Association of Remdesivir Treatment With Mortality Among Hospitalized Adults With COVID-19 in the United States

Anand P. Chokkalingam, PhD; Jennifer Hayden, MS; Jason D. Goldman, MD, MPH; Hu Li, MBBS, PhD; Julius Asubonteng, PhD; Essy Mozaffari, PharmD, MPH, MBA; Christopher Bush, MPH; Jocelyn R. Wang, MS; Amanda Kong, PhD; Anu O. Osinusi, MD, MPH; Robert L. Gottlieb, MD, PhD

Abstract

IMPORTANCE SARS-CoV-2, which causes COVID-19, poses considerable morbidity and mortality risks. Studies using data collected during routine clinical practice can supplement randomized clinical trials to provide needed evidence, especially during a global pandemic, and can yield markedly larger sample sizes to assess outcomes for important patient subgroups.

OBJECTIVE To evaluate the association of remdesivir treatment with inpatient mortality among patients with COVID-19 outside of the clinical trial setting.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study in US hospitals using health insurance claims data linked to hospital chargemaster data from December 1, 2018, to May 3, 2021, was conducted among 24856 adults hospitalized between May 1, 2020, and May 3, 2021, with newly diagnosed COVID-19 who received remdesivir and 24856 propensity score–matched control patients.

EXPOSURE Remdesivir treatment.

MAIN OUTCOMES AND MEASURES All-cause inpatient mortality within 28 days of the start of remdesivir treatment for the remdesivir-exposed group or the matched index date for the control group.

RESULTS A total of 24 856 remdesivir-exposed patients (12 596 men [50.7%]; mean [SD] age, 66.8 [15.4] years) and 24 856 propensity score–matched control patients (12 621 men [50.8%]; mean [SD] age, 66.8 [15.4] years) were included in the study. Median follow-up was 6 days (IQR, 4-11 days) in the remdesivir group and 5 days (IQR, 2-10 days) in the control group. There were 3557 mortality events (14.3%) in the remdesivir group and 3775 mortality events (15.2%) in the control group. The 28-day mortality rate was 0.5 per person-month in the remdesivir group and 0.6 per person-month in the control group. Remdesivir treatment was associated with a statistically significant 17% reduction in inpatient mortality among patients hospitalized with COVID-19 compared with propensity score–matched control patients (hazard ratio, 0.83 [95% CI, 0.79-0.87]).

CONCLUSIONS AND RELEVANCE In this retrospective cohort study using health insurance claims and hospital chargemaster data, remdesivir treatment was associated with a significantly reduced inpatient mortality overall among patients hospitalized with COVID-19. Results of this analysis using data collected during routine clinical practice and state-of-the-art methods complement results from randomized clinical trials. Future areas of research include assessing the association of remdesivir treatment with inpatient mortality during the circulation of different variants and relative to time from symptom onset.

Introduction

SARS-CoV-2 poses considerable morbidity and mortality risk.\textsuperscript{1-3} Current clinical guidelines recommend treatment with remdesivir, a direct-acting nucleotide analogue prodrug inhibitor of coronavirus RNA–dependent RNA polymerase, for hospitalized patients with mild-to-moderate and severe COVID-19.\textsuperscript{4-6} as well as an early intervention to prevent progression to hospitalization for outpatients with 1 or more risk factors for progression.\textsuperscript{5,7} Regulatory approval\textsuperscript{8} and treatment guidelines were based on evidence from phase 3 randomized clinical trials (RCTs), including the Adaptive COVID-19 Treatment Trial 1 (ACTT-1)\textsuperscript{9}: a randomized, placebo-controlled trial that demonstrated improved clinical recovery for patients receiving remdesivir. However, ACTT-1, conducted early in the pandemic, was not formally powered to assess for mortality benefit overall or for subgroups of patients receiving differing levels of oxygen support. An initial report from the open-label World Health Organization Solidarity trial showed no statistically significant mortality benefit for remdesivir treatment.\textsuperscript{10} The final study report, with a larger sample size, found no improvement in mortality for the full study population; however, a statistically significant mortality benefit was observed for patients receiving oxygen without mechanical ventilation. This finding was later confirmed in a meta-analysis.\textsuperscript{11} A second living meta-analysis also confirmed the mortality benefit associated with remdesivir treatment for patients who initiated treatment when receiving supplemental oxygen and without mechanical ventilation at baseline.\textsuperscript{12} No deaths were reported during the efficacy period for early outpatient use of remdesivir in the placebo-controlled PINETREE trial (NCT04501952)\textsuperscript{7}; thus, assessment of mortality is most salient to patients hospitalized for COVID-19.

Although blinded evidence from RCTs is considered the criterion standard, there are mixed results between some previously published trials and the effectiveness of remdesivir treatment in pandemic conditions.\textsuperscript{9-12} Results from “real-world data”\textsuperscript{13-15} (ie, data collected during routine clinical practice) can complement trial results, especially during a global pandemic when rapidly changing clinical management outpaces the development and execution of new trials.\textsuperscript{16,17} Leveraging existing data collected during routine clinical practice to emulate a target trial can expedite needed evidence for patient care and clinical decision-making.\textsuperscript{18} Moreover, markedly larger sample sizes than those found in RCTs can adequately power studies to assess outcomes among important patient subgroups. COVID-19 presents unique challenges to conducting rigorous observational studies using routinely collected clinical practice data.\textsuperscript{16-19} We sought to evaluate the association of remdesivir treatment and inpatient mortality among patients with COVID-19 in a large, geographically representative hospitalization data set in the US outside of the clinical trial setting. We hypothesized that remdesivir use for patients hospitalized with COVID-19 would be associated with a lower incidence of inpatient mortality.

Methods

Data Source

This retrospective cohort study used deidentified data from the HealthVerity ecosystem, including hospital chargemaster data from approximately 400 hospitals and medical and pharmacy claims from commercial, Medicare, and Medicaid health plans between December 1, 2018, and May 3, 2021. The data source covers all Census Bureau divisions in the US, although individuals from the Southern region are overrepresented based on geographic distribution of the US population (eMethods in the Supplement). The study was approved and patient consent was waived under an applicable exemption for deidentified data by the WCG institutional review board and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.\textsuperscript{20}
Definitions
COVID-19 diagnosis was defined as an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnosis code of U07.1 (COVID-19, virus identified) in any position on a medical claim, inclusive of inpatient hospital encounters. Remdesivir exposure was defined as an inpatient hospital encounter with either an *ICD-10* procedure code corresponding to remdesivir administration in the peripheral or central vein (XW033E5 or XW043E5) or a text string including “remdesivir” in the hospital chargemaster code description identified by a text search followed by manual review of the returned descriptions. To define COVID-19 disease severity, we further refined an algorithm to define oxygen support status.21 In this adaptation, we identified the following categories: room air (no demonstrable use of supplemental oxygen), low-flow oxygen, high-flow oxygen or noninvasive ventilation, and invasive mechanical ventilation or extracorporeal membrane oxygenation.21 The definitions for other covariates, including comorbidities, are provided in eTable 1 in the Supplement.

The index date was defined as the day during the inpatient stay when remdesivir treatment was initiated for each patient in the remdesivir-exposed cohort and the corresponding day of hospitalization for the patient’s propensity score (PS)–matched control (eFigure 1 in the Supplement). Demographic characteristics and COVID-19 severity were assessed on the index date; comorbidities were measured in the 12 months prior to, and excluding, the index date. Concomitant medications were assessed between hospital admission and the index date.

Study Population
This study included patients hospitalized with newly diagnosed COVID-19 between May 1, 2020, the date of remdesivir’s emergency use authorization, and May 3, 2021. All hospitalized patients aged 18 years or older with a COVID-19 diagnosis recorded any time during the hospitalization, activity in the data source starting at least 12 months prior to the index date, and at least 1 medical claim or chargemaster record in the 12 months before the index date were eligible. Patients with evidence of clinical trial participation, prior COVID-19 inpatient hospitalization, or prior use of remdesivir were excluded (Figure 1).

Among the eligible patient cohort, a 2-stage approach was used to achieve balance in baseline characteristics between remdesivir-exposed and PS-matched control patients (eMethods and eFigure 1 in the Supplement). In the first stage, we used 1:1 risk-set sampling (RSS) to match patients initiating remdesivir treatment with control patients based on the following covariates: categorical patient age and sex, COVID-19 disease severity (oxygen requirement and intensive care unit status between hospital admission and matching), categorized number of days between hospital admission and day of matching, corticosteroid use, and calendar time (±3 days of hospitalization). The index date was assigned as the day of matching, which was the first day of remdesivir treatment for the exposed persons and the corresponding time from hospital admission for the matched controls (eMethods in the Supplement). Creating an RSS cohort allowed us to identify a pool of potential control patients that approximates the standard of care without remdesivir treatment. Because patients were matched on calendar time, the circulating COVID-19 variants and treatment recommendations at the time of hospitalization would have been the same for the matched cohorts. Given how RSS is conducted, for example, where patients who initiated remdesivir treatment on day 1 were matched to patients who did not initiate remdesivir on day 1, matched controls had not received remdesivir as of the index date but may have initiated it later.

In the second stage, we subsequently used the pool of eligible patients in the RSS cohort to perform PS matching to identify cohorts of PS-matched remdesivir-exposed patients and control patients. We used PS methods to adjust for baseline differences between the remdesivir-exposed and control groups. Our final analytic cohort consisted of remdesivir-exposed patients who were PS-matched to control patients on the following covariates: patient demographics (age, sex, geographic region); comorbidities defined by aggregates of *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* Procedure Coding System called the Clinical
Classifications Software Refined; concomitant medications (corticosteroids, HIV protease inhibitors, hydroxychloroquine-chloroquine, immunomodulators, convalescent plasma); and COVID-19 disease severity (baseline oxygen support status, intensive care unit admission, and number of days since hospitalization). Refer to eTable 1 in the Supplement for definition of covariates included in the PS model. We assessed baseline covariate balance between the exposed and control patients in the PS-matched cohort using absolute standardized differences, applying a threshold of 0.10 difference to indicate well-balanced groups.22

**Statistical Analysis**

The primary outcome was time to all-cause inpatient death, defined as a discharge status of “expired,” within 28 days of index. We performed 2 prespecified analyses: initial-treatment and as-treated approaches. The initial-treatment analyses assumed that patients continued their treatment, similar to the intention-to-treat approach used in RCTs. Given the high degree of crossover to remdesivir in the control group and differential censoring, the focus of this article is on the more conservative initial-treatment analysis. Patients were censored on the earliest occurrence of discharge or maximum follow-up of 28 days. Cause-specific hazards models were applied to the PS-matched cohort to estimate hazard ratios (HRs) and 95% CIs of remdesivir compared with control patients (α = .05). No covariates were included in the models as these were well adjusted in the RSS and PS matching. Subgroup analyses by oxygen support requirement status at the time of remdesivir initiation were also performed. Propensity score matching was done separately within each oxygen requirement group.
support requirement subgroup. The as-treated analysis is presented in the eMethods in the Supplement.

Last, 2 post hoc analyses were performed: a competing risk analysis was conducted using the Fine-Gray subdistribution hazard regression model24-26 and a tipping point analysis was performed using the E-value.27 Details of these analyses can be found in the eMethods in the Supplement.

Data were analyzed using the previously validated Aetion Evidence Platform,28 version r4.25.0.20210511 (Aetion Inc) and R, version 3.4.2 (R Group for Statistical Computing). The E-value was calculated using an online calculator that is available publicly.27,29,30

Results

Patients

There were 1143770 patients with any inpatient hospitalizations admitted between May 1, 2020, and May 3, 2021, of whom 113579 met the specified eligibility criteria (Figure 1). Of these, 39 775 (35.0%) received remdesivir; the median number of days from admission to remdesivir initiation was 1 day (IQR, 0.5-1.0 days) (eFigure 2 in the Supplement). After RSS and PS matching, 24 856 remdesivir-exposed patients were matched to 24 856 control patients. Demographic and clinical characteristics were well balanced between the groups, overall and within oxygen support requirement subgroups; all absolute standardized differences were less than 0.10 with complete overlap of PSs (Table; eTables 2 and 3 and eFigure 3 in the Supplement). More information on the patient population can be found in the eResults in the Supplement.

The mean (SD) age was 66.8 (15.4) years (median, 68 years [IQR, 57-77 years]) for remdesivir-exposed patients and 66.8 (15.4) years (median, 67 years [IQR, 57-77 years]) for PS-matched control patients; female patients comprised 47.9% of each group (Table). The most common comorbid condition categories among remdesivir-exposed patients and matched-control patients were metabolic (19 208 [77.3%] and 19 189 [77.2%]), hypertension (17 921 [72.1%] and 17 902 [72.0%]), and respiratory conditions (17 155 [69.0%] and 17 163 [69.0%]). Between hospital admission and the index date, 7361 patients in the PS-matched cohort (29.6%) were in the intensive care unit. Corticosteroids were used for 17 507 patients (70.4%) in the exposed group and 17 459 patients (70.2%) in the control group; the use of other COVID-19 medications at baseline was infrequent (eTable 4 in the Supplement). Regarding baseline use of oxygen, most patients were breathing room air (remdesivir group, 15 947 [64.2%] and control group, 15 967 [64.2%] with no charges for supplemental oxygen), followed by low-flow oxygen (remdesivir, 5434 [21.9%] and controls, 5402 [21.7%]) (Table). A total of 2706 patients (10.9%) in the remdesivir group and 2721 patients (10.9%) in the control group were receiving baseline high-flow oxygen or noninvasive ventilation and 769 patients (3.1%) in the remdesivir group and 766 patients (3.1%) in the control group were receiving baseline extracorporeal membrane oxygenation or invasive mechanical ventilation.

In the initial-treatment analysis, follow-up was a median of 6 days (IQR, 4-11 days) in the exposed group and 5 days (IQR, 2-10 days) in the control group. Most patients in both groups were censored at discharge (81.0% of the exposed group [n = 20 121] and 80.8% of the control group [n = 20 093]; eTable 5 in the Supplement). In the control group, 6259 patients (25.2%) eventually received remdesivir treatment and were censored at initiation in the as-treated analysis (eTable 6 in the Supplement).

Inpatient Mortality

In the initial-treatment analysis, we observed 3557 mortality events (14.3%) in the remdesivir group and 3775 mortality events (15.2%) in the control group. The 28-day mortality rate was 0.5 per person-month in the remdesivir group and 0.6 per person-month in the control group. In the traditional Cox proportional hazards regression model, remdesivir initiation at index was associated with a statistically significant 17% reduction in inpatient mortality (HR, 0.83 [95% CI, 0.79-0.87]) (Figure 2). Cumulative incidence curves are presented in eFigure 4 in the Supplement. In the oxygen
support requirement subgroup analyses, statistically significant mortality reductions were observed across each subgroup, including patients breathing room air (HR, 0.88 [95% CI, 0.82-0.94]), patients receiving low-flow oxygen (HR, 0.81 [95% CI, 0.73-0.90]), patients receiving high-flow oxygen or noninvasive ventilation (HR, 0.77 [95% CI, 0.71-0.85]), and patients receiving extracorporeal membrane oxygenation or invasive mechanical ventilation (HR, 0.83 [95% CI, 0.73-0.95]) (Figure 2). Results for the as-treated analysis were similar (eFigure 5 in the Supplement). In the tipping point analysis, the E-value for the HR of 0.83 was 1.70, meaning the HR could be explained completely by residual confounding if an unmeasured confounder had a relative risk association of 1.70 or greater.

Table. Patient Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PS matched, No. (%)</th>
<th>Absolute standardized difference^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Remdesivir group (n = 24 856)</td>
<td>Control group (n = 24 856)</td>
</tr>
<tr>
<td>Age, y</td>
<td>66.8 (15.4)</td>
<td>66.8 (15.4)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>68 (57-77)</td>
<td>67 (57-77)</td>
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<tr>
<td>Geographic region</td>
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<td></td>
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<tr>
<td>Northeast</td>
<td>4062 (16.3)</td>
<td>4095 (16.5)</td>
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<tr>
<td>Midwest</td>
<td>2332 (9.4)</td>
<td>2341 (9.4)</td>
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<tr>
<td>South</td>
<td>12 235 (49.2)</td>
<td>12 189 (49.0)</td>
</tr>
<tr>
<td>West</td>
<td>6221 (25.0)</td>
<td>6225 (25.0)</td>
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<tr>
<td>Other, unknown, or missing</td>
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<td>6 (0.02)</td>
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<td>Sex</td>
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<tr>
<td>Female</td>
<td>11 917 (47.9)</td>
<td>11 906 (47.9)</td>
</tr>
<tr>
<td>Male</td>
<td>12 596 (50.7)</td>
<td>12 621 (50.8)</td>
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<td>Unknown</td>
<td>343 (1.4)</td>
<td>329 (1.3)</td>
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<tr>
<td>Oxygen support status^b</td>
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<tr>
<td>Room air</td>
<td>15 947 (64.2)</td>
<td>15 967 (64.2)</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>5434 (21.9)</td>
<td>5402 (21.7)</td>
</tr>
<tr>
<td>High-flow oxygen or NIV</td>
<td>2706 (10.9)</td>
<td>2721 (10.9)</td>
</tr>
<tr>
<td>ECMO or IMV</td>
<td>769 (3.1)</td>
<td>766 (3.1)</td>
</tr>
<tr>
<td>ICU</td>
<td>7361 (29.6)</td>
<td>7361 (29.6)</td>
</tr>
<tr>
<td>Time since hospitalization, d</td>
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<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.87 (2.47)</td>
<td>1.92 (2.33)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.00 (1.00-2.00)</td>
<td>1.00 (1.00-2.00)</td>
</tr>
<tr>
<td>Concomitant medications^c</td>
<td></td>
<td></td>
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<tr>
<td>Corticosteroids</td>
<td>17 507 (70.4)</td>
<td>17 459 (70.2)</td>
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<tr>
<td>Immunomodulators</td>
<td>208 (0.8)</td>
<td>218 (0.9)</td>
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<tr>
<td>Interferon</td>
<td>8 (0.03)</td>
<td>12 (0.05)</td>
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<tr>
<td>Tocilizumab</td>
<td>167 (0.7)</td>
<td>205 (0.8)</td>
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<tr>
<td>Siltuximab</td>
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<td>0</td>
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<tr>
<td>Sarilumab</td>
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<td>0</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>33 (0.1)</td>
<td>3 (0.01)</td>
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<td>Baseline clinical covariates based on CCSR^d</td>
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<tr>
<td>Metabolic disease</td>
<td>19 208 (77.3)</td>
<td>19 189 (77.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 081 (44.6)</td>
<td>11 057 (44.5)</td>
</tr>
<tr>
<td>Obesity^g</td>
<td>8197 (33.0)</td>
<td>8185 (32.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 921 (72.1)</td>
<td>17 902 (72.0)</td>
</tr>
<tr>
<td>Kidney disease</td>
<td></td>
<td></td>
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<tr>
<td>Acute</td>
<td>6172 (24.8)</td>
<td>6157 (24.8)</td>
</tr>
<tr>
<td>Chronic</td>
<td>6208 (25.0)</td>
<td>6151 (24.7)</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>17 155 (69.0)</td>
<td>17 163 (69.0)</td>
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<tr>
<td>Musculoskeletal or connective tissue disease</td>
<td>14 804 (59.6)</td>
<td>14 741 (59.3)</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>13 991 (56.3)</td>
<td>14 013 (56.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CCSR, Clinical Classifications Software Refined; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; PS, propensity score.

^a Absolute standardized difference.22

^b Measured in risk-set sample on day of remdesivir administration.

^c Defined as the absence of the following procedures: low-flow oxygen, high-flow oxygen or NIV, or IMV or ECMO.

^d Measured in PS matching between inpatient admission and remdesivir administration. Concomitant medications included in the PS were convalescent plasma, corticosteroids, HIV protease inhibitors, hydroxychloroquine-chloroquine, and immunomodulators (see eTable 1 in the Supplement for definitions of covariates and references and eTable 4 in the Supplement for full patient characteristics).

^e Measured 365 days prior to inpatient admission.

^f Comorbidities included in the PS were abnormal blood pressure (hypertension); abnormal blood pressure (hypotension); behavioral; blood; cerebrovascular disease; conductive disorders or dysrhythmias; diabetes; digestive; diseases in arteries, arterioles, or capillaries; disease of pulmonary circulation; diseases in veins, lymphatic vessels, or lymph nodes; endocrine; factors associated with health status; infection; ischemic heart disease; heart failure; malformations; metabolic; mood or neurologic; musculoskeletal or connective tissue; neoplasms; neurologic; obesity; other and unspecified disorder of the circulatory system; other forms of heart disease; other signs or symptoms; kidney (acute); kidney (chronic); rheumatic fevers or disease; respiratory; smoking; and transplant (see eTable 1 in the Supplement for definitions of clinical covariates and references and eTable 4 in the Supplement for full patient characteristics).

^g Defined as body mass index 30 or higher (calculated as weight in kilograms divided by height in meters squared).
with remdesivir exposure and with inpatient mortality. In the post hoc initial-treatment analysis treating discharge as a competing risk using the Fine-Gray subdistribution hazard model, a similar overall reduction in mortality with remdesivir initiation at index was observed (subdistribution HR, 0.88 [95% CI, 0.85-0.92]) (eFigure 6 in the Supplement).

**Discussion**

In this large US-based retrospective cohort study with nearly 25,000 remdesivir-exposed hospitalized patients identified between May 1, 2020, and May 3, 2021, remdesivir treatment was associated with an overall significantly reduced inpatient mortality among patients hospitalized with COVID-19 compared with PS-matched control patients. Our findings support the results of the ACTT-1 trial, which noted numerically lower inpatient mortality by day 29 in the remdesivir-treated group, a result that was not statistically significant as the trial was not powered for this secondary outcome (HR, 0.73 [95% CI, 0.52-1.03]). Similar inpatient mortality results were noted among hospitalized adults receiving remdesivir vs the local standard of care in the World Health Organization Solidarity open-label trial, which observed a statistically significant 13% reduction in the mortality rate among patients in the subgroup who required oxygen but not mechanical ventilation. These results among inpatients are bolstered by recent RCT findings noting that outpatient use of remdesivir was associated with an 87% reduction in the risk of hospitalization for COVID-19 among high-risk patients.

Nonrandomized studies using data collected during routine clinical practice have been published that support the mortality benefit associated with remdesivir treatment among hospitalized patients with COVID-19. Olander et al conducted a comparative analysis using data from an international phase 3, randomized, open-label trial of remdesivir for patients with severe COVID-19 vs an international, contemporary clinical cohort of patients receiving standard of care. Propensity score matching was applied to balance the exposure and control groups by clinical status (7-point ordinal score), age, sex, race, country, obesity, comorbidities, and use of investigational COVID-19 medications. The authors observed lower mortality within 28 days of follow-up among 368 patients receiving remdesivir compared with 1399 patients receiving standard of care (odds ratio, 0.67 [95% CI, 0.47-0.95]). Diaz et al conducted a retrospective cohort study comparing remdesivir treatment with best supportive care among patients hospitalized with COVID-19 between February and May 2020. After applying eligibility criteria similar to a clinical trial and performing multivariate adjustment, Diaz et al observed a significant decrease in mortality (HR, 0.60 [95% CI, 0.40-0.90]) among 286 patients who received remdesivir vs 852 patients receiving only supportive care. In both studies, the association of remdesivir treatment with lower mortality predominated for the subgroup

**Figure 2. Mortality by Oxygen Support Level Subgroup Using Cause-Specific Hazards Model (Initial Treatment)**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Control group</th>
<th>Remdesivir group</th>
<th>Favors remdesivir</th>
<th>Favors comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, No.</td>
<td>Events, No.</td>
<td>Person-months</td>
<td>Rate per person-month</td>
</tr>
<tr>
<td>Overall</td>
<td>24,856</td>
<td>3775</td>
<td>6072</td>
<td>0.6</td>
</tr>
<tr>
<td>Room air</td>
<td>15,709</td>
<td>1553</td>
<td>3492</td>
<td>0.4</td>
</tr>
<tr>
<td>Low-flow oxygen</td>
<td>5523</td>
<td>725</td>
<td>1296</td>
<td>0.6</td>
</tr>
<tr>
<td>High-flow oxygen or NIV</td>
<td>2646</td>
<td>1007</td>
<td>912</td>
<td>1.1</td>
</tr>
<tr>
<td>ECMO/IMV</td>
<td>728</td>
<td>450</td>
<td>312</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Patients were censored on the earliest occurrence of discharge to home, inpatient death, or maximum follow-up of 28 days. Room air was defined as the absence of the following procedures: low-flow oxygen, high-flow oxygen or noninvasive ventilation (NIV), or invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO). HR indicates hazard ratio.
of patients receiving low-flow oxygen. In contrast, in an analysis using the US Veterans Health Administration database (between May and October 2020), Ohl et al. observed no association with mortality among 1172 patients receiving remdesivir and 1172 PS-matched controls (HR, 1.06 [95% CI, 0.83-1.36]). Patients in that study were PS matched on illness severity; however, illness severity was based on patients' vital signs rather than supplied oxygen support intensity, which was unavailable in the Veterans Administration data set. Mozaffari et al. published a study using a different US-based hospitalization database including patients hospitalized between August and November 2020. The authors examined 28 855 patients with COVID-19 receiving remdesivir within the first 2 days of hospitalization matched to 16 687 patients who did not receive remdesivir. Consistent with our findings, Mozaffari et al. also observed a reduction in mortality with remdesivir treatment, with an HR of 0.76 (95% CI, 0.70-0.83) at 14 days and 0.89 (95% CI, 0.82-0.96) at 28 days.

**Strengths and Limitations**

This analysis has several strengths. First, we used robust methods, including RSS and PS matching to balance the exposure and control groups. By including calendar time in the RSS, along with the number of days between hospitalization and index date, hospital baseline oxygen support level, and inpatient corticosteroid use, and by PS matching across a broad range of baseline covariates, the remdesivir-exposed and matched control cohorts were well balanced, minimizing potential confounding and time-related bias. We also conducted post hoc competing risk analyses, despite ongoing debate of whether using nonparametric survival analysis or competing risk analysis is appropriate in the context of an acute illness such as COVID-19 with a short follow-up period, and found clinically similar point estimates. In addition, we attempted to emulate a hypothetical “target trial” by using risk-set sampling, thus chronologically mimicking the randomization process. Second, the sample size of this analysis, 24 856 remdesivir-exposed patients, is larger than previous RCTs and observational data analyses of remdesivir. This large sample size permitted robustly powered assessments of inpatient mortality, including within oxygen support level subgroups. Third, because these data come from a wide range of hospitals across the US, and because of the minimal inclusion and exclusion criteria, these results represent clinical observations among hospitalized patients with COVID-19 in the US. Fourth, sensitivity analyses were conducted using different study parameters and the results support the robustness of the findings.

This analysis is also subject to limitations. First, not all remdesivir-exposed hospitalized patients were included in the analysis if a corresponding control patient could not be identified for RSS or PS matching. Owing to rapidly evolving treatment regimens, fewer patients with more severe COVID-19 were available to serve as controls. Despite this, RSS matching resulted in just 5.9% of all remdesivir-exposed patients (2328 of 39 775) not being included in either of the 2 cohorts (eTable 3 in the Supplement). Second, because of changes in clinical care, we observed a sizable amount of crossover to remdesivir among control patients, and consequent right-censoring in the as-treated analysis (eTables 5 and 6 in the Supplement). Third, hospital baseline oxygen support levels were defined entirely by procedural, diagnosis, and revenue codes and may be misclassified. Specifically, the definition of “room air” relied on the absence of hospital charge codes for other oxygen support. This may have led to an overestimation of the number of patients breathing room air alone, based on our expectations from contemporary COVID-19 treatment guidelines. The potential association of this shortcoming with outcomes was mitigated by the fact that such misclassification is unlikely to be differential between the remdesivir-exposed and matched control cohorts when baseline oxygen support level was used as a balancing factor. However, it is possible that the findings for remdesivir in the subgroup of patients who were breathing room air only may be influenced by a heterogeneous subgroup of patients who actually received supplemental oxygen at index; consequently, results for this subgroup must be viewed cautiously. Nevertheless, the lower mortality rate among the patients in the subgroup receiving no supplemental oxygen appears to reflect a lower-risk physiology of these patients, as anticipated. In addition, a small number of patients were recorded as having both death and discharge events (0.2%), which was nondifferential between both groups.
Last, despite the methods used to achieve balance between cohorts, there may be residual or unmeasured confounding factors that could have influenced the study results. Information on COVID-19 symptoms, in particular, time from symptom onset to hospitalization or remdesivir administration, which has been shown to be associated with improved outcomes with remdesivir treatment,7,39,40 may not be accurately captured in this data source that relies on health care interactions and diagnosis coding. Additional measures not available in the data source include alternative disease severity scores, as well as race and ethnicity. As receipt of COVID-19 vaccine did not require insurance coverage, vaccination is definitively underascertained in these data, and thus was not assessed. Hospital characteristics, such as hospital practices and policies allocating remdesivir to patients, particularly early in the pandemic, and other factors associated with treatment decisions, could also not be assessed. In the tipping point analysis, the E-value is 1.70 for the HR point estimate of 0.83. It is conceivable that unmeasured confounders (such as those associated with disease severity or with race and ethnicity) could be present. As we controlled for disease severity based on oxygen support status and intensive care unit admission and other demographic factors, it would be unlikely that residual confounding would surpass this tipping point. This study did not analyze treatments or concomitant medications received after index or mortality information after discharge as only data on inpatient mortality were available in this data source. As the time period of this study ended prior to the rise of the Delta and Omicron variants, future research should be conducted to evaluate the association of remdesivir treatment with inpatient mortality when those variants were dominant.

Conclusions

The results of this retrospective cohort study analyzing health insurance claims linked to chargemaster data using state-of-the-art methods demonstrate that remdesivir treatment was associated with a significantly reduced inpatient mortality overall, consistent with the published literature and trial results. Future areas of research include assessing the association of remdesivir treatment with inpatient mortality during the circulation of different variants and relative to time from symptom onset.
Acquisition, analysis, or interpretation of data: Chokkalingam, Hayden, Goldman, Li, Asubonteng, Bush, Wang, Kong, Osinusi, Gottlieb.

Drafting of the manuscript: Chokkalingam, Bush, Kong, Osinusi, Gottlieb.

Critical revision of the manuscript for important intellectual content: Chokkalingam, Hayden, Goldman, Li, Asubonteng, Mozaffari, Bush, Wang, Osinusi, Gottlieb.


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REFERENCES


**SUPPLEMENT.**

**eMethods.**

**eResults.**

**eTable 1.** Definitions for Covariates Included in the PS Model (Unless Otherwise Noted)

**eTable 2.** Demographic and Clinical Characteristics of Patients Hospitalized for COVID-19 by Administration of Remdesivir Among Hospitalized Patients Meeting the Study Eligibility Criteria (Before Risk Set Sampling)

**eTable 3.** Patient Characteristics of Patients Receiving Remdesivir but Not Included in the Risk Set Sampling-Matched or Propensity Score-Matched Cohorts

**eTable 4.** Patient Characteristics Matched on RSS Status and Matched Further on Propensity Score

**eTable 5.** Distribution of Censoring Reasons by Treatment Status in the Initial-Treatment (IT) PS-Matched Cohort

**eTable 6.** Distribution of Censoring Reasons by Treatment Status in the As-Treated (AT) PS-Matched Cohort

**eFigure 1.** Study Design

**eFigure 2.** Mean Days From Admission to Remdesivir Administration by Quarter Between 2020 and 2021

**eFigure 3.** Propensity Score Distribution Before and After PS-Matching

**eFigure 4.** Cumulative Incidence of Inpatient Mortality for Remdesivir-Exposed and Referent Control Patients

**eFigure 5.** Mortality by Oxygen Support Level Subgroup Using Cause-Specific Hazards Model (As-Treated)

**eFigure 6.** Mortality by Oxygen Support Level Subgroup Using Fine-Gray Subdistribution Hazard Model (Initial-Treatment)