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Remdesivir Reduced Mortality in Immunocompromised Patients Hospitalized for COVID-19 Across Variant Waves: Findings From Routine Clinical Practice

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Background. Immunocompromised patients are at high risk of severe coronavirus disease 2019 (COVID-19) and death, yet treatment strategies for immunocompromised patients hospitalized for COVID-19 reflect variations in clinical practice. In this comparative effectiveness study, we investigated the effect of remdesivir treatment on inpatient mortality among immunocompromised patients hospitalized for COVID-19 across all variants of concern (VOC) periods.

Methods. Data for immunocompromised patients hospitalized for COVID-19 between December 2020 and April 2022 were extracted from the US PINC AI™ Healthcare Database. Patients who received remdesivir within 2 days of hospitalization were matched 1:1 using propensity score matching to patients who did not receive remdesivir. Additional matching criteria included admission month, age group, and hospital. Cox proportional hazards models were used to examine the effect of remdesivir on risk of 14- and 28-day mortality during VOC periods.

Results. A total of 19 184 remdesivir patients were matched to 11 213 non-remdesivir patients. Overall, 11.1% and 17.7% of remdesivir patients died within 14 and 28 days, respectively, compared with 15.4% and 22.4% of non-remdesivir patients. Remdesivir was associated with a reduction in mortality at 14 (hazard ratio [HR], 0.70; 95% confidence interval, .62–.78) and 28 days (HR, 0.75; 95% CI, .68–.83). The survival benefit remained significant during the pre-Delta, Delta, and Omicron periods.

Conclusions. Prompt initiation of remdesivir in immunocompromised patients hospitalized for COVID-19 is associated with significant survival benefit across all variant waves. These findings provide much-needed evidence relating to the effectiveness of a foundational treatment for hospitalized COVID-19 patients among a high-risk population.

Keywords. COVID-19; remdesivir; immunocompromised; mortality; comparative effectiveness research.

Immunocompromised patients are at higher risk of hospitalization, morbidity, and mortality due to coronavirus disease 2019 (COVID-19) [1–4]. With reduced vaccine efficacy and ongoing viral evolution leading to immune evasiveness, there remains an ongoing need for effective therapeutics to treat COVID-19 in immunocompromised patients [5–8].

Intravenous remdesivir treatment is an important first-line antiviral for managing immunocompromised patients hospitalized for COVID-19 for several reasons. In the era following viral escape from key neutralizing monoclonal antibodies [9, 10], there is a high risk of drug–drug interactions between the oral antiviral, ritonavir-boosted nirmatrelvir, used for early treatment of COVID-19, and cornerstone immunosuppressant medications for solid organ transplant recipients, particularly calcineurin inhibitors and mammalian target-of-rapamycin inhibitor drugs [11–13]. There are also concerns and hesitation regarding intensifying background immunosuppression with drugs, such as dexamethasone, since this may further prolong severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication, increase the risk of secondary infections with other pathogens, and contribute to selection and transmission of new SARS-CoV-2 variants [14, 15].

Immunocompromised patients have largely been omitted or underrepresented in COVID-19 clinical trials due to ethical and feasibility concerns. As a result, clinical guidelines currently rely on evidence generated in the general population to provide recommendations relating to the treatment of COVID-19 in this high-risk population [14, 16–18]. This represents a

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considerable evidence gap regarding optimal treatment strategies in immunocompromised patients that requires urgent attention through real-world data studies. In the late pandemic phase, immunocompromised patients remain disproportionately at a higher risk of progression to severe disease than the general population, and clinical questions persist on the best way to manage this vulnerable group.

Remdesivir has demonstrated efficacy across the COVID-19 disease severity spectrum in clinical trials [19–21] and effectiveness in real-world comparative effectiveness studies [22–24], including reductions in mortality [25, 26]. In PINETREE, a randomized, double-blind, placebo-controlled clinical trial conducted among high-risk patients (including some immunocompromised patients) in the outpatient setting, remdesivir was associated with a reduced risk of hospitalization or death (hazard ratio [HR], 0.13; 95% confidence interval [CI], .03–.59) [21]. Similarly, remdesivir administration in high-risk patients reduced the risk of hospitalization or emergency department visit and in-hospital deterioration in observational studies [27–30]. For example, among a cohort (N = 126) of high-risk patients hospitalized with COVID-19 in Mexico City, treatment with remdesivir significantly reduced hospitalization or death (HR, 0.16; 95% CI, .06–.44) [30]. Further evidence relating to the effectiveness of remdesivir in this vulnerable patient population is urgently required to inform clinical decision-making and update COVID-19 clinical guidelines.

In this study, we compared all-cause inpatient mortality in immunocompromised patients who received remdesivir upon hospital admission for COVID-19 to mortality in those who did not receive remdesivir during their hospitalization across different variant waves of the pandemic.

METHODS

Study Design and Data Source

This was a retrospective, comparative effectiveness study using patient-level hospitalization records that were extracted from the US PINC AI Healthcare Database. This hospital administrative dataset captures data for up to 25% of all hospitalizations that occur in 48 states of the United States. The data provider determined that less than 1% of patient records had missing information for most data elements.

Study Population

The study included patients aged ≥18 years hospitalized between 1 December 2020 and 30 April 2022, with a primary discharge diagnosis of COVID-19 (*International Classification of Diseases, 10th revision, Clinical Modification* [ICD-10-CM] code U07.1) that was also flagged as "present on admission" and an ICD-10-CM code for immunocompromised conditions as defined in Supplementary Table 1. Patients were excluded if they met any of the following criteria: were pregnant, incomplete hospital records, hospitalized for fewer than 3 days, transferred from hospice, transferred to or from another hospital, admitted for an elective procedure, or received remdesivir as part of a clinical trial.

Definition of Study Variables

Baseline was considered as the first 2 days of hospitalization. Since time stamps are unavailable in the deidentified database, admittance at 00:01 or 23:59 would be considered "day 1" of admission. Thus, 2 days provide at least 1 full calendar day for clinical decisions to be made and implemented. Baseline covariates are defined in Supplementary Table 1 and include demographics, comorbidities, hospital characteristics, admission month, admission from a skilled nursing facility, hospital ward type on admission, concomitant COVID-19 medications, admission diagnoses (respiratory failure, hypoxemia, sepsis, pneumonia), and COVID-19 severity identified through supplementary oxygen requirement. Baseline supplemental oxygen requirement was categorized as no supplemental oxygen charges in hospitals documented to charge for supplemental oxygen (NSOc), low-flow oxygen (LFO), high-flow/noninvasive ventilation (HFO/NIV), and invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO). Periods for the variants of concern (VOC) were defined as pre-Delta (December 2020–April 2021), Delta (May 2021–November 2021), and Omicron (December 2021–April 2022) based on the predominant circulating SARS-CoV-2 variant during these periods in the United States [31, 32].

Remdesivir patients received at least 1 dose of remdesivir within 2 days of hospitalization for COVID-19. Non-remdesivir patients did not receive remdesivir at any time during their hospitalization for COVID-19.

Statistical Analyses

All-cause inpatient mortality was assessed at 14 and 28 days and was defined as a discharge status of either "expired" or "hospice." Patients who were discharged alive were censored at 14 days or 28 days.

Propensity score (PS) methods were used to match remdesivir patients to non-remdesivir patients. PSs were estimated separately for each category of baseline supplemental oxygen requirement and each variant period using logistic regression models including all baseline covariates. To account for differences in hospital COVID-19 management practices that may have evolved with each VOC timeframe, a 1:1 preferential within-hospital matching approach with replacement with a caliper distance of 0.2 times standard deviation of the logit of PS was implemented as follows: patients who received remdesivir were matched to non-remdesivir patients within the caliper and the same age group (18–49, 50–64, ≥65 years) and within the two-three groups of admission month in the VOC period within the same hospital; the unmatched patients in

the remdesivir group were then matched to non-remdesivir patients within the caliper and the same age group (18–49, 50–64, ≥ 65 years) and with the two-three groups of admission month in the VOC period in another remdesivir-using hospital of the same bed size (0–199, 200–499, 500+ beds).

There was no limit to the number of times a non-remdesivir patient was available for matching. Matching was undertaken within each stratum of baseline supplemental oxygen requirement and each VOC period (eg, a remdesivir patient in the Delta phase is matched to a non-remdesivir patient in the Delta phase). Further, all patients included in the analysis were required to have at least 3 days of hospital stay from administration of remdesivir. This emulates previous study design approaches [20, 22, 26].

Time to mortality was assessed using Kaplan–Meier curves and compared using log-rank tests. Cox proportional hazards models were used to assess the effect of remdesivir treatment on inpatient mortality. Models were adjusted for hospital-level effects and the following key covariates: age (as a continuous variable), admission month, hospital ward type on admission, and baseline COVID-19 treatments. A robust (sandwich) variance estimator was used to account for potential patient replication. All analyses are presented overall and stratified by VOC period and baseline supplemental oxygen requirement.

RESULTS

This study included 51 123 immunocompromised adults hospitalized for COVID-19 in 819 hospitals between December 2020 and April 2022. Of these, 30 397 patients met the eligibility criteria, including 19 184 (63.1%) who initiated remdesivir in the first 2 days of hospitalization and 11 213 (36.9%) patients who did not initiate remdesivir during hospitalization for COVID-19 (Figure 1). There were 2438 (8.0%) patients who were administered remdesivir after the first 2 days of hospitalization and these patients were excluded from the analyses to avoid complex differential censoring and focus the analysis on those admitted for a primary diagnosis of COVID-19, present on admission, and either received or did not receive remdesivir promptly, emulating a randomized controlled trial.

Following 1:1 matching with replacement, 14 169 remdesivir patients were matched to 5341 unique non-remdesivir patients (equivalent to 14 169 non-remdesivir patients based on matching with replacement). A total of 5015 patients administered remdesivir within 2 days of hospitalization were not matched. Among these unmatched remdesivir patients, the median length of stay was 3.0 days (interquartile range [IQR], 2.0–7.0) compared with 6.0 days (IQR, 4.0–12.0) among matched remdesivir patients (Supplementary Table 2).

Baseline characteristics, including types of immunosuppressive conditions were well balanced following matching, with all covariates demonstrating a standardized difference of <0.15 (Table 1). In the matched cohort, 59% of patients were aged ≥65 years, 40% did not require supplemental oxygen, 39% required LFO, 19% required HFO/NIV, and 2% required IMV/ECMO at baseline. The median duration of remdesivir therapy was 5 days (IQR, 5.0–5.0), with 68.2% and 1.8% of patients completing the full 5-day course and 10-day course, respectively.

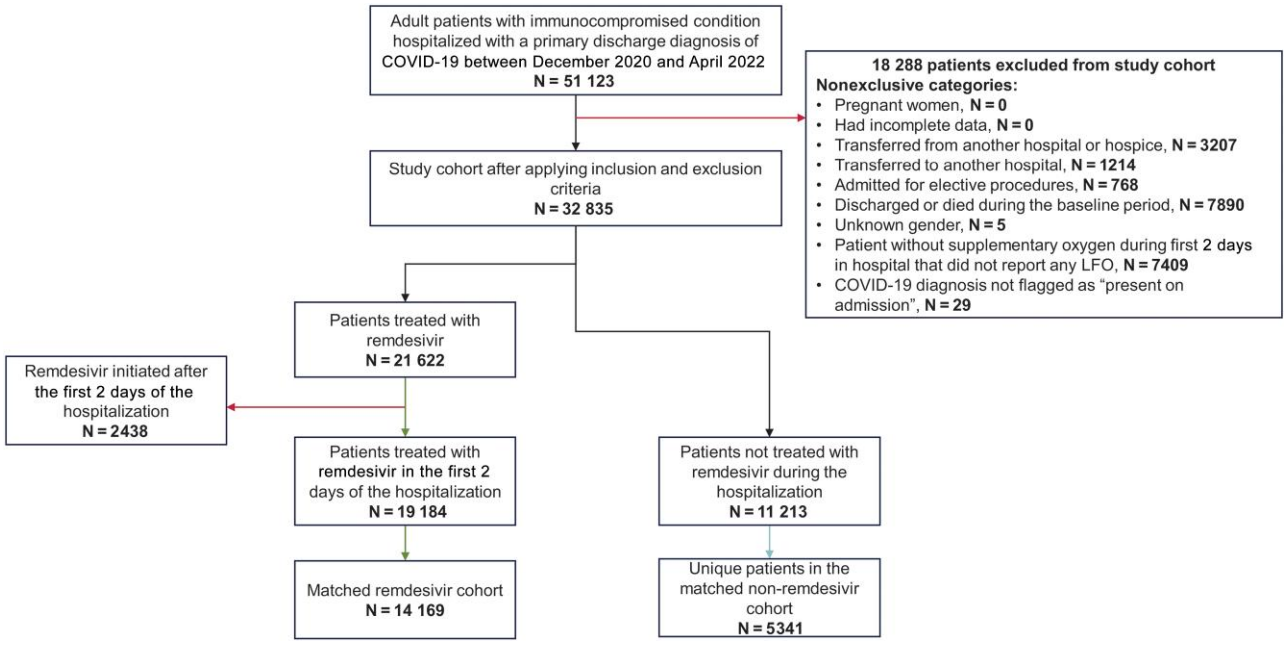

Figure 1. Study population. Abbreviations: COVID-19, coronavirus disease 2019; LFO, low-flow oxygen.

Table 1. Demographic and Hospital Characteristics of Immunocompromised Patients Hospitalized for Coronavirus Disease 2019

Characteristic		Before Matching, %		After Matching, %	
		Non-Remdesivir n = 11 213	Remdesivir n = 19 184	Non-Remdesivir n = 14 169	Remdesivir n = 14 169
Age group, y	18–49	13	15	12	12
	50–64	28	31	29	29
	65+	59	54	59	59
Gender	Female	50	51	51	51
Race	White	71	75	75	75
	Black	20	15	15	15
	Asian	1	2	1	2
	Other	8	8	9	8
Ethnicity	Hispanic	10	14	11	13
	Non-Hispanic	80	77	80	78
	Unknown	10	9	9	9
Primary payor	Commercial	19	25	22	23
	Medicare	67	60	65	64
	Medicaid	9	9	9	8
	Other	5	6	4	5
Variant period	Pre-Delta	32	33	32	32
	Delta	32	39	39	39
	Omicron	36	28	29	29
Admission source	Transfer from a skilled nursing facility or intermediate care facility	2	1	2	2
Hospital size, no. of beds	<100	6	7	6	6
	100–199	14	18	16	16
	200–299	20	18	19	18
	300–399	20	18	19	20
	400–499	11	9	10	10
	500+	29	30	30	30
Hospital location	Urban	87	87	89	88
	Rural	13	13	11	12
Teaching hospital		45	40	40	41
Region	Midwest	23	21	21	21
	Northeast	9	11	11	10
	South	55	55	55	55
	West	13	13	13	14
Immunocompromised conditions	Cancer	25	22	23	23
	Solid organ and hematopoietic stem cell transplant	10	7	8	8
	Hematologic malignancies	18	16	18	17
	Moderate or severe primary immunodeficiencies	33	34	33	34
	Immunosuppressive medications	35	43	42	43
	Asplenia	3	3	3	3
	Bone marrow failure/Aplastic anemia	21	16	18	16
	Human immunodeficiency virus	2	2	1	2
	Toxic effects of antineoplastics	5	4	4	4
Comorbidities	Obesity	30	36	36	35
	Chronic obstructive pulmonary disease	31	34	34	34
	Cardiovascular disease	86	82	84	84
	Diabetes mellitus	41	39	40	40
	Renal disease	40	26	30	28
	Cancer	24	22	23	23
Hospital ward on admission	General ward	82	81	82	82
	Intensive care unit	18	19	18	18
Diagnosis on admission	Sepsis	<1	<1	<1	<1
	Pneumonia/respiratory failure	6	6	6	6
Other treatments at baseline	Anticoagulants	35	24	27	25
	Corticosteroids	77	95	96	95

Table 1. Continued

Characteristic		Before Matching, %		After Matching, %	
		Non-Remdesivir n = 11 213	Remdesivir n = 19 184	Non-Remdesivir n = 14 169	Remdesivir n = 14 169
	Convalescent plasma	2	8	5	5
	Tocilizumab	4	6	5	5
	Baricitinib	5	5	5	6
Baseline supplemental oxygen requirements	No supplementary oxygen charges	50	40	40	40
	Low-flow oxygen	31	38	39	39
	High-flow oxygen/Non-invasive ventilation	15	20	19	19
	Invasive mechanical ventilation/Membrane oxygenation	4	2	2	2

Unadjusted mortality rates were significantly lower among remdesivir patients compared with non-remdesivir patients across all VOC periods and all levels of baseline supplemental oxygen requirement (Figure 2, Supplementary Table 3). Briefly, 11.1% and 17.7% of remdesivir patients died within 14 days and 28 days, respectively, compared with 15.4% and 22.4% of non-remdesivir patients.

After adjusting for baseline and clinical covariates, remdesivir treatment on admission was associated with significantly lower mortality risk at 14 days (HR, 0.70; 95% CI, .62–.78) and 28 days (HR, 0.75; 95% CI, .68–.83; Figure 3). This mortality benefit was seen during each VOC period but was most pronounced during the pre-Delta period at 14 days (pre-Delta: HR, 0.59 and 95% CI, .48–.71; Delta: HR, 0.77 and 95% CI, .65–.92; Omicron: HR, 0.75 and 95% CI, .63–.90) and at 28 days (pre-Delta: HR, 0.65 and 95% CI, .56–.76; Delta: HR, 0.79 and 95% CI, .68–.91; and Omicron: HR, 0.84 and 95% CI, .72–.97).

Remdesivir was associated with significantly lower mortality compared with non-remdesivir among subgroups of patients with NSOc on admission (14 days: HR, 0.71 and 95% CI, .58–.87; 28 days: HR, 0.78 and 95% CI, .66–.93), those who required LFO on admission (14 days: HR, 0.56 and 95% CI, .46–.68; 28 days: HR, 0.62 and 95% CI, .53–.72), and those who required HFO/NIV or IMV/ECMO on admission (14 days: HR, 0.83 and 95% CI, .70–.99; 28 days: HR, 0.86 and 95% CI, .75–.99). Adjusted analyses were not conducted separately for HFO/NIV (n = 5432) and IMV/ECMO (n = 434) since the sample size provided insufficient power.

DISCUSSION

Immunocompromised patients represent a vulnerable population at high-risk for breakthrough COVID-19 infections following vaccination and for progression to severe COVID-19. Yet, our understanding of optimal treatments for COVID-19 in hospitalized patients who are immunocompromised is limited [2, 7]. In this comparative effectiveness study of remdesivir, comprising the largest cohort of immunocompromised patients hospitalized for COVID-19 to date, remdesivir initiation on admission was associated with a significant reduction in all-cause inpatient mortality. Remdesivir survival benefit was observed across all VOC periods. Of the eligible patient population, 19 184 (63.1%) patients promptly initiated remdesivir on admission, yet 11 213 (36.9%) did not. Of the patients who never received remdesivir, 3179 (28.4%) subsequently died, thus highlighting a key missed opportunity to improve the outcomes of these patients.

In the United States, immunocompromised patients were prioritized to receive the serial-dose messenger RNA COVID-19 vaccines during phase 1 of the vaccine rollout from December 2020 onward. Since then, the Centers for Disease Control and Prevention has progressively updated the recommendations to include additional doses and boosters for immunocompromised patients in August 2021, September 2021, and March 2022 [33]. The proportion of immunocompromised patients who had received at least 2 doses surpassed 80% by July 2021 [8]. However, given the risk of breakthrough infections and the elevated risk of progression to severe disease in this population, appropriate management of these patients with effective treatments remains an essential clinical priority. While immunocompromised patients represent a large proportion of patients hospitalized for COVID-19 [34], this is an understudied patient population due to their exclusion or underrepresentation in clinical trials. Treatment recommendations in COVID-19 clinical guidelines for immunocompromised patients mirror those for the general population. Specifically, the National Institutes of Health COVID-19 guidelines recommend that antivirals and immunomodulators be used in hospitalized, immunocompromised patients not requiring supplemental oxygen or requiring LFO [14]. However, these recommendations are based on findings from clinical trials and observational studies in the nonimmunocompromised population from the early phase of the pandemic. Our findings therefore complement and build on existing evidence across the VOC periods for

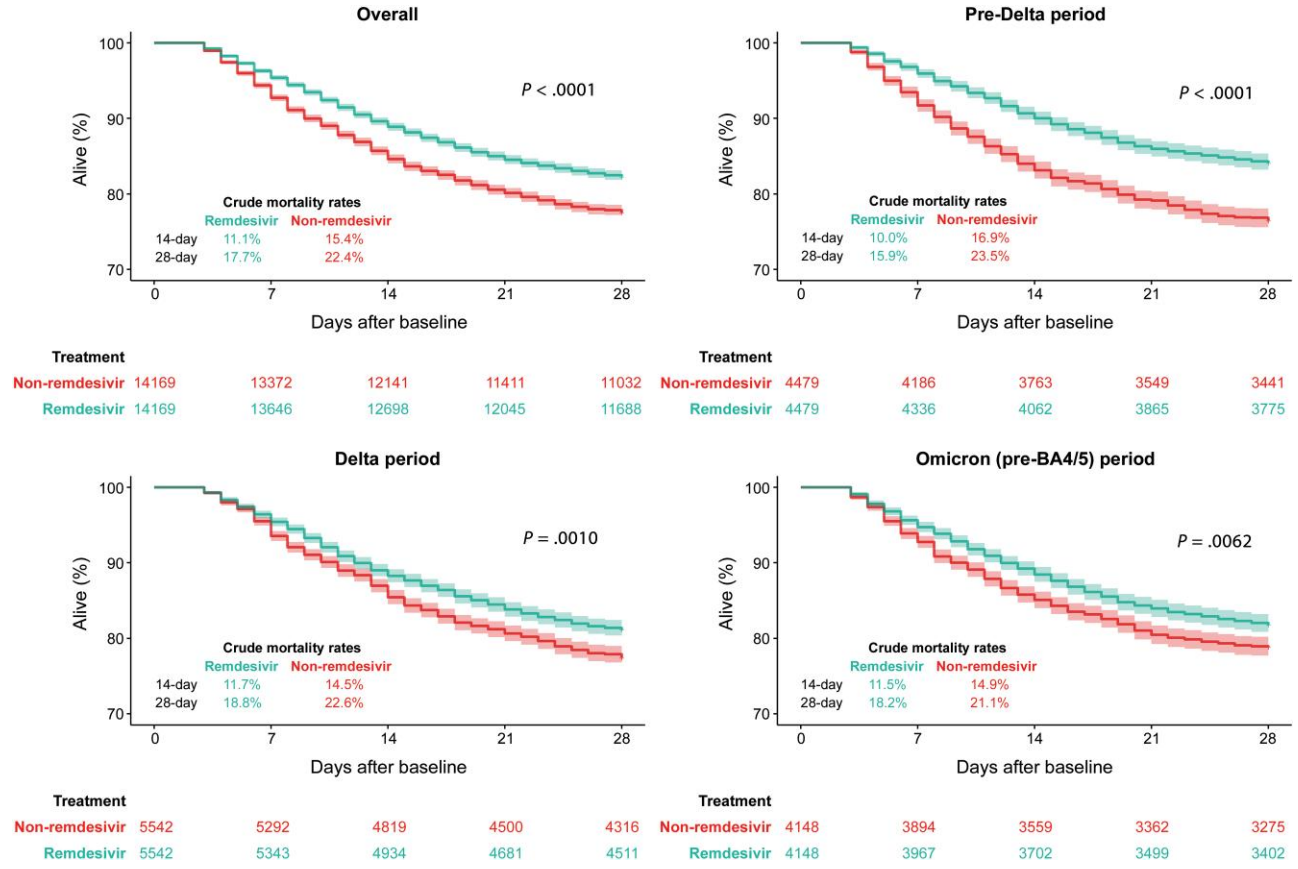

Figure 2. Kaplan–Meier curves for time to mortality among immunocompromised patients across the coronavirus disease 2019 variant periods. "Days after baseline" refers to the time during which outcomes were assessed following the 2-day period in which remdesivir treatment administration was identified (baseline).

immunocompromised patients to inform clinical decision-making and guideline recommendation considerations. To focus on patients with COVID-19 present on admission and compare those individuals who did or did not receive remdesivir in a timely manner, we excluded patients who were administered remdesivir after the first 2 days of hospitalization. Consequently, findings may not represent patients who initiated remdesivir later. However, given that immunocompromised patients may harbor viable virus for extended periods, it can be expected that remdesivir initiation beyond the initial 2 days of hospitalization will have beneficial effects [35].

Remdesivir has established efficacy and effectiveness in the general population with manifestations of COVID-19 pneumonia requiring hospitalization, as demonstrated in clinical trials such as ACTT-1, SIMPLE moderate, and SOLIDARITY, and real-world data studies [19, 20, 22–24, 26]. Further, in the PINETREE clinical trial of nonhospitalized patients with COVID-19 at high-risk for disease progression that included 53 (5% of study population) immunocompromised and/or cancer patients, remdesivir reduced the risk of COVID-19–related hospitalization or death by 28% compared with placebo [21]. In a previous comparative effectiveness study that used data for the general population from the US PINC AI Healthcare Database, remdesivir was associated with a significant reduction in mortality at 14 days (HR, 0.76; 95% CI, .70–.83) and 28 days (HR, 0.89; 95% CI, .82–.96), aligning closely with findings from this study (14 days: HR, 0.70; 95% CI, .62–.78 and 28 days: HR, 0.75; 95% CI, .68–.83) [26].

The 28-day inpatient mortality rate was 17.7% among remdesivir-treated and 22.4% among patients not treated with remdesivir. These rates are higher than those reported for immunocompromised patients included in the EPICOVIDEHA (estimated as 15%) but lower than those reported in the World Health Organization ISARIC Clinical Characterization Protocol UK prospective cohort study (29%) [36, 37]. Explanations for such disparities are numerous but are likely to be predominantly related to differences in case mix, including vaccination status, COVID-19 severity, and type of immunocompromised conditions of included patients.

The use of corticosteroids on admission was high in this study (95% remdesivir and 96% non-remdesivir matched cohort). Although the RECOVERY trial demonstrated that dexamethasone might reduce 28-day mortality among hospitalized COVID-19 patients, there is evidence indicating detrimental

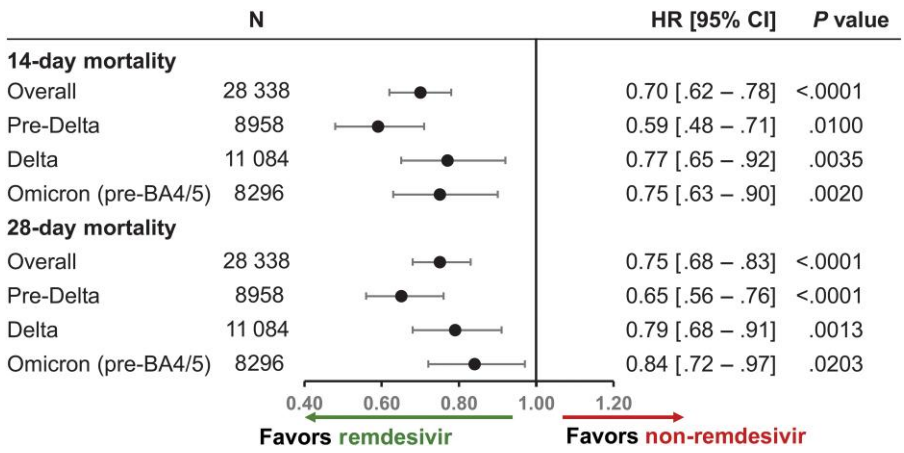

Figure 3. 14-day and 28-day mortality among immunocompromised patients across the coronavirus disease 2019 variant periods (adjusted Cox proportional hazards model). Immunocompromised conditions included cancer, solid organ and hematopoietic stem cell transplant, hematologic malignancies, moderate or severe primary immunodeficiencies, immunosuppressive medications, asplenia, bone marrow failure/aplastic anemia, human immunodeficiency virus, and toxic effects of antineoplastics. Estimates adjusted for age, admission month, hospital ward on admission (intensive care unit vs general ward), and baseline treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab). Abbreviations: CI, confidence interval; HR, hazard ratio.

effects of corticosteroids in immunocompromised patients and patients with COVID-19 of low severity [38–43].

A strength of this large study is that it provides important insights regarding an understudied population across multiple waves of the pandemic and helps to fill a considerable knowledge gap in the treatment of COVID-19 in immunocompromised patients. There are several limitations of this study. First, data on time of symptom onset or time since first positive test were unavailable in this hospital database. Given that the duration of symptoms prior to hospitalization may vary considerably among immunocompromised patients, there is likely to be variation in time since symptom onset. However, analyses were stratified by baseline supplemental oxygen requirements to compare patients at similar levels of disease severity, and benefits were observed across different disease severities. The cohort was also restricted to patients admitted to the hospital for COVID-19 as the primary reason, which was also flagged as "present on admission" to ensure a homogeneous cohort. Second, laboratory data to assess potential contraindications to remdesivir were only available for a subset of patients. To understand the impact of potential contraindication, sensitivity analyses were undertaken to assess renal function. For the subset of patients with available laboratory values, representing approximately 26% of the study cohort, baseline median serum creatinine values were similar between the 2 treatment groups before and after matching (before matching: remdesivir, 1.0; IQR, 0.8–1.4 mg/dL and non-remdesivir, 1.2; IQR, .9–2.1 mg/dL; after matching: remdesivir, 1.0; IQR, .8–1.4 mg/dL and non-remdesivir, 1.1; IQR, .8–1.6 mg/dL). These findings indicate that renal function was not significantly different between remdesivir and non-remdesivir patients. Third, vaccination data were unavailable in the database due to disparate sources of vaccination and the absence of a national patient-level vaccine data warehouse across the United States. To minimize any differences in vaccination status, patients were matched according to age group and variant period, thereby accounting for the rollout of vaccinations in the United States for different age groups, over time, as well as for the changing variants. Immunocompromised patients were prioritized for an early vaccination wave relatively homogeneously. Preferential matching within the same hospital was also undertaken to minimize any differences in regional availability of vaccines, resources, and practice styles. Fourth, baseline supplemental oxygen was captured using billing charges for supplemental oxygen. Since some hospitals include charges for supplemental oxygen within room charges, patients from hospitals with no charges for supplemental oxygen were excluded from the analyses to ensure data were from hospitals that uniformly reported supplemental oxygen requirements. Prior analyses have demonstrated that patients identified as NSOc using this approach had a lower risk of mortality than those requiring supplemental oxygen [26]. Finally, data on antiviral use or any other treatment administered prior to hospitalization were unavailable, which may have led to residual confounding. The contribution from previous antiviral therapies is likely limited. The first emergency use authorization (EUA) for neutralizing monoclonal antibodies that target the spike protein was issued in November 2020 [44, 45]. However, once hospitalized for COVID-19, the decision to use remdesivir would be an independent decision not predicated on prior therapy. Furthermore, outpatient small-molecule antivirals received EUA in the United States in late 2021 and early 2022 and, hence, were not available for most of the study period [46, 47].

Using a large dataset from routine clinical practice, we demonstrate a consistent and significant survival benefit associated with prompt remdesivir initiation in high-risk immunocompromised patients hospitalized for COVID-19. Most clinical guidelines currently recommend the administration of remdesivir in this patient population despite limited evidence among immunocompromised patients [14, 16, 18]. Findings from this study lend further support to these recommendations and help to address a key knowledge gap cited by clinical guidelines. However, given that a large population of hospitalized immunocompromised patients were not administered remdesivir, there may be considerable room for improvement and standardization in managing these vulnerable patients hospitalized for COVID-19 to improve patient survival outcomes.

Remdesivir, with its established efficacy and safety profile and widespread availability, is an important therapeutic option for treatment of COVID-19 in immunocompromised patients.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. All authors contributed substantially to the manuscript and agreed to the final submitted version.

Ethics approval and consent to participate. An ethics approval and informed consent were not required for this study. This analysis of data from the Premier Healthcare Database (US PINC AI Healthcare Database) was conducted under an exemption from the Institutional Review Board oversight for US-based studies using deidentified healthcare records, as dictated by Title 45 Code of Federal Regulations (45 CFR 46.101(b)(4)).

Availability of data and methods. The data that support the findings of this study are available from Premier, Inc (https://www.premierinc.com/). Restrictions apply to the availability of these data, which were used under license for this study.

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Potential conflicts of interest. E. M., E. L., R. G., M. C., and M. B. report employment and being stockholders with Gilead Sciences during the conduct of the study. A. C., S. H. R., and H. J. report funding for study and medical writing provided to their institution (Certara) from Gilead Sciences during the conduct of the study. R. L. G reports serving on scientific advisory boards for AbbVie, Eli Lilly, Gilead Sciences, GSK, Roche, Johnson & Johnson (coronavirus disease 2019 [COVID-19]–related randomized clinical trial, coordinating principal investigator), and Kinevant Sciences (academic steering committee, study investigator; fees to Baylor Scott & White Research Institute); serving as a consultant for Gilead Sciences (honoraria for lectures), Johnson & Johnson, and Kinevant Sciences (through his institution); serving on a speaker bureau for Pfizer unrelated to COVID-19; his institution received a gift-in-kind from Gilead Sciences to facilitate a multicenter clinical trial outside the scope of COVID-19; a de minimis investment in AbCellera; grants or contracts as a study investigator (fees to Baylor Scott & White Research Institute) from Regeneron, Eli Lilly, Gilead, Pfizer, JNJ, and Roivant Sciences (Kinevant Sciences); and receipt of travel support for original scientific presentations from Gilead Sciences. C. C.-M. reports payment or honoraria for lectures/speaker from AstraZeneca and participation on advisory board for Gilead Sciences. A. C. K. reports grants from the National Institutes of Health Adaptive COVID-19 Treatment Trial. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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