Remdesivir use and outcomes during the FDA COVID-19 emergency use authorization period

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Abstract
Background: Remdesivir (RDV) was approved for treatment of coronavirus disease 2019 (COVID-19), in May 2020 under US Food and Drug Administration emergency use authorization (EUA). Clinical outcomes related to RDV use in hospitalized patients during the EUA period are not well described.

Methods: We conducted a retrospective study of patients who received RDV under EUA. The primary outcome was clinical recovery by day 14 as determined by an eight-category ordinal scale. Secondary outcomes included recovery and survival to day 28, and adverse events. Recovery and survival were calculated using a stratified log-rank Kaplan–Meier estimator and a Cox proportional hazards model.

Results: Overall, 164 patients received RDV between May and October 2020, and 153 (93.3%) had evaluable data. Most (77.1%) were hospitalized within 10 days of symptom onset, and 79.7% started RDV within 48 hours. By days 14 and 28, 96 (62.7%) and 117 patients (76.5%) met the definition of clinical recovery, respectively. Median time to recovery was 6 days [interquartile range (IQR) 4–12]. Mortality rates were 6.5% and 11.8% by days 14 and 28, respectively. Age and time to start of RDV after hospital admission were predictive of recovery and 28-day mortality.

Conclusions: In this real-world experience, outcomes after 5 days of RDV therapy were comparable to those of clinical trials. Disease severity, age, and dexamethasone use influenced clinical outcomes. Time to RDV initiation appeared to affect recovery and 28-day mortality, a finding that should be explored further. Mortality rate decreased over the analysis period, which could be related to dexamethasone use and improved management of COVID-19.

Keywords: coronavirus, COVID-19, emergency use authorization (EUA), outcomes, remdesivir

Introduction
Coronavirus disease 2019 (COVID-19), caused by the novel coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], has infected millions of individuals and has been associated with over 2 million global fatalities within one year. Although several antiviral agents have been considered as potential treatments over the course of the pandemic, remdesivir (RDV) emerged as the most promising. RDV, a pro-drug nucleotide analog that inhibits viral RNA-dependent RNA polymerase, prevents replication via premature termination of RNA synthesis. Based on initial data from the Adaptive COVID-19 Treatment Trial (ACTT-1), in May 2020 the US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) permitting RDV use in hospitalized patients. The EUA included hospitalized children (≥3.5 kg) and
adults with severe COVID-19. In August 2020, the FDA expanded EUA eligibility to all hospitalized adults and children (≥3.5 kg) regardless of disease severity.5 RDV allocations between May and September 2020 were managed by the federal government and state health departments. Faced with limited RDV supplies, our institution established prioritization criteria based on best available data. On 22 October 2020, RDV received FDA approval for hospitalized patients 12 years and older with COVID-19.6

Given the limited real-world data on RDV use, we evaluated clinical outcomes of patients at our hospital who received RDV during the EUA period. We modeled this analysis after the ACTT-1 trial, while including patients with estimated glomerular filtration rate (eGFR) <30 mL/min. In addition, we described internal allocation, stewardship and monitoring strategies deployed by the anti-infective stewardship team (AST). Our processes may help inform stewardship strategies at other institutions, particularly if new EUA agents emerge.

Methods

Design and procedures
We conducted a retrospective study of hospitalized patients who received at least one dose of RDV under EUA at Massachusetts General Hospital between May and October 2020. An electronic medical record (EMR) query identified patients who received ≥1 dose(s) of RDV. Patients were excluded if they transitioned to any RDV-related clinical trial or received RDV at an outside facility with inaccessible records. Two independent investigators used an electronic form to extract demographics, comorbidities, disease severity, disease course, RDV administrations, other treatments, adverse events and clinical outcomes.

Disease severity and outcomes were classified on the day of index hospitalization, day of RDV initiation, and 14 and 28 days after RDV initiation according to the eight-category ordinal scale (Supplemental Table 1) described in the ACTT-1 trial.4 For each assessment, the highest category met on that day was recorded. Information on symptom onset was based on patient, or designee’s, reporting. If laboratory values were unavailable on the day of RDV initiation, values within 24 hours were used. If 14 or 28-day outcomes were unavailable, the previously documented outcome was carried over. The study protocol was approved by the Mass General Brigham Institutional Review Board (protocol 2020P001677) with a waiver of consent granted for review of medical records.

Internal allocation and stewardship
Due to the scarcity of initial RDV supplies, criteria were established using ACTT-1 data to sustain equitable allocation. Initial allocation was to already hospitalized patients (first phase of availability) followed by all newly admitted patients meeting criteria who were proactively reviewed by the AST. The AST contacted the primary team to offer RDV and monitored usage via real-time EMR notifications. All RDV orders contained: (a) criteria for use; (b) confirmation of patient assent and; (c) a preset treatment duration of 5 days (200 mg intravenously on day 1, followed by 100 mg intravenously daily on days 2–5). Five days of RDV treatment was based on two open-label clinical trials, the EUA language, and with conservation in mind.7,8 RDV continuation for up to 10 days was determined on a case-by-case basis.

Outcomes
The primary outcome was the proportion of patients recovered by day 14, defined as a score of 1, 2 or 3 on the ordinal scale. Secondary outcomes included time to recovery after the first RDV dose, as well as recovery and all-cause mortality by day 28. Safety outcomes were identified as related to RDV therapy per EUA recommendations, including laboratory abnormalities and rate of treatment cessation secondary to adverse reactions.

Statistical analysis
Patient demographics and characteristics were summarized using proportion, or median and interquartile range (IQR), as appropriate. Chi square and Wilcoxon rank-sum tests were used to compare patient characteristics stratified by recovery by days 14 and 28 after starting RDV. Fatality rate was calculated as the number of patients who died within the 28-day study period and stratified by month of hospital admission. Logistic regression models were constructed to
assess associations between clinical recovery by days 14 and 28, and 28-day mortality with baseline demographics and clinical characteristics. Models were constructed to include age, disease severity on admission, concurrent dexamethasone and variables in the bivariate analysis with p-values ≤0.2. Goodness of fit was assessed via the Hosmer–Lemeshow test.

A stratified log-rank test of time to recovery using the Kaplan–Meir (K–M) method was used to calculate event rates and 95% confidence intervals (CIs), stratified by disease severity on RDV day 1. For time to recovery and time to death analyses, data for patients who did not recover and data for patients who died were censored on day 29, as was done in the ACTT-1 trial.1 Prespecified secondary analyses included a stratified log-rank test of time to recovery by dichotomized disease severity (ordinal scale ≤5 versus >5) on RDV day 1, and a Cox proportional hazards model in which ordinal scale on RDV day 1 was the main effect. Adjusted hazard ratios (HRs) and 95% CIs were calculated using the Cox proportional hazards model, adjusting for potential prespecified covariates identified in the ACTT-1 trial1 and subsequent studies as potential confounders. No interaction terms or time-dependent covariates were included. Analyses were performed using STATA version 16.1 (StataCorp, College Station, USA), R version 3.6.1 (the R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patients

A total of 163 patients received at least one dose of RDV during the study period. Ten patients were excluded: six transitioned to an RDV clinical trial, two transferred from an outside hospital with incomplete records, one deferred additional treatment for renal concerns and one completed RDV treatment at an outside hospital. Two pediatric patients (aged 8 and 13 years) were included in the analysis. Demographics, comorbidities, concurrent treatments and RDV treatment characteristics are summarized in Table 1 and Supplemental Table 2. Most patients (118, 77.1%) were hospitalized within 10 days of symptom onset (median 6 days, IQR 3–9). Data on symptom onset were missing for six patients. On hospital day 1 and RDV day 1, most patients were classified as ordinal scale 5 (92, 60.1% and 97, 63.4%, respectively). RDV was usually initiated within 48 hours of admission (122 patients, 79.7%) and administered for an intended 5-day course (151 patients, 98.7%). Other than corticosteroids, all other COVID-19-directed treatments were initiated in the context of a clinical trial (Table 1). Disease severity on hospital day 1 and RDV day 1, and status on days 14 and 28, are summarized in Supplemental Figure 1.

Clinical recovery

By days 14 and 28 after starting RDV, 96 (62.7%) and 117 (76.5%) patients, respectively, met the definition of clinical recovery. Median time to recovery was 6 days (IQR 4–12). Four of the 96 patients who initially achieved clinical recovery within the first 14 days later worsened and were re-hospitalized within 14 days. Similarly, two of the 117 patients initially achieving recovery by day 28 worsened and were re-hospitalized within 28 days.

In the bivariate analysis, patients who did not achieve clinical recovery by day 14 were more likely to present with greater disease severity (p < 0.001) and receive the first RDV dose beyond 48 hours of admission (p = 0.01) (Table 1). In the logistic regression, age [adjusted odds ratio (aOR) 0.97, 95% CI 0.94–0.99], disease severity on admission (aOR 0.14, 95% CI 0.07–0.28) and receipt of RDV beyond 48 hours of admission (aOR 0.13, 95% CI 0.04–0.41) correlated with lack of clinical recovery by day 14. Similar results were noted for factors associated with achieving clinical recovery by day 28 (data not shown).
Table 1. Patient demographics and clinical characteristics stratified by achieving recovery by day 14 after starting RDV.

| Characteristic                     | All patients (N=153) | Recovery by day 14 (n=96) | No recovery by day 14 (n=57) |
|-----------------------------------|----------------------|---------------------------|-----------------------------|
| Age (years) – median (IQR)        | 61 [47–73]           | 59 [45–74]                | 63 [56–72]                  |
| Male – n (%)                      | 94 [61.4]            | 54 [56.3]                 | 37 [64.9]                   |
| Pregnancy – n (%)                 | 4 [2.6]              | 3 [3.1]                   | 1 [1.8]                     |
| Breastfeeding – n (%)             | 2 [1.3]              | 2 [2.1]                   | 0 [0]                       |
| Race or ethnic group – n (%)      |                      |                           |                             |
| African American                  | 5 [3.3]              | 4 [4.2]                   | 1 [1.8]                     |
| Asian                             | 1 [0.65]             | 0 [0]                     | 1 [1.8]                     |
| Hispanic                          | 56 [36.6]            | 37 [38.5]                 | 19 [33.3]                   |
| White                             | 80 [52.3]            | 49 [51.0]                 | 31 [54.4]                   |
| Other/unknown                     | 11 [7.2]             | 6 [6.3]                   | 5 [8.8]                     |
| BMI in kg/m² – median (IQR)       | 30 [27–34]           | 30 [28–35]                | 28 [26–33]                  |
| Days from symptom onset to hospital admission – median (IQR)b | 6 [3–9] | 6 [4–9] | 7 [3–10] |
| Days from symptom onset to RDV – median (IQR)b | 8 [5–10] | 7 [5–10] | 8 [6–13] |
| ≤10 days – n (%)                  | 111 [72.5]           | 73 [76.0]                 | 38 [66.7]                   |
| Comorbidities – n (%)             |                      |                           |                             |
| Chronic lung diseasea             | 39 [25.5]            | 30 [31.3]                 | 9 [15.8]                    |
| Chronic heart disease             | 29 [19]              | 17 [17.7]                 | 12 [21.1]                   |
| Chronic kidney disease            | 22 [14.4]            | 12 [12.5]                 | 10 [17.5]                   |
| Diabetes mellitus (type 2)        | 47 [30.7]            | 24 [25.0]                 | 23 [40.4]                   |
| Cancer                            | 20 [13.1]            | 11 [11.5]                 | 9 [15.8]                    |
| Other immunocompromise            | 20 [13.1]            | 13 [13.5]                 | 7 [12.3]                    |
| None                              | 31 [20.3]            | 19 [19.8]                 | 12 [21.1]                   |
| NIAID ordinal scale score on hospital day 1 – n [%]a | 1                      | 0                          | 0                           |
|                                  | 2                      | 0                          | 0                           |
|                                  | 3                      | 0                          | 0                           |
|                                  | 4                      | 27 [17.6]                 | 23 [23.9]                   | 4 [7.0] |
|                                  | 5                      | 92 [60.1]                 | 69 [71.9]                   | 23 [40.4] |
|                                  | 6                      | 9 [5.9]                   | 2 [2.1]                     | 7 [12.3] |
|                                  | 7                      | 25 [16.3]                 | 2 [2.1]                     | 23 [40.4] |

(continued)
Table 1. (continued)

| Characteristic | All patients (N=153) | Recovery by day 14 (n=96) | No recovery by day 14 (n=57) |
|----------------|----------------------|---------------------------|-------------------------------|
| Concurrent therapies – n (%) |                      |                           |                               |
| Dexamethasone     | 72 (47.1)            | 47 (48.9)                 | 25 (43.9)                     |
| Any steroid       | 93 (60.1)            | 57 (59.4)                 | 36 (63.2)                     |
| Enrolled in a clinical trial<sup>a,b</sup> | 56 (36.6) | 28 (29.2) | 28 (49.1) |
| None             | 36 (23.5)            | 26 (27.1)                 | 10 (17.5)                     |
| Days from hospital admission to RDV – median (IQR) | 1 (1–2) | 1 (1–2) | 1 (1–4) |
| Early RDV (within 48 hours) – n (%)<sup>a</sup> | 122 (79.7) | 83 (86.4) | 39 (68.4) |
| Days of RDV therapy – median (IQR)<sup>a</sup> | 5 (5–5) | 5 (4–5) | 5 (5–5) |
| Days from RDV to recovery’ – median (IQR) | 6 (4–12) | 5 (4–8) | 19 (17–26)<sup>i</sup> |
| NIAID ordinal scale score on hospital day 1 – median (IQR) | | | |
| 4               | 5 (4–7)              | 5 (4–6)                   | 17 (16–18)                    |
| 5               | 6 (4–10)             | 6 (4–8)                   | 19 (17–27)                    |
| 6               | 16 (8–24)            | 7 (6–8)                   | 20 (16–26)                    |
| 7               | 19 (14–26)           | 9 (4–14)                  | 20 (19–26)                    |

IQR, interquartile range; BMI, body mass index; NIAID, National Institute of Allergy and Infectious Diseases; RDV, remdesivir.

<sup>a</sup>Tests of association between cohort characteristics and recovery status were performed using chi-square and Wilcoxon rank sum tests; p<0.05.

<sup>b</sup>Data missing for six patients (three in each group).

<sup>c</sup>Clinical lung disease defined as asthma, chronic obstructive pulmonary disease (COPD) or chronic oxygen (O<sub>2</sub>) need; chronic heart disease was defined as coronary artery disease (CAD) or congestive heart failure (CHF).

<sup>d</sup>Clinical trials included (a) placebo controlled trials of tocilizumab, hydroxychloroquine, sarilumab, zanubritinib and interferon lambda, or (b) open-label trial of inhaled nitric oxide in mechanically ventilated patients.

<sup>e</sup>Seven patients received one dose of RDV [four stopped due to apparent adverse reactions, while three were stopped due to death (one) or transition to comfort measures (two)].

<sup>f</sup>Overall median days (IQR) to recovery within for the entire cohort was 6 (4–12).

<sup>i</sup>Thirty-six patients did not achieve recovery in the 28-day study period (18 of whom died by day 28).

Day 1 recovered by 14 and 28-days, respectively, p<0.001 (Supplemental Figure 2).

In the unadjusted Cox proportional hazards model, the effect of RDV day 1 ordinal score on recovery was HR 0.42 (95% CI 0.33–0.53). The magnitude of this effect was smaller after adjusting for potential confounders but remained statistically significant (HR 0.32, 95% CI 0.24–0.43). In the adjusted Cox model, significant predictors of recovery included age decade (aHR 0.82, 95% CI 0.73–0.93), admission body mass index (BMI) (aHR 1.03, 95% CI 1.00–1.05), number of dexamethasone doses (aHR 0.95, 95% CI 0.91–0.99) and number of days from hospital admission to first RDV dose (aHR 0.79, 95% CI 0.69–0.89). Results were similar in sensitivity analyses modeling ordinal scale as dichotomous and modeling time to RDV initiation as days from symptom onset (Table 2).

### 28-Day Mortality

Overall, 10 (6.5%) and 18 (11.8%) patients died by days 14 and 28, respectively (Table 3). Compared with survivors, patients who died by day 28 were older (74 versus 60 years, p=0.01), presented with greater disease severity (p=0.003),
had at least one comorbidity \((p=0.02)\) and received RDV beyond 48 hours of admission \((p=0.01)\). Receipt of dexamethasone was numerically higher in the 28-day survivor group \((49.6\% \text{ versus } 27.8\%, p=0.08)\) (Table 3). In the logistic regression, age \((\text{aOR } 1.06, 95\% \text{ CI } 1.01–1.1)\), disease severity on admission \((\text{aOR } 3.5, 95\% \text{ CI } 1.8–7.1)\), receipt of RDV beyond 48 hours of admission \((\text{aOR } 13.8, 95\% \text{ CI } 2.8–68.7)\) and no receipt of dexamethasone \((\text{aOR } 4.4, 95\% \text{ CI } 1.12–17.15)\) correlated with 28-day mortality. Most fatalities \((13/18, 72.2\%)\) occurred in May and June 2020, with a trend in decreased mortality thereafter. The monthly decline in 28-day mortality was coupled with a decline in the percentage of patients requiring mechanical ventilation on admission and an increase in dexamethasone use following the RECOVERY trial\(^9\) announcement in June 2020 (Supplemental Figure 3). All eight patients who received RDV beyond the first 48 hours of hospital admission and were deceased by day 28 died in May 2020.

Overall, the 28-day mortality rate was stratified by disease severity, as indicated by ordinal score 4 \(2/27, 7.4\%\), ordinal score 5 \(6/92, 6.5\%\), ordinal score 6 \(2/9, 22.2\%\) and ordinal score 7 \(8/25, 32\%\). K–M-estimated survival probability was 93.5\% \((95\% \text{ CI } 89.6–97.5\%\)) and 88.2\% \((95\% \text{ CI } 83.3–93.5\%\)) at 14 and 28 days, respectively. In the cohort with ordinal score \(\leq 5\) on RDV day 1, 14 and 28-day survival probabilities were 98.1\% and 96.4\%, respectively. Conversely, in the cohort with ordinal score \(>5\) on RDV day 1, lower 14 and 28-day survival probabilities were observed as 81.0\% and 66.7\%, respectively, \(p<0.001\) (Supplemental Figure 4).

**Safety**

A total of 21 patients \((13.7\%)\) experienced adverse events. The most common adverse reactions were allergic-type reactions (rash, hives, jitteriness) and decrease in eGFR. Six patients discontinued RDV early due to nausea \((n=3)\), increase in alanine
transaminase (n = 1), and infusion reactions (n = 2). Of six patients who experienced decrease in eGFR to <30 mL/min, RDV was temporarily held for three, while the remaining three patients discontinued before completing the intended course. Seven patients had a baseline eGFR <30 mL/min (median age: 77 years, male: 6/7, NIAID score 7 on admission: 2/7, recovery by day 28: 3/7, death by day 28: 2/7). Six of the seven patients with a baseline eGFR <30 mL/min received the powder formulation of RDV due to its lower cyclodextrin content compared to the liquid formulation. Patients with a baseline eGFR <30 mL/min did not experience an increase in adverse events compared to patients with baseline eGFR ≥30 mL/min (Supplemental Table 3).

**Discussion**

We describe clinical outcomes for patients hospitalized with COVID-19 at our tertiary care center who received RDV under EUA. Many (62.7%) patients recovered within 14 days of starting RDV, and most (76.5%) recovered by 28 days. The overall 28-day mortality rate was 11.8%. Disease severity and time to RDV were predictors of recovery and mortality. Notably, 28-day mortality appeared to decline during the study period, coinciding with increased dexamethasone use, decreased need for mechanical ventilation on admission, and likely greater experience with COVID-19 management.

Five phase III clinical trials assessing the benefits of RDV for hospitalized patients with COVID-19 are available and findings are heterogeneous.\(^4,7,8,10,11\) In the ACTT-1 trial, RDV was superior to placebo in shortening time to recovery (10 versus 15 days) in adults.\(^4\) Conversely, a study in China compared RDV with placebo in hospitalized adults with COVID-19 pneumonia, and showed no significant clinical benefits. However,
Table 3. Mortality by day 28 after starting RDV.

|                        | Survived to day 28 (n=135, 88.2%) | Died by day 28 (n=18, 11.8%) | p-Value<sup>a</sup> |
|------------------------|-----------------------------------|------------------------------|---------------------|
| Age (years) – median (IQR) | 60 [46–70]                       | 74 [60–80]                  | 0.01                |
| Male – no. (%)          | 80 [59.3]                         | 11 [61.1]                   | 1                   |
| Race or ethnic group – no. (%) |                                  |                             | 0.97                |
| African American        | 4 [2.9]                           | 1 [5.6]                     |                     |
| Asian                  | 1 [0.74]                          | 0 [0]                       |                     |
| Hispanic               | 49 [36.3]                         | 7 [38.9]                    |                     |
| White                  | 71 [52.6]                         | 9 [50.0]                    |                     |
| Other/unknown          | 10 [7.4]                          | 1 [5.6]                     |                     |
| BMI – kg/m² median (IQR) | 30 [27–34]                       | 30 [27–35]                  | 0.98                |
| Days from symptom onset<sup>b</sup> to hospital admission – median (IQR) | 6 [4–9]                          | 5 [3–7]                     | 0.46               |
| Days from symptom onset<sup>b</sup> to RDV – median (IQR) | 8 [5–10]                          | 8 [6–14]                      | 0.40               |
| ≤10 days – no. (%)      | 100 [74.1]                        | 11 [61.1]                   | 0.27                |
| Days from hospital admission to RDV – median (IQR) | 1 [1–2]                          | 2 [1–6]                     | 0.005               |
| Early RDV (within 48 hours) – n (%) | 112 [82.9]                       | 10 [55.6]                   | 0.01                |
| Score on NIAID ordinal scale on hospital day 1 – no. (%) |                                  |                             | 0.003               |
| 1                      | 0 [0]                             | 0 [0]                       |                     |
| 2                      | 0 [0]                             | 0 [0]                       |                     |
| 3                      | 0 [0]                             | 0 [0]                       |                     |
| 4                      | 25 [18.5]                         | 2 [11.1]                    |                     |
| 5                      | 86 [63.7]                         | 6 [33.3]                    |                     |
| 6                      | 7 [5.2]                           | 2 [11.1]                    |                     |
| 7                      | 17 [12.6]                         | 8 [44.4]                    |                     |
| Comorbidities<sup>c</sup> – n (%) |                                  |                             |                     |
| Chronic lung disease   | 32 [23.7]                         | 7 [38.9]                    | 0.25                |
| Chronic heart disease  | 25 [18.5]                         | 4 [22.2]                    | 0.75                |
| Chronic kidney disease | 18 [13.3]                         | 4 [22.2]                    | 0.29                |
| Diabetes mellitus type 2 | 38 [28.1]                        | 9 [50]                      | 0.09                |
| Cancer                 | 17 [12.6]                         | 3 [16.7]                    | 0.63                |

(continued)
the trial was underpowered and terminated early due to decreased COVID-19 incidence. In an open-label study of patients aged ≥12 years hospitalized with COVID-19 pneumonia and oxygen saturation of 94% or less but not requiring mechanical ventilation, clinical status on day 14 did not differ between 5 or 10 days of RDV. In another analysis of patients aged ≥12 years hospitalized with COVID-19 pneumonia and oxygen saturation >94% on room air, those randomly assigned to 5 days of RDV but not 10 days had a significant improvement in clinical status on day 11 compared with standard care. Finally, in the World Health Organization (WHO)-sponsored SOLIDARITY trial that examined the use of multiple antivirals in patients hospitalized with COVID-19 across 30 countries, RDV had no effect on 28-day in-hospital mortality. Notably, while reported outcomes were similar, nearly all patients in this study received 5 days of RDV compared to 10 days in ACTT-1.

Although early initiation of RDV may be associated with improved outcomes, this has not been well described across available studies. Our study found early initiation of RDV (i.e. within 48 hours of hospital admission), appeared to correlate with recovery and 28-day mortality. However, all eight patients who received RDV beyond the first 48 hours of admission and were deceased by day 28 died in May 2020, which may reflect the initial days of allocation when patients received RDV later in their hospital course. We also observed that concurrent use of dexamethasone conferred benefit, including improved 28-day survival. Nearly half (47.1%) of our patients received dexamethasone, with 60.7% receiving one or more doses of any corticosteroid. Dexamethasone use increased after the RECOVERY trial reported a 28-day mortality benefit in patients requiring mechanical ventilation or supplemental oxygen. Mortality rates in our cohort decreased as dexamethasone use increased substantially; however, this may also be confounded by time, as care for COVID-19 patients likely improved with more experience managing the disease. Of note, corticosteroid use was not common (23%) in ACTT-1 and was only permitted for non-COVID indications (e.g. adrenal insufficiency, acute respiratory distress syndrome (ARDS)).

We modeled our analysis on ACTT-1, as our hospital RDV criteria were derived from that trial. Distribution of disease severity and the likelihood of recovery based on severity stratification were similar; however, more patients in the RDV arm of ACTT-1 had scores of 6 or 7 (45%) than our cohort (22.2% on RDV day 1). Our observed median time to recovery with RDV (K–M estimate 9 days; 95% CI 7–12 days) fell within the range suggested by ACTT-1 (10 days; 95% CI 9–11 days). We also observed that patients with less severe COVID-19 who received RDV were more likely to recover than those with more severe disease (e.g. requiring early mechanical ventilation). Observed 28-day mortality was 11.8%, also within the range identified in the RDV arm of ACTT-1 (11.4%; 95% CI 9–14.5). Notably, while reported outcomes were similar, nearly all patients in this study received 5 days of RDV compared to 10 days in ACTT-1.

| Table 3. (continued) | Survived to day 28 (n = 135, 88.2%) | Died by day 28 (n = 18, 11.8%) | p-Valuea |
|----------------------|-----------------------------------|-------------------------------|----------|
| Other immunocompromise | 20 (14.8)                          | 0 (0)                         | 0.08     |
| None                 | 31 (23.0)                          | 0 (0)                         | 0.02     |
| Concurrent dexamethasone – no. (%) | 67 (49.6)                             | 5 (27.8)                      | 0.08     |
| Concurrent steroids (any steroid) – no. (%) | 85 (63.0)                              | 8 (44.4)                      | 0.13     |
| Days from RDV to death – median (IQR) | N/A                                 | 12 (6–25)                     | N/A      |

IQR, interquartile range; BMI, body mass index; RDV, remdesivir; NIAID, National Institute of Allergy and Infectious Diseases. aTests of association between cohort characteristics and recovery status were performed using Chi-square and Wilcoxon rank sum. bData missing for six patients (three in each group). cChronic lung disease defined as asthma, chronic obstructive pulmonary disease (COPD) or chronic oxygen (O2) need; chronic heart disease was defined as coronary artery disease (CAD) or congestive heart failure (CHF).
Rates of adverse events were comparable to those observed in other studies and RDV was well tolerated. Notably, patients with renal impairment (i.e. eGFR <30 mL/min) were permitted to receive RDV at our institution. While there are no pharmacokinetic data for RDV in this population and accumulation of the excipient betadex sulfobutyl ether sodium may cause renal toxicity, infectious diseases (ID), ID pharmacy, and nephrology services collaboratively agreed the potential benefits of RDV likely outweighed the potential risks in many patients with renal impairment using the 5-day course. Therefore, use was permitted with approval from ID and nephrology services. The powder formulation of RDV was preferentially used when available, due to the lower excipient content compared to the liquid formulation (3 g versus 6 g per 100 mg RDV dose, respectively). No notable adverse events were observed in these patients compared to the larger cohort, which is consistent with other limited analyses of patients with impaired renal function who received RDV.12,13

Our findings should be interpreted with several considerations. This study was retrospective in nature and did not include a control group, and thus findings are subject to the inherent limitations of this methodology. However, we believe our results are meaningful given current widespread use of RDV in hospital settings, and several analyses were performed to control for potential confounding variables. Most patients in our study received 5 days of therapy in accordance with institutional recommendations, and therefore outcomes may not be consistent with those after 10-day treatment courses. The effect of therapies used in combination with RDV on clinical outcomes was difficult to quantify, and several patients were enrolled in placebo controlled trials without known treatment allocation. Finally, several patients received concomitant treatment with corticosteroids, including dexamethasone, based on findings from the RECOVERY trial, which may have affected our findings over time.

Conclusion
In this real-world experience, outcomes after 5 days of RDV therapy were similar to those reported in randomized clinical trials. Disease severity, age and dexamethasone use influenced clinical outcomes. Time to RDV initiation appeared to influence recovery and 28-day mortality, a finding that should be explored further. Mortality rate decreased over the analysis period, which could be related to dexamethasone use and improved management of COVID-19.

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Author contributions
MB, RE, EH and AL conceptualized the study. MA, MB, and RE and AL designed the study and data collection plans. MA, MB, RE, RG, AL, MM and MP were involved in data collection. LB and RE completed the data analysis. LB, MB and RE wrote the first draft. MA, RG, EH, AL, MM and MP critically revised the first draft. All the co-authors reviewed and approved the version of the article to be published.

Conflict of interest statement
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