19: A systematic review and meta-analysis. *PLOS ONE.* 2020;15(12):e0243705.
10. Reddy Vegivinti CT, Pederson JM, Saravu K, et al. Remdesivir therapy in patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. *Annals of Medicine and Surgery.* 2021;62:43-48.
11. Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ.* 2020;370:m2980.
12. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *New England Journal of Medicine.* 2020;383(19):1813-1826.
13. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *New England Journal of Medicine.* 2020;383(19):1827-1837.
14. Paranjape N, Husain M, Priestley J, Koonjah Y, Watts C, Havlik J. Early Use of Remdesivir in Patients Hospitalized With COVID-19 Improves Clinical Outcomes: A Retrospective Observational Study. *Infectious Diseases in Clinical Practice.* 9000;Publish Ahead of Print.
15. Rezagholizadeh A, Khiali S, Sarbakhsh P, Entezari-Maleki T. Remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis. *European Journal of Pharmacology.* 2021;897:173926.
16. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet.* 2020;395(10236):1569-1578.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

17. Young B, Tan TT, Leo YS. The place for remdesivir in COVID-19 treatment. *The Lancet Infectious Diseases.* 2021;21(1):20-21.
18. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 2020;324(11):1048-1057.
19. Department of Pharmacy QMH, Hospital Authority. *Interim Drug Treatment Handbook for COVID-19, 10th Version.* 10th version ed. 2021.
20. Wong CKH, Wan EYF, Luo S, et al. Clinical outcomes of different therapeutic options for COVID-19 in two Chinese case cohorts: A propensity-score analysis. *EClinicalMedicine.* 2021;32.
21. Gupta S, Wang W, Hayek SS, et al. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. *JAMA Internal Medicine.* 2021;181(1):41-51.
22. Monedero P, Gea A, Castro P, et al. Early corticosteroids are associated with lower mortality in critically ill patients with COVID-19: a cohort study. *Critical Care.* 2021;25(1):2.
23. Renoux C, Azoulay L, Suissa S. Biases in evaluating the safety and effectiveness of drugs for covid-19: designing real-world evidence studies. *American Journal of Epidemiology.* 2021.
24. Gilead Sciences I. An Open Letter from Daniel O'Day, Chairman & CEO, Gilead Sciences. https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/an-open-letter-from-daniel-oday-chairman--ceo-gilead-sciences. Published 2020. Accessed 28/05/2021.
25. Hospital Authority. *Hospital Authority Ordinance (Chapter 113) - Revision to list of charges.* 2017.
26. Knight SR, Ho A, Pius R, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. *BMJ.* 2020;370:m3339.
27. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011;30(4):377-399.
28. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biom J.* 2009;51(1):171-184.
29. Garibaldi BT, Wang K, Robinson ML, et al. Comparison of Time to Clinical Improvement With vs Without Remdesivir Treatment in Hospitalized Patients With COVID-19. *JAMA Network Open.* 2021;4(3):e213071-e213071.
30. Goldberg E, Ben Zvi H, Sheena L, et al. A real-life setting evaluation of the effect of remdesivir on viral load in COVID-19 patients admitted to a large tertiary centre in Israel. *Clinical Microbiology and Infection.* 2021;27(6):917.
31. Olender SA, Perez KK, Go AS, et al. Remdesivir for Severe Coronavirus Disease 2019 (COVID-19) Versus a Cohort Receiving Standard of Care. *Clinical Infectious Diseases.* 2020.
32. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med.* 2021;384(6):497-511.
33. Frediansyah A, Nainu F, Dhama K, Mudatsir M, Harapan H. Remdesivir and its antiviral activity against COVID-19: A systematic review. *Clinical Epidemiology and Global Health.* 2021;9:123-127.
34. Lin HXJ, Cho S, Meyyur Aravamudan V, et al. Remdesivir in Coronavirus Disease 2019 (COVID-19) treatment: a review of evidence. *Infection.* 2021;49(3):401-410.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

35. Garcia-Beltran WF, Lam EC, Astudillo MG, et al. COVID-19-neutralizing antibodies predict disease severity and survival. *Cell.* 2021;184(2):476-488.e411.
36. Li K, Huang B, Wu M, et al. Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19. *Nature Communications.* 2020;11(1):6044.
37. Masiá M, Telenti G, Fernández M, et al. SARS-CoV-2 Seroconversion and Viral Clearance in Patients Hospitalized With COVID-19: Viral Load Predicts Antibody Response. *Open Forum Infectious Diseases.* 2021;8(2):ofab005.
38. Campbell J, Whittington M, Rind D, Pearson S. *Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19; Updated Report.*: Institute for Clinical and Economic Review; November 10, 2020 2020.
39. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239-1242.

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Figure Legends

Figure 1. Comparison of clinical status by days from admission in COVID-19 patients who received early treatment with remdesivir and those who did not

Figure 2. Mean and 95% confidence interval of WHO Clinical Progression Scale Score (a), Ct value (b), and cumulative direct medical costs (USD) (c) of COVID-19 patients in those who received early treatment with remdesivir and those who did not

Figure 3. Kaplan-Meier survival curves for clinical improvement on WHO clinical progression scale, low viral load, IgG antibody, and in-hospital death between COVID-19 patients in those who received early treatment with remdesivir and those who did not

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Table 1. Baseline characteristics of COVID-19 patients in those who received early treatment with remdesivir and those who did not before and after multiple imputation and propensity score matching

Baseline characteristics	Before matching					After matching				
	Remdesivir (n=411)		Control (n=10,008)		SMD¶	Remdesivir (n=352)		Control (n=1,347)		SMD¶
	N / Mean	% / SD	N / Mean	% / SD		N / Mean	% / SD	N / Mean	% / SD	
Age, years †	65.7	13.4	44.5	19.7	1.09	65.2	13.7	66.7	13.7	0.11
≤65	178	(43.3%)	8,507	(85.0%)	0.97	156	(44.3%)	624	(46.3%)	0.04
>65	233	(56.7%)	1,501	(15.0%)		196	(55.7%)	723	(53.7%)	
Sex										
Male	237	(57.7%)	4,798	(47.9%)	0.20	198	(56.3%)	738	(54.8%)	0.03
Female	174	(42.3%)	5,210	(52.1%)		154	(43.8%)	609	(45.2%)	
Pandemic wave										
1 and 2 (18th Jan 2020 - 30th Apr 2020)	12	(2.9%)	1026	(10.3%)	0.30	340	(96.6%)	89	(6.6%)	0.15
3 and 4 (1st May 2020 to 31st Jan 2021)	399	(97.1%)	8982	(89.8%)		0	(0.0%)	1258	(93.4%)	
Symptomatic on admission	335	(81.5%)	6,976	(69.7%)	0.28	288	(81.8%)	1083	(80.4%)	0.04
Time from onset to admission, days †	3.9	3.3	4.1	4.6	0.04	3.7	3.0	3.9	3.9	0.04
Living region										
New Territories or Hong Kong Island	248	(60.3%)	5546	(55.4%)	0.10	214	(60.8%)	720	(53.5%)	0.15
Kowloon or Others	163	(39.7%)	4462	(44.6%)		138	(39.2%)	617	(45.8%)	
First attended hospital										
Acute hospital	97	(23.6%)	2209	(22.1%)	0.04	76	(21.6%)	320	(23.8%)	0.05
Non-acute hospital	314	(76.4%)	7799	(77.9%)		276	(78.4%)	1027	(76.2%)	
Pre-existing comorbidities on admission										
Hypertension	253	(61.6%)	2,158	(21.6%)	0.89	204	(58.0%)	793	(58.9%)	0.02

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Diabetes mellitus	177	(43.1%)	1,080	(10.8%)	0.78	131	(37.2%)	502	(37.3%)	0.00
Chronic heart disease	59	(14.4%)	337	(3.4%)	0.39	46	(13.1%)	167	(12.4%)	0.02
Chronic lung disease	50	(12.2%)	363	(3.6%)	0.32	40	(11.4%)	149	(11.1%)	0.01
Chronic kidney disease	41	(10.0%)	234	(2.3%)	0.32	31	(8.8%)	119	(8.8%)	0.00
Liver disease	36	(8.8%)	450	(4.5%)	0.17	27	(7.7%)	117	(8.7%)	0.04
Malignancy	12	(2.9%)	108	(1.1%)	0.13	12	(3.4%)	36	(2.7%)	0.04
Long-term medications										
ACEI/ARB	123	(29.9%)	906	(9.1%)	0.55	103	(29.3%)	400	(29.7%)	0.01
Antiplatelet	77	(18.7%)	539	(5.4%)	0.42	61	(17.3%)	230	(17.1%)	0.01
Lipid-lowering agent	174	(42.3%)	1,121	(11.2%)	0.75	135	(38.4%)	538	(39.9%)	0.03
NSAID	86	(20.9%)	751	(7.5%)	0.39	70	(19.9%)	260	(19.3%)	0.01
Concomitant use of interferon-β-1b within 2 days of admission	214	(52.1%)	2,519	(25.2%)	0.57	174	(49.4%)	757	(56.2%)	0.14
Admission via emergency department	214	(52.1%)	3,250	(32.5%)	0.40	173	(49.1%)	688	(51.1%)	0.04
Clinical severity on admission§										
Score (range 0-10) †	4.6	1.0	4.1	0.4	1.04	4.4	0.9	4.3	0.8	0.11
No oxygen therapy (Score 4)	297	(72.3%)	9551	(95.4%)	0.66	279	(79.3%)	1122	(83.3%)	0.11
Supplemental oxygen without ventilation (Score 5-6)	105	(25.6%)	445	(4.5%)		68	(19.3%)	215	(16.0%)	
Mechanical ventilation (Score 7-9)	9	(2.2%)	12	(0.1%)		5	(1.4%)	10	(0.7%)	
4C mortality score on admission (range 0-21) †	6.6	3.3	2.4	2.8	1.46	6.2	3.2	6.2	3.2	0.02
Laboratory parameters on admission [normal range] †										
White blood cell, $\times 10^9$/L [3.7-9.2 $\times 10^9$/L]	6.0	2.6	5.7	2.1	0.14	5.8	2.2	5.4	2.3	0.16
Neutrophil, $\times 10^9$/L [1.7-5.8 $\times 10^9$/L]	4.5	2.5	3.6	1.8	0.51	4.2	2.1	3.9	2.2	0.16
Lymphocyte, $\times 10^9$/L [1.0-3.1 $\times 10^9$/L]	1.0	0.5	1.5	0.8	0.63	1.0	0.5	1.0	0.4	0.03
Platelet, $\times 10^9$/L [145-370 $\times$109/L]	187.5	63.1	228.1	74.2	0.55	189.0	64.2	184.0	59.2	0.08
Lactate dehydrogenase, U/L [110-210 U/L]	328.6	153.2	206.7	73.3	1.56	299.1	120.2	275.3	122.1	0.20
Creatine kinase, U/L [26-192 U/L]	304.6	495.7	138.9	251.9	0.62	270.3	452.6	227.7	467.2	0.09
Total bilirubin, μmol/L [5-27 μmol/L]	9.1	6.4	8.6	6.7	0.07	9.1	6.8	8.8	6.0	0.04
C-reactive protein, mg/L [<50 mg/L]	63.8	62.1	12.8	28.2	1.68	53.4	54.0	41.7	53.5	0.22

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Cycle threshold value, cycle	22.1	5.4	24.4	7.2	0.33	22.1	5.6	21.9	6.5	0.03

Note: ACEI = angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blockers; NSAID = Nonsteroidal anti-inflammatory drugs; SD = standard deviation; SMD = standardized mean difference

† Age, time from onset to admission, clinical severity, 4C mortality score, and laboratory parameters on admission are presented in mean ± SD

§ Clinical severity is classified according to WHO Clinical Progression Scale

¶ SMD of ≤0.2 indicates covariate balance between remdesivir and matched control groups

Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Table 2. Comparison of clinical improvement on WHO clinical progression scale, hospital discharge, recovery, in-hospital death, and composite outcomes between COVID-19 patients in those who received early treatment with remdesivir and those who did not

Outcomes	Remdesivir	Control	Remdesivir vs Control		
	% (N)	% (N)	HR †	95% CI	P-value
Clinical improvement on WHO clinical progression scale by ≥ 1 score	96.3% (352)	84.0% (1,347)	1.14	(1.01, 1.29)	0.038
Hospital discharge (score ≤ 3)	94.0% (352)	81.3% (1,347)	1.06	(0.93, 1.20)	0.372
Recovery (score ≤ 4)	83.6% (73)	59.6% (225)	1.16	(0.87, 1.57)	0.314
Viral clearance (first negative PCR result)	36.1% (352)	30.4% (1,347)	1.06	(0.87, 1.30)	0.552
Low viral load (Ct value ≥ 35)	40.6% (352)	28.1% (1,347)	1.51	(1.24, 1.83)	<0.001
IgG antibody	94.0% (352)	80.4% (1,347)	1.50	(1.31, 1.70)	<0.001

Outcomes	% (N)	% (N)	HR ‡	95% CI	P-value
In-hospital death or invasive mechanical ventilation (score ≥ 7)	10.7% (347)	11.3% (1,337)	0.95	(0.67, 1.37)	0.796
In-hospital death or invasive mechanical ventilation (score ≥ 7) or intensive care unit admission	5.9% (290)	6.8% (1,184)	0.92	(0.55, 1.53)	0.747
In-hospital death, invasive mechanical ventilation, vasopressors, dialysis, or ECMO (score ≥ 9)	6.0% (350)	6.6% (1,342)	0.87	(0.55, 1.38)	0.556
In-hospital death (score = 10)	4.3% (352)	6.7% (1,347)	0.58	(0.34, 0.99)	0.045

Note: HR = hazard ratio; CI = confidence interval;

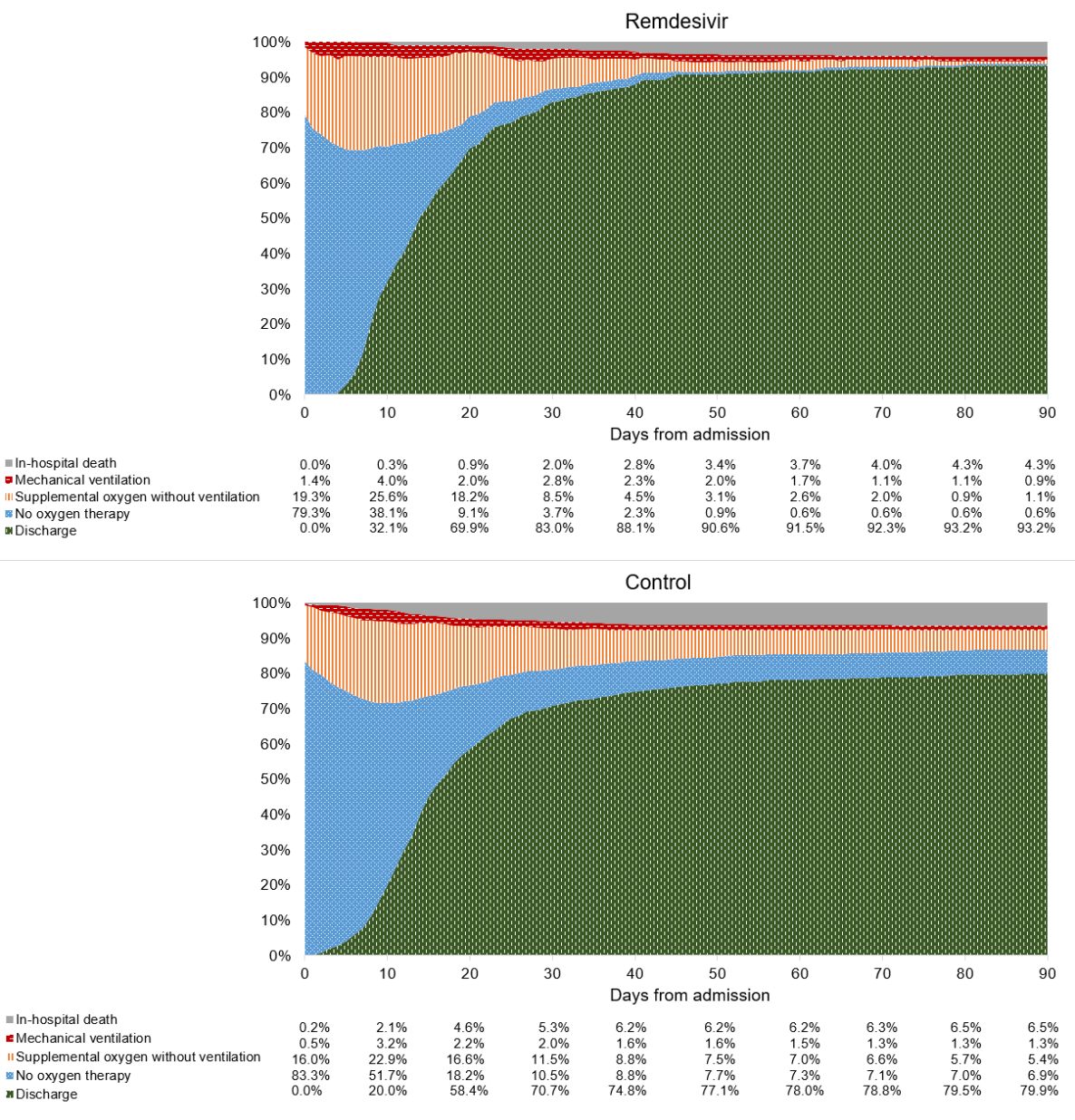
† HR >1 (or <1) indicates early treatment with remdesivir was associated with better (worse) clinical improvement, early (late) hospital discharge, recovery, viral clearance, low viral load, or IgG antibody compared to the matched control group;

‡ HR >1 (or <1) indicates early treatment with remdesivir was associated with higher (lower) risk of in-hospital death and composite outcomes compared to the matched control group.

Accepted Manuscript

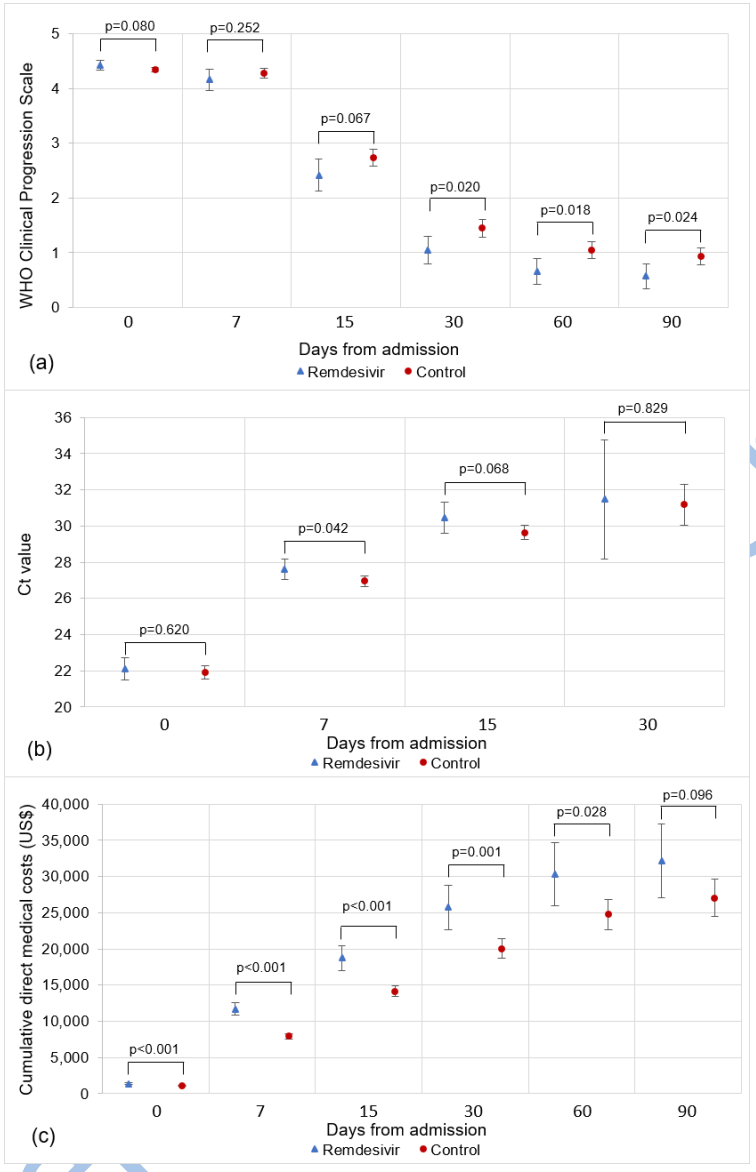
Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Figure 1



Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

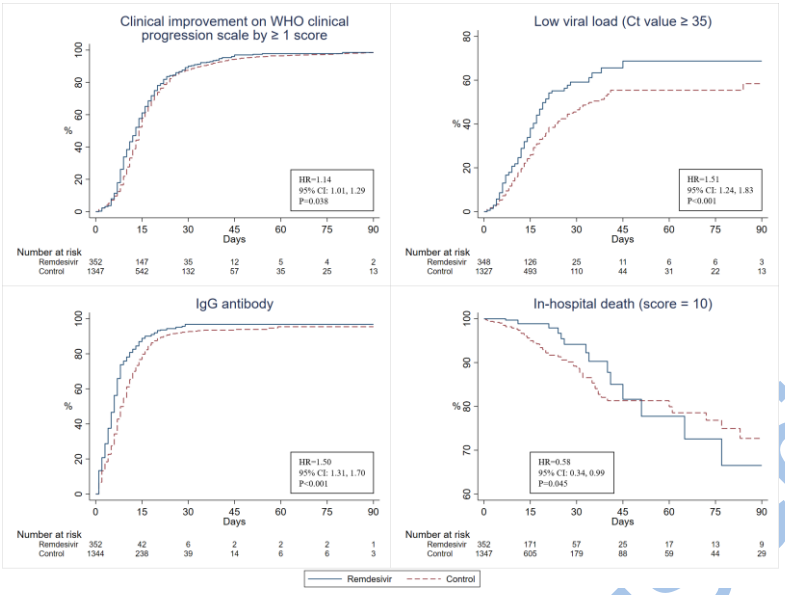
Figure 2



Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022

Figure 3



Accepted Manuscript

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab631/6321803 by guest on 24 January 2022