REAL-WORLD EFFECTIVENESS OF REMDESIVIR IN ADULTS HOSPITALIZED WITH COVID-19: A RETROSPECTIVE, MULTICENTER COMPARATIVE EFFECTIVENESS STUDY

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Summary: Remdesivir was significantly associated with an increased likelihood of clinical improvement in patients on no or low-flow oxygen and a reduction in mortality among individuals on low-flow oxygen. Routine use of remdesivir in sicker patients is unlikely to be beneficial.

ABSTRACT

Background

There is an urgent need to understand the real-world effectiveness of remdesivir in the treatment of SARS-CoV-2.

Methods

This was a retrospective comparative effectiveness study. Individuals hospitalized in a large private healthcare network in the US from February 23, 2020 through February 11, 2021 with a positive test for SARS-CoV-2 and ICD-10 diagnosis codes consistent with symptomatic COVID-19 were included. Remdesivir recipients were matched to controls using time-dependent propensity scores. The primary outcome was time to improvement with a secondary outcome of time to death.

Results

Of 96,859 COVID-19 patients, 42,473 (43.9%) received at least one remdesivir dose. The median age of remdesivir recipients was 65 years, 23,701 (55.8%) were male and 22,819 (53.7%) were non-white. Matches were found for 18,328 patients (43.2%). Remdesivir recipients were significantly more likely to achieve clinical improvement by 28 days (adjusted hazard ratio [1.19, 95% confidence interval (CI), 1.16-1.22]). Remdesivir patients on no oxygen (aHR 1.30, 95% CI 1.22-1.38) or low-flow oxygen (aHR 1.23, 95% CI 1.19-1.27) were significantly more likely to achieve clinical improvement by 28 days. There was no significant impact on the likelihood of mortality overall (aHR 1.02, 95% CI 0.97-1.08). Remdesivir recipients on low-flow oxygen were significantly less likely to die than controls (aHR 0.85, 95% CI 0.77-0.92; 28-day mortality 8.4% [865 deaths] for remdesivir patients, 12.5% [1,334 deaths] for controls).

Conclusions

These results support the use of remdesivir for hospitalized COVID-19 patients on no or low-flow oxygen. Routine initiation of remdesivir in more severely ill patients is unlikely to be beneficial.

Keywords: remdesivir, COVID-19, SARS-CoV-2, real-world effectiveness, therapeutics

INTRODUCTION

As of December 1, 2021, there have been over 260 million cases of SARS-CoV-2 infection, the virus that causes COVID-19, with greater than 5 million deaths.[1] There remains an urgent need to deploy therapeutics to improve COVID-19 outcomes. Remdesivir, a nucleoside analog that inhibits SARS-CoV-2 replication, reduced the time to clinical improvement in 1,062 patients in the National Institutes of Health (NIH) Adaptive COVID-19 Treatment Trial (ACTT).[2] A study of 237 patients in Hubei, China did not show a statistically significant benefit for remdesivir, but the trial was stopped early due to a lack of COVID-19 cases.[3] The open-label Solidarity trial (2,743 remdesivir recipients), sponsored by the World Health Organization (WHO;)[4], did not show a mortality benefit and the open-label DisCoVeRy study (429 remdesivir recipients)[5] did not show a difference in outcomes.

Data on the real-world effectiveness of remdesivir has also yielded conflicting results. One retrospective study from a single health system showed that among 342 recipients, remdesivir reduced the time to clinical improvement by 2 days but did not decrease mortality.[6] A retrospective study of 1,172 remdesivir patients from the Veterans Health Administration (VA),[7] a UK retrospective study of 1,549 remdesivir recipients[8] and two small multicenter retrospective studies (including 368 and 286 remdesivir patients)[9,10] did not demonstrate a mortality benefit. The VA study also found an increased length of stay for remdesivir recipients.[7] A larger industry-sponsored retrospective study of 28,555 remdesivir patients from the Premier Healthcare Database showed an overall improvement in mortality at 14 and 28 days, including a benefit in some critically ill patients.[11] A post-hoc analysis of the ACTT-1 trial suggested that remdesivir may reduce progression to invasive mechanical ventilation (IMV) and death, even among patients who were already receiving IMV.[12]

These discordant findings have contributed to variation in remdesivir use[13] and while the US Food and Drug Administration (FDA) granted full approval for remdesivir,[14] the World Health Organization (WHO) recommends against its routine administration.[15] Given the ongoing pandemic, it is critical to examine the real-world effectiveness of remdesivir using large populations, which can

allow for analyses within distinct clinical subgroups. Using a dataset from a large, geographically diverse multi-hospital health system in the United States, we quantified the effectiveness of remdesivir in the treatment of hospitalized patients with COVID-19, with a focus on patients with different disease severity at time of treatment initiation.

METHODS

Study Design and Participants

The COVID-19 Consortium of HCA Healthcare and Academia for Research GEneration (CHARGE) is a group of 10 academic centers in partnership with HCA Healthcare and the federal Agency for Health Research and Quality (AHRQ).[16] HCA Healthcare comprises over 2,000 care sites including more than 180 acute-care facilities. This system conducts over 32 million annual patient encounters, including approximately 6% of all inpatient care in the US.[17] As of July 2021, over 180,000 COVID-19 patients had been admitted to HCA facilities.

We included patients hospitalized for COVID-19 at HCA hospitals in the US between February 23, 2020 and February 11, 2021. Diagnosis of COVID-19 was determined by the detection of SARS-CoV-2 using any nucleic acid test with an FDA Emergency Use Authorization (EUA) combined with specific ICD-10 codes that indicate symptomatic infection (**Appendix Table 1**). Only a patient's first hospitalization after COVID-19 diagnosis was considered for analysis. Discharge and readmission within 24 hours was considered a continuous care episode. This study was conducted according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for comparative effectiveness research.[18] It was approved by a Johns Hopkins and an external Institutional Review Board (WIRB-Copernicus Group [WCG]) as minimum risk with a waiver of consent.

Data Collection

HCA Healthcare partnered with its research affiliates, Sarah Cannon and HCA Healthcare Research Institute, to aggregate electronic health record (EHR) data in an enterprise data warehouse. Only data from facilities using a single EHR system were included, accounting for >90% of affiliated facilities. Data included socio-demographics, past medical history, ICD-10 codes, laboratory data, vital signs, medications, oxygen support (e.g. low-flow nasal cannula, high-flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NIPPV), IMV and extracorporeal membrane oxygenation (ECMO)), length of stay, location of discharge, and death. Limited data sets were accessible via a secure platform hosted within a private virtual network.

Exposure to Remdesivir

HCA guidelines for the use of remdesivir consistent with the initial FDA EUA were established.[19] Guidelines were updated to align with FDA recommendations following full approval.[14,20] At the time of analysis, guidelines recommended a 5-day treatment course for patients with an oxygen saturation less than 94% or the need for oxygen.

Outcomes

The primary outcome was time to clinical improvement from the first day of remdesivir treatment or the matched day, defined as a 2-point decrease in the 8-point WHO severity score or discharged alive from the hospital without worsening of the WHO severity score within 28 days (see **Appendix Table 2**).[6,21] Failure of clinical improvement was censored at the last day of follow-up or 28-days, whichever came first. The secondary outcome was time to death from the first day of remdesivir treatment or the matched day. Patients who were discharged alive to “home” or “self-care” were censored at 28 days.[22] Patients who were discharged to another health care facility without a known death date were censored at last follow-up. Patients discharged to hospice with a recorded death date were included in the death group.

Statistical Analyses

To account for the non-randomized use of remdesivir and the variable timing of administration, we used time-dependent propensity score (PS) matching to create pairs of individuals, one patient treated with remdesivir and the other the most similar patient eligible for treatment at the time of remdesivir initiation but who did not receive remdesivir. The PS was computed using a time-dependent Cox proportional hazards regression model with the time from admission to the first dose of remdesivir being the outcome. Dexamethasone was included as a matching variable (see **Supplement**).[6,23,24] In order to account for changes in the pandemic over time, an individual that received remdesivir prior to October 1, 2020 had to be matched to a control patient hospitalized before October 1, 2020 (**Appendix Figure 1**). An additional time constraint was imposed such that a patient who received k days of treatment with remdesivir was matched to a control patient who stayed in the hospital at least k days (up to a maximum of 5) beyond the matching day.[6] This condition avoids matching remdesivir patients to individuals who were healthy enough to be discharged soon after the matching day and would not have been considered candidates for remdesivir treatment.

We used Cox proportional hazards regression models to estimate the association between remdesivir treatment and outcomes of interest on the matched sets.[25] We included demographics, oxygen delivery device, vital signs, key laboratory data, comorbidities (including the Charlson Comorbidity Index[26]) and COVID-19-specific medications (e.g. dexamethasone, tocilizumab, etc.) in the models (**Table 1**). Data were analyzed using R, version 4.0.2 (R Foundation for Statistical Computing).

Sensitivity Analyses

We performed four sensitivity analyses. First, we excluded individuals who received corticosteroids. Second, we excluded individuals treated before July 1, 2020. Third, we reduced the number of days that control patients had to remain in the hospital after the matched day to 4 days and 3 days. Fourth, we repeated analyses after matching patients who received both remdesivir and dexamethasone to patients who received dexamethasone alone.

RESULTS

Characteristics of Individuals in Cohort

Of 96,859 COVID-19 patients between February 23, 2020 and February 11, 2021, 42,473 (43.9%) patients received at least one dose of remdesivir (**Figure 1**). Of those receiving remdesivir, 13,907 (32.7%) stopped treatment before 5 days, 27,018 (63.6%) received a 5-day course, and 1548 (3.6%) received treatment of more than 5 day. The median time from admission to first dose of remdesivir was 1 day (interquartile range [IQR] 0,2) and the median duration of remdesivir treatment was 5 days (IQR 4,5 days). Of those receiving remdesivir, the median age was 65 years, 23,701 (55.8%) were male and 22,819 (53.7%) were non-white. Of 18,328 successfully matched remdesivir patients (43.2% of eligible patients), 8,207 patients (73.2%) were treated before October 1 and 10,121 patients (32.4%) after October 1. **Table 1** shows the demographic and clinical characteristics of remdesivir recipients and control patients at hospital admission and after matching. **Appendix Table 3** shows characteristics of unmatched remdesivir and control patients. **Appendix Table 4 and 5** show the characteristics of remdesivir and matched control patients stratified by no or low flow oxygen.

Time to clinical improvement

Of 36,656 matched individuals, 13,569 (74.0%) of the patients who received remdesivir and 12,510 (68.3%) of controls achieved clinical improvement before 28 days with a median time to clinical improvement of 7 days (IQR 5,19) in the remdesivir recipients and 9 days (IQR 5,28) for controls. Remdesivir patients were statistically significantly more likely to achieve clinical improvement at 28 days than controls (adjusted hazard ratio [aHR] 1.19 [95% confidence interval (CI), 1.16-1.22]; **Figure 2A).** Remdesivir patients receiving no oxygen were statistically significantly more likely to achieve clinical improvement (aHR 1.30, CI 1.22-1.38; **Figure 2B**; median 5 days (IQR 4,13) for remdesivir compared to 7 days (IQR 5,15) in controls). Remdesivir patients receiving low-flow oxygen were also statistically significantly more likely to achieve clinical improvement (aHR 1.23, CI 1.19-1.27; **Figure 2C**; median of 6 days (IQR 4,11) for remdesivir compared to 7 days (IQR 5,15) in controls). Remdesivir patients receiving HFNC and NIPPV had a trend towards a lower likelihood of improvement (aHR 0.95 [95% CI 0.89-1.01] for HFNC/NIPPV; **Figure 2D**; median of 15 days (IQR, 7,28) compared to 17 days (IQR, 8,28) in controls). Remdesivir patients receiving IMV at the time of initiation also had a trend towards a reduced likelihood of improvement (aHR 0.92 [95% CI 0.81-1.04] for IMV; **Figure 2E**; median of 28 days in both groups; (IQR, 10,28 in remdesivir patients compared to IQR, 9,28 in controls).

Time to death

There was no significant impact of remdesivir on mortality overall (aHR 1.02, CI 0.97-1.08; 28-day mortality of 15.7% [2,879 deaths] for remdesivir patients compared to 19.6% [3,586 deaths] for matched controls; **Figure 3A**). Patients on room air did not have an improvement in mortality (aHR 1.08, CI 0.92-1.27; 28-day mortality of 11.4% [325 deaths] for remdesivir patients compared to 13.3% [329 deaths] for matched controls; Figure 3B). However, remdesivir recipients on low-flow oxygen were statistically significantly less likely to die (aHR 0.85, CI 0.77-0.92; 28-day mortality of 8.4% [865 deaths] for remdesivir patients compared to 12.5% [1,334 deaths] for matched controls;

Figure 3C). Remdesivir patients receiving HFNC or NIPPV were statistically significantly more likely to die (aHR 1.10 [95% CI 1.01-1.20]; 28 day mortality of 28.6% [1,137 deaths] in remdesivir patients compared to 34.0% (1,237 deaths) in matched controls**; Figure 3D).** Remdesivir patients receiving IMV had a trend towards a higher risk of death (aHR 1.17 [95% CI 1.04-1.32]; 28 day mortality of 46.7% [552 deaths] in remdesivir patients compared to 43.9% [686 deaths] for matched controls; **Figure 3E**).

Sensitivity Analyses

When considering the 929 patients who received remdesivir without corticosteroids, the results in terms of time to clinical improvement did not substantively change. In the time to death analysis, remdesivir-only patients on low-flow oxygen no longer derived a statistically significant mortality benefit, although the effect size was in a similar direction (aHR 0.65 [95% CI, 0.29-1.49]; see **Supplement, Appendix Table 5, Appendix Figure 3, Appendix Figure 4**).

If we only considered patients who were treated with remdesivir after July 1, 2021, the results did not substantively change (see **Supplement**, **Appendix Figure 5** and **Appendix Figure 6**).

There were no substantive changes if the requirement that control patients remain in the hospital for the same duration of treatment as their remdesivir counterparts was dropped to 4 days, although the magnitude of the benefit was decreased (see **Supplement**). If the requirement was dropped to 3 days, remdesivir was associated with a lower likelihood of clinical improvement overall (aHR 0.88 [95% CI 0.86-0.90]). There were no significant effects on mortality overall (aHR 1.02 [95% CI 0.97-1.06]) or in any subgroup.

When considering the 70,133 patients who received dexamethasone, 39,146 also received remdesivir. Of these, 15,058 were successfully matched to patients who did not receive remdesivir (**Appendix Figure 7**). Remdesivir was associated with a statistically significant benefit overall (aHR 1.21 [95% CI, 1.18-1.25)]; see **Supplement, Appendix Figure 8A**), in patients on room air (aHR 1.31

[95% CI, 1.23-1.41)], **Appendix Figure 8B**) and in patients on low-flow oxygen (aHR 1.24 [95% CI, 1.20-1.28)], **Appendix Figure 8C**). In the time to death analysis, remdesivir patients on low-flow oxygen had a statistically significant mortality benefit (aHR 0.83 [95% CI, 0.76-0.91)]; see **Supplement, Appendix Figure 9**).

DISCUSSION

As of December 2021, remdesivir is the only COVID-19 treatment that has received full FDA approval, but questions remain about its real-world effectiveness. In this retrospective multicenter study of hospitalized adults in the United States, remdesivir was associated with a statistically significant increase in the likelihood of clinical improvement, with that benefit driven by patients on no or low-flow oxygen. Remdesivir did not improve mortality overall but was associated with a statistically significant increased likelihood of survival in patients on low-flow oxygen.

These findings suggest that remdesivir is mostly likely to benefit patients who are less severely ill at the time of administration and should preferentially be used in patients who are receiving no or low-flow oxygen; most patients requiring advanced levels of respiratory support are likely past the point where anti-viral therapies will be effective. This finding is in keeping with the current recommendations of the Infectious Disease Society of America (IDSA), the NIH, and the Surviving Sepsis Campaign that do not support the routine use of remdesivir in patients already on IMV or ECMO.[27-29] Ongoing clinical trials testing novel COVID-19 therapeutics against a standard of care that includes remdesivir must consider this variable efficacy by disease severity.

Our study has several strengths. We included data from over 160 hospitals across 21 states making the findings generalizable to a wide range of health systems. Our dataset included longitudinal vital signs and laboratory data, allowing for more detailed matching than in the Premier Healthcare Database retrospective study.[11] Our study also included a larger percentage of non-white participants than have previously been studied in remdesivir trials,[2,30,31] further expanding the

generalizability of the results to populations that have borne a disproportionate burden during the pandemic.[32-34] Our results are concordant with the ACTT-1 trial, which was a well-designed double-blinded placebo-controlled trial that showed a similar decrease in time to clinical improvement in remdesivir treated patients. While ACTT-1 was not powered to detect differences in mortality, patients who were receiving low-flow oxygen at enrollment had a significant reduction in mortality, similar to our results.

Our primary analyses accounted for the use of dexamethasone and other anti-inflammatory therapies that have been shown to improve outcomes in COVID-19.[22,35,36] In sensitivity analyses we found that remdesivir alone as well as remdesivir plus dexamethasone (compared to dexamethasone alone) were associated with a statistically significant increase in the likelihood of clinical improvement. Remdesivir plus dexamethasone was also associated with a statistically significant decrease in mortality (compared to dexamethasone alone) in those on low-flow oxygen. This suggests that the benefits seen in the primary analysis were driven at least in part by remdesivir and not by concomitant anti-inflammatory therapies.

Our study has limitations. Unmeasured variables could affect our treatment effect estimates. We were unable to match approximately half of the remdesivir patients, largely due to the fact that many patients received at least one dose of remdesivir, particularly after October 1, 2020. Symptom onset was not available in the dataset, so we were not able to examine whether or not the benefit of remdesivir differed based on timing of treatment. Since antiviral therapies are likely most effective early in the disease course, differential timing of treatment could bias outcomes towards specific groups. COVID-19 outcomes have improved over time,[37,38] which we accounted for by matching remdesivir patients to control patients based on admission before October 1, 2020. The early months of the pandemic presented unique challenges to health systems beyond broader secular trends. We examined this impact in sensitivity analyses excluding patients hospitalized

before July 1, 2020. Our study was conducted prior to the widespread use of vaccines and the emergence of variants such as Delta and Omicron which could impact generalizability.

When health systems are overwhelmed by COVID-19 cases, outcomes for COVID-19 patients are worse[39,40] and care for non-COVID diseases is limited.[41,42] The finding that remdesivir patients achieved clinical improvement two days sooner than matched controls could reduce the strain on healthcare systems during COVID-19 surges. This finding contrasts with a VA study that showed an increased length of stay among remdesivir recipients.[7] The majority of discharges among control patients in the VA study occurred within 3 days of matching. Since ACTT-1 excluded patients expected to be discharged within 72 hours of randomization,[2] we imposed a requirement that controls remain in the hospital for the treatment duration of the remdesivir patients (up to 5 days) in order to exclude patients who were well enough to be discharged without COVID-specific therapy. Our findings were sensitive to this requirement when it was reduced to 3 days.

In this large, multicenter retrospective cohort study, treatment with remdesivir significantly increased the likelihood of clinical improvement in patients on no or low-flow oxygen, and significantly reduced mortality in patients receiving low-flow oxygen. These results support the use of remdesivir for patients hospitalized with COVID-19 on no or low-flow oxygen and suggest that routine initiation of remdesivir in patients already requiring HFNC, NIPPV or IMV is unlikely to be beneficial.

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Conflicts of Interest

Dr. Garibaldi is a member of the FDA Pulmonary-Asthma Drug Advisory Committee and has received consulting fees from Janssen Research and Development, LLC, Gilead Life Sciences, Inc, and Atea Pharmaceuticals, Inc.; reports that HCA Healthcare provided data through the HCA Charge Consortium for the present manuscript; has received honoraria for lectures from Gilead Life Sciences, LLC (prepared all of the material and spoke about COVID-19 therapeutics, including their previously published work on remdesivir); serves on John Hopkins COVID DSMB for small clinical trials at John Hopkins; Board member, Society of Bedside Medicine (serve on board of non-profit dedicated to promoting innovation, education and research on the role of the clinical encounter in 21st century medicine). Dr. Alexander received doctoral training support from the National Heart, Lung and Blood Institute Pharmacoepidemiology T32 Training Program (T32HL139426); is past Chair and a current member of FDA's Peripheral and Central Nervous System Advisory

Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a past member of OptumRx's National P&T Committee. Ms. Andersen and Mr. Joseph received doctoral training support from the National Heart, Lung and Blood Institute Pharmacoepidemiology T32 Training Program (T32HL139426-03). Josh Betz and Robert Bollinger are entitled to equity and royalty payments from miDiagnostics. Dr. Bollinger is entitled to equity and royalty payments from emocha Health; is a consultant for Merck & Co, Hologic, Wondros, Emocha Health, Avis Budget Group, and Hip Hop Public Health; reports grants or contracts paid to the institution from the National Institutes of Health and Arab Gulf University, Bahrain; participation on a Data Safety Monitoring Board or Advisory Board for Merck and emocha Health. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. Dr. Fisher reports participating in the HCA Employee Stock Purchase Plan. Dr. Joseph reports consulting fees and stock or stock options from Takeda Pharmaceuticals. Dr. Robinson reports funding for the present manuscript from Fisher Center Discovery Program, Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases, Johns Hopkins University paid to the institution; grants or contracts from Rapid Acceleration of Diagnostics (RADx)/NIH and Critical Path Institute/FDA paid to the institution.

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Table 1. Patient Characteristics Before and After Propensity Score Matching

Characteristics	All Patients (at Day 0)			Propensity Score - Matched Patients (at matched day)		
	All Remdesivir (n = 42473)	All Control (n = 54386)	Standardized Difference	Matched Remdesivir (n = 18328)	Matched Control (n = 18328)	Standardized Difference
Demographics:						
Male	23701 (55.8%)	27607 (50.8%)	0.10	10120 (55.2%)	9764 (53.3%)	0.04
Race Black	5638 (13.3%)	11213 (20.6%)	-0.20	2843 (15.5%)	3308 (18%)	-0.07
Race Latinx	19654 (46.3%)	23188 (42.6%)	0.05	5711 (31.2%)	5120 (27.9%)	0.07
Race White	4442 (10.5%)	4916 (9%)	0.07	8027 (43.8%)	8257 (45.1%)	-0.03
Race Others[c]	12739 (30%)	15069 (27.7%)	0.10	10120 (55.2%)	9764 (53.3%)	0.04
Age, Median (IQR)	65 (53,76)	66 (52,78)	0.05	1747 (9.5%)	1643 (9%)	0.02
BMI, Median (IQR)	30.5 (26.6,36.2)	29 (24.9,34.3)	-0.02	66 (54,76)	69 (56,79)	-0.14
			0.21	30 (26.1,35.6)	29.2 (25,34.7)	0.10
O2 Devices, no. (%):	10353 (24.4%)	23206 (42.7%)				
No Supplemental Oxygen	24473 (57.6%)	25859 (47.5%)	-0.59	2856 (15.6%)	2476 (13.5%)	0.06
Low Flow Supplemental Oxygen	3590 (8.5%)	1438 (2.6%)	0.28	10314 (56.3%)	10652 (58.1%)	-0.04
High Flow Nasal Cannula	3026 (7.1%)	1702 (3.1%)	0.28	2364 (12.9%)	2198 (12%)	0.03
CPAP or BiPAP	1031 (2.4%)	2181 (4%)	0.20	1613 (8.8%)	1440 (7.9%)	0.03
Mechanical Ventilator			-0.09	1181 (6.4%)	1562 (8.5%)	-0.08
Vital Signs, Mean (SD):		37.1 (0.6)				
Temperature (^{o}Celsius)	37.1 (0.6)	86.5 (15.7)	0.08	36.9 (0.5)	36.9 (0.5)	-0.04
Pulse (beats per minute)	87.1 (14.7)	132.3 (20.4)	0.04	82.4 (14.3)	83.2 (15.1)	-0.05
Systolic BP (mmHg)	132.2 (18.2)	72.8 (10)	-0.01	130.8 (17.2)	131.2 (18.6)	-0.02
Diastolic BP (mmHg)	72.7 (9)	307.7	0.00	72.4 (8.5)	71.8 (9.3)	0.06
SpO_2/FiO_2	241.1 (99.6)	(112.2)	-0.63	234.2 (105.2)	221.7 (107)	0.12
Laboratory Results, Mean (SD):						
Absolute lymphocyte count (K cells/mm^3)	1.1 (4)	1.2 (1.6)	-0.04	1 (2.5)	1.1 (2.1)	-0.01
Platelet count (K cells/mm^3)	220.8 (89.1)	225.2 (98.2)	-0.05	233.7 (99.9)	223.5 (98)	0.10
White blood cell count (K cells/mm^3)	8.3 (6.7)	8.3 (6.1)	0.00	8.8 (6.6)	8.8 (5.5)	0.01
Hemoglobin (g/dL)	13.3 (2)	12.7 (2.3)	0.27	12.6 (2.1)	12.2 (2.3)	0.18
Albumin (g/dL)	3.2 (0.6)	3.2 (0.7)	-0.07	3 (0.6)	2.9 (0.7)	0.09
Alanine aminotransferase (U/L)	48.4 (54.2)	54.7 (145.2)	-0.06	50.9 (108.1)	48.2 (76)	0.03
Glomerular filtration rate (mL/min/1.73m^2)	70.5 (27.5)	64.1 (34.2)	0.21	72.9 (29.3)	65.8 (34.5)	0.22
Past Diagnoses, no. (%)[d]						
Hypertension	29683 (69.9%)	38298 (70.4%)	-0.01	13228 (72.2%)	14017 (76.5%)	-0.10
Congestive heart failure	6971 (16.4%)	10358 (19%)	-0.07	3327 (18.2%)	4465 (24.4%)	-0.15
Chronic kidney disease	7079 (16.7%)	13573 (25%)	-0.21	3820 (20.8%)	5613 (30.6%)	-0.23
Diabetes	19287 (45.4%)	23647 (43.5%)	0.04	8764 (47.8%)	8941 (48.8%)	-0.02
Asthma	3640 (8.6%)	3751 (6.9%)	0.06	1521 (8.3%)	1278 (7%)	0.05
COPD/Chronic Lung Disease	6173 (14.5%)	7290 (13.4%)	0.03	2841 (15.5%)	3132 (17.1%)	-0.04
Cancer	1585 (3.7%)	1958 (3.6%)	0.01	769 (4.2%)	783 (4.3%)	0.00
Liver Disease	2646 (6.2%)	3546 (6.5%)	-0.01	1193 (6.5%)	1537 (8.4%)	-0.07
AIDS/HIV	90 (0.2%)	165 (0.3%)	-0.02	49 (0.3%)	54 (0.3%)	-0.01
Transplant	257 (0.6%)	345 (0.6%)	0.00	145 (0.8%)	133 (0.7%)	0.01
Charlson Comorbidity Index:	11510 (27.1%)	13725 (25.2%)				
=0	26324 (62%)	31854 (58.6%)	0.04	4523 (24.7%)	3265 (17.8%)	0.17
1-4	4630 (10.9%)	8722 (16%)	0.07	11201 (61.1%)	11226 (61.3%)	0.00
>=5			-0.15	2600 (14.2%)	3796 (20.7%)	-0.17
Concomitant Medications, no. (%):						
Acetaminophen	30389 (71.5%)	35490 (65.3%)	0.12	13428 (73.3%)	13459 (73.4%)	-0.02
Dexamethasone	39146 (92.2%)	30987 (57%)	0.87	15209 (83%)	14247 (77.7%)	0.11
Prednisone	10772 (25.4%)	9854 (18.1%)	0.17	5693 (31.1%)	4514 (24.6%)	0.14
Hydrocortisone			0.04	608 (3.3%)	748 (4.1%)	-0.04
Tocilizumab			0.06	739 (4%)	699 (3.8%)	0.01

	1385 (3.3%) 1172 (2.8%)	1391 (2.6%) 1020 (1.9%)				

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SpO2:FIO2, ratio of peripheral blood oxygen saturation to fraction of inspired oxygen.

SI conversion factors: To convert 10; lymphocyte count and white blood cell count x 10^9/L, by 0.001; platelet count x 10^9 per

liter, by 1.0; hemoglobin to g/L, by 10.0; albumin to grams per liter, by 10; alanine aminotransferase to microkatals per liter, by 0.0167.

a Data shown are from day 0 of hospital admission.

b Data shown are from the day of remdesivir treatment initiation.

c Comprised non-White, non-Black, and non-Latinx patients.

d Only the Charlson Comorbidity Index was used in the Cox proportional hazards models. Individual comorbidities are shown but were not used in matching.

Figure Legends

Figure 1. Description of Patients Included in the Analysis

Figure 2. Unadjusted cumulative incidence curves for time to clinical improvement are shown for the entire remdesivir and matched control cohort (A); patients requiring no oxygen at time of treatment (B); patients requiring low-flow oxygen at the time of treatment (C); patients requiring HFNC or NIPPV at time of treatment (D); and patients requiring IMV at time of treatment (E). aHR indicates adjusted hazard ratio; HFNC=high flow nasal cannula; IMV=invasive mechanical ventilation; NIPPV=non-invasive positive pressure ventilation

Figure 3. Unadjusted Kaplan-Meier survival curves are shown for the entire remdesivir and matched control cohort (A); patients requiring no oxygen at time of treatment (B); patients requiring low-flow oxygen at the time of treatment (C); patients requiring HFNC or NIPPV at time of treatment (D); and patients requiring IMV at time of treatment (E). aHR=adjusted hazard ratio; HFNC=high flow nasal cannula; IMV=invasive mechanical ventilation; NIPPV=non-invasive positive pressure ventilation

Figure 1

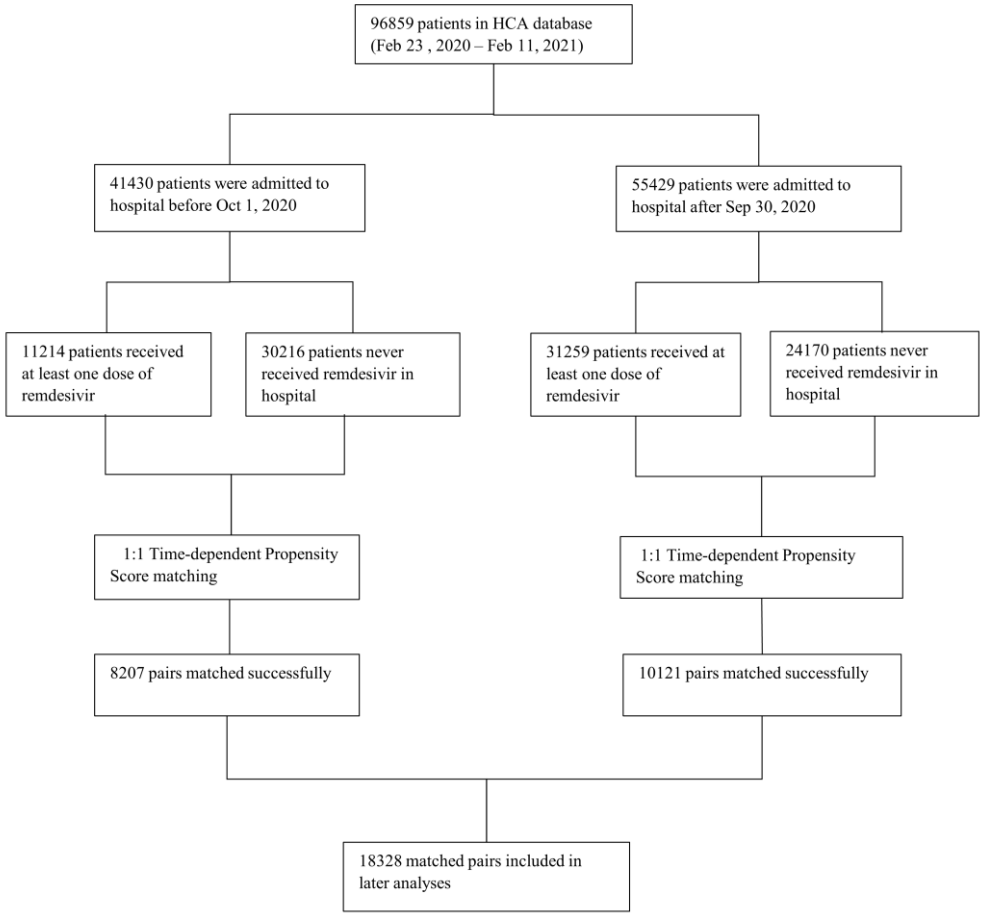

96859 patients in HCA database (Feb 23 , 2020 – Feb 11, 2021)
41430 patients were admitted to hospital before Oct 1, 2020
55429 patients were admitted to hospital after Sep 30, 2020
11214 patients received at least one dose of remdesivir
30216 patients never received remdesivir in hospital
31259 patients received at least one dose of remdesivir
24170 patients never received remdesivir in hospital
1:1 Time-dependent Propensity Score matching
1:1 Time-dependent Propensity Score matching
8207 pairs matched successfully
10121 pairs matched successfully
18328 matched pairs included in later analyses

Figure 2

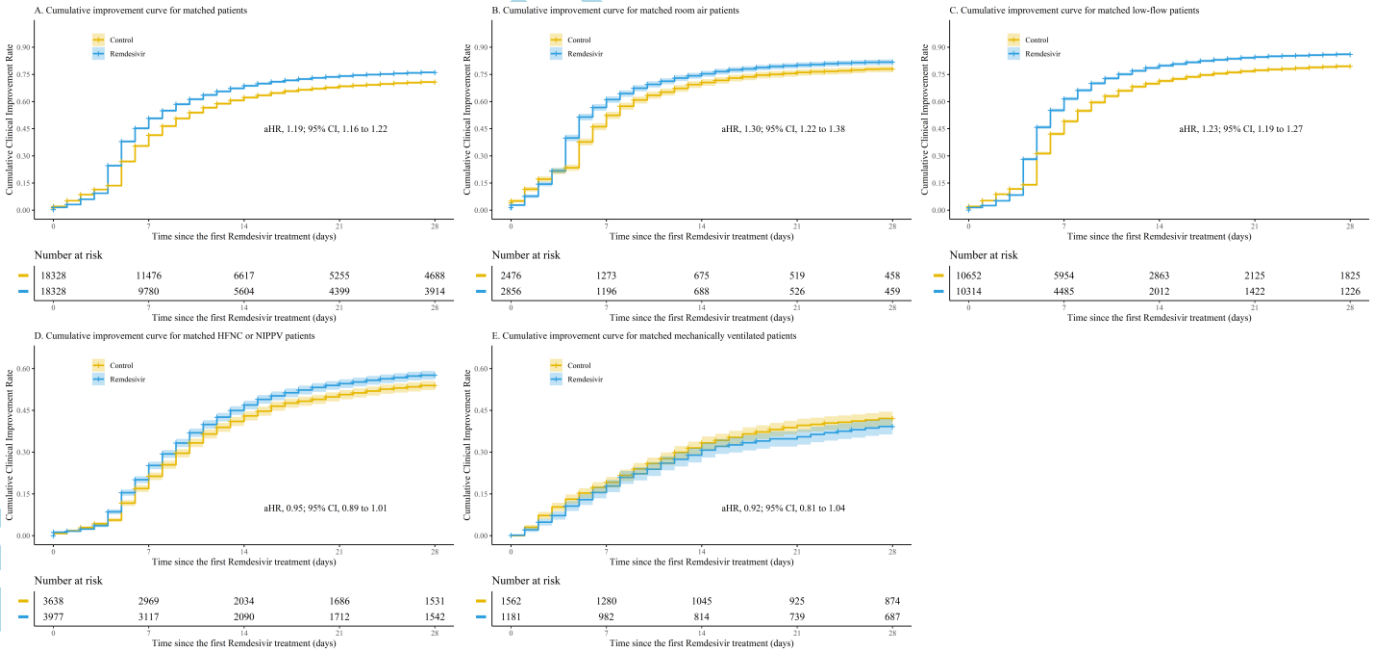
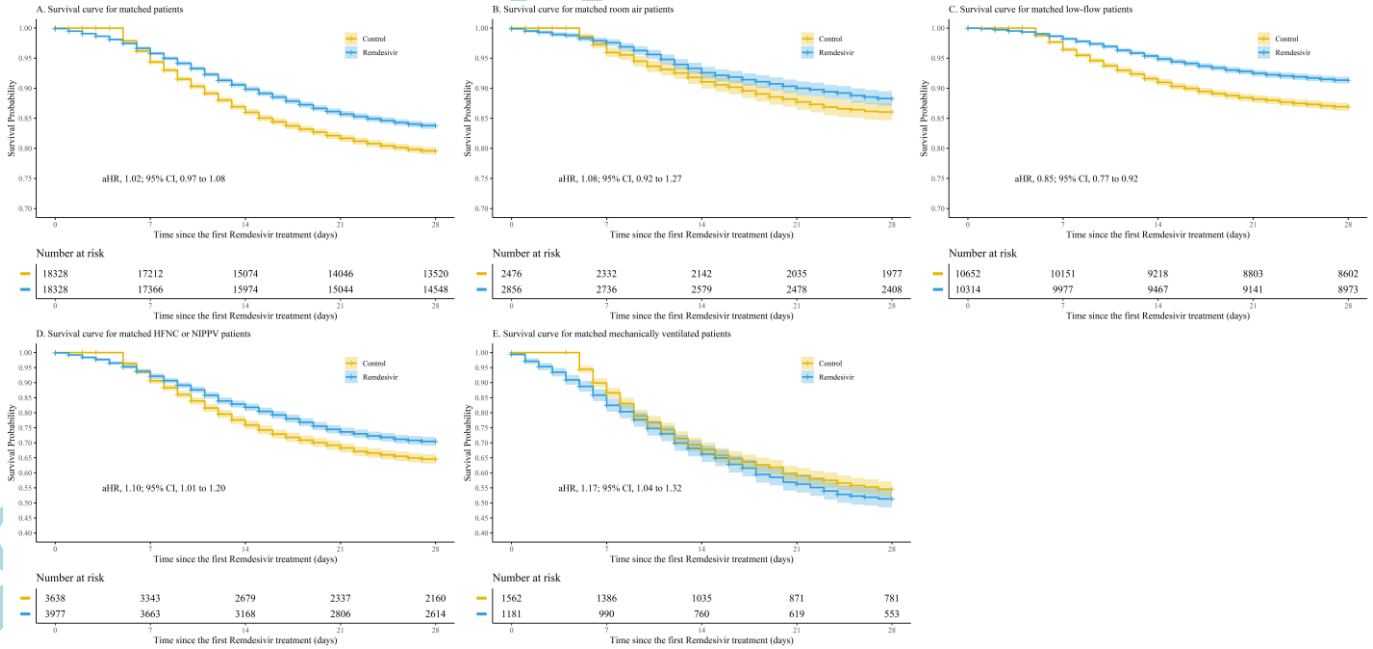

A. Cumulative improvement curve for matched patients
Control
Remdesivir
Cumulative Clinical Improvement Rate
aHR, 1.19; 95% CI, 1.16 to 1.22
Time since the first Remdesivir treatment (days)
Number at risk
18328 11476 6617 5255 4688
18328 9780 5604 4399 3914
B. Cumulative improvement curve for matched room air patients
aHR, 1.30; 95% CI, 1.22 to 1.38
2476 1273 675 519 458
2856 1196 688 526 459
C. Cumulative improvement curve for matched low-flow patients
aHR, 1.23; 95% CI, 1.19 to 1.27
10652 5954 2863 2125 1825
10314 4485 2012 1422 1226
D. Cumulative improvement curve for matched HFNC or NIPPV patients
aHR, 0.95; 95% CI, 0.89 to 1.01
3638 2969 2034 1686 1531
3977 3117 2090 1712 1542
E. Cumulative improvement curve for matched mechanically ventilated patients
aHR, 0.92; 95% CI, 0.81 to 1.04
1562 1280 1045 925 874
1181 982 814 739 687

Figure 3


A. Survival curve for matched patients
Control
Remdesivir
Survival Probability
aHR, 1.02; 95% CI, 0.97 to 1.08
Time since the first Remdesivir treatment (days)
Number at risk
18328 17212 15074 14046 13520
18328 17366 15974 15044 14548
B. Survival curve for matched room air patients
aHR, 1.08; 95% CI, 0.92 to 1.27
2476 2332 2142 2035 1977
2856 2736 2579 2478 2408
C. Survival curve for matched low-flow patients
aHR, 0.85; 95% CI, 0.77 to 0.92
10652 10151 9218 8803 8602
10314 9977 9467 9141 8973
D. Survival curve for matched HFNC or NIPPV patients
aHR, 1.10; 95% CI, 1.01 to 1.20
3638 3343 2679 2337 2160
3977 3663 3168 2806 2614
E. Survival curve for matched mechanically ventilated patients
aHR, 1.17; 95% CI, 1.04 to 1.32
1562 1386 1035 871 781
1181 990 760 619 553