Effectiveness of Remdesivir Treatment Protocols Among Patients Hospitalized with COVID-19

A Target Trial Emulation

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Background: Remdesivir is recommended for certain hospitalized patients with COVID-19. However, these recommendations are based on evidence from small randomized trials, early observational studies, or expert opinion. Further investigation is needed to better inform treatment guidelines with regard to the effectiveness of remdesivir among these patients.

Methods: We emulated a randomized target trial using chargemaster data from 333 US hospitals from 1 May 2020 to 31 December 2021. We compared three treatment protocols: remdesivir within 2 days of hospital admission, no remdesivir within the first 2 days of admission, and no remdesivir ever. We used baseline comorbidities recorded from encounters up to 12 months before admission and identified the use of in-hospital medications, procedures, and oxygen supplementation from charges. We estimated the cumulative incidence of mortality or mechanical ventilation/extracorporeal membrane oxygenation with an inverse probability of censoring weighted estimator. We conducted analyses in the total population as well as in subgroups stratified by level of oxygen supplementation.

Results: A total of 274,319 adult patients met the eligibility criteria for the study. Thirty-day in-hospital mortality risk differences for patients adhering to the early remdesivir protocol were −3.1% (95% confidence interval = −3.5%, −2.7%) compared to no early remdesivir and −3.7% (95% confidence interval −4.2%, −3.2%) compared to never remdesivir, with the strongest effect in patients needing high-flow oxygen. For mechanical ventilation/extracorporeal membrane oxygenation, risk differences were minimal.

Conclusions: We estimate that, among hospitalized patients with COVID-19, remdesivir treatment within 2 days of admission reduced 30-day in-hospital mortality, particularly for patients receiving supplemental oxygen on the day of admission.

Keywords: COVID-19; Real-world evidence; Remdesivir; Trial emulation

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Due to contractual agreements with the data provider, the data used to produce this manuscript are not available for distribution. The analytic code is available upon request to the corresponding author.

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The global coronavirus disease 2019 (COVID-19) pandemic prompted an unprecedented worldwide search for effective treatments. The emergence of highly transmissible variants,[1–6] along with evidence of waning vaccine effectiveness,[7–12] suboptimal vaccine uptake,[13] and reduced vaccine protection against emerging variants[14,15] only increased the need for effective and accessible treatments for COVID-19 patients.

International efforts, such as the Solidarity Trial[16] and the Adaptive COVID-19 Treatment Trial (ACTT-1),[17] created

an infrastructure for assessing the effectiveness of COVID-19 potential treatments. Several investigational drugs and monoclonal antibodies have received emergency use authorizations from the US Food and Drug Administration for treatment of COVID-19.[18] Two drugs, remdesivir and baricitinib, received full approval from the US Food and Drug Administration at the time of writing (July 2022).[19] Current guidelines developed for the treatment of hospitalized COVID-19 patients were informed by evidence from small or limited trials, observational studies, and expert opinions.[20,21]

For hospitalized patients requiring low-flow oxygen support, current US National Institutes of Health guidelines recommend remdesivir, dexamethasone, or their combination.[20] This recommendation is based on results from ACTT-1 showing that remdesivir reduced oxygen flow escalation, invasive ventilation, and mortality.[17] However, replication of these findings has been mixed, with similar results being estimated in the Canadian Treatments for COVID-19 (CATCO) trial[22] but no effect being identified in the Solidarity[16] or DisCoVeRy[23] trials. For patients requiring high-flow oxygen support, US National Institutes of Health guidelines recommend either remdesivir with concurrent dexamethasone or dexamethasone alone.[20] This combination was not evaluated in clinical trials and is based on cohort studies[24–26] and the theoretical impact of remdesivir on viral clearance.[27–30] Remdesivir monotherapy is not recommended for high-flow patients based on an ACTT-1 subgroup analysis that found no effect on recovery time or survival,[17] a finding replicated in the CATCO trial.[22] For patients requiring invasive ventilation, the guidelines recommend against the remdesivir monotherapy due to lack of effect in the ACTT-1[17] and Solidarity,[16] and CATCO[22] trials. For hospitalized patients requiring no supplemental oxygen, the guidelines report insufficient evidence for any recommendation regarding remdesivir.[20]

Using data collected during patient admissions at a large group of hospitals in the US, our aim in this study is to estimate the effects of remdesivir treatment protocols for preventing in-hospital mortality and initiation of mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO) among hospitalized adults with COVID-19.

METHODS

Study Design and Population

We acquired deidentified records from hospital chargemasters from a commercial data source including all inpatient records for billable products, procedures, and services provided during admissions at 333 hospitals across 40 states in the United States, as detailed in prior studies.[31,32] We included patients with a COVID-19 diagnosis code (eAppendix; http://links.lww.com/EDE/C15) present in any location on the admitting record between 1 May 2020 and 31 December 2021. We excluded patients who were less than 18 years of age, pregnant, had missing information on age, sex, or hospital region, or if they received either emergency department observational unit care before admission or transferred from another hospital or unknown source. We included only the first admission for each patient. This analysis of deidentified administrative data was approved by the Advarra Institutional Review Board.

Patient Characteristics and Medication Use

ICD-10 codes were used to identify comorbidities and acute conditions present at admission, including obesity, diabetes, cancer, chronic kidney disease, pulmonary disease including asthma, liver disease, cardiovascular disease, hypertension, heart failure, cerebrovascular disease, dementia, history of smoking, autoimmune diseases, human immunodeficiency virus, pneumonia, systemic inflammatory response syndrome (SIRS), myocarditis, acute respiratory failure, acute respiratory distress syndrome (ARDS), and cardiomyopathy (eAppendix; http://links.lww.com/EDE/C15). Information on COVID-19 vaccination status was not available.

The timing of in-hospital diagnoses was unavailable, so we used medications and procedures as proxies for complications, including thromboembolism, congestive heart failure, myocardial infarction, acute kidney injury, and sepsis (eAppendix; http://links.lww.com/EDE/C15). The use of remdesivir, dexamethasone, convalescent plasma, aspirin, and biologic immunomodulators (tocilizumab, baricitinib, sarilumab, and tofacitinib) during hospitalization was identified using automated text searches of charge descriptions and National Drug Codes (see eAppendix; http://links.lww.com/EDE/C15 for search strings and codes). Timing of supplemental oxygen support, MV, ECMO, and intensive care unit admission were classified using hospital charge codes.

Statistical Analysis

We estimated the 30-day risk of in-hospital mortality and, separately, MV/ECMO, for three treatment protocols: initiate remdesivir on the day of or day following admission (the "early remdesivir" protocol), do not initiate remdesivir on the day of or day following admission (the "no early remdesivir" protocol), and never initiate remdesivir (the "never remdesivir" protocol). To estimate the risk of each outcome had all patients adhered to a given protocol, we used a target trial emulation approach to mimic the results of a hypothetical randomized controlled and identify and address important sources of bias (details are included in the eAppendix; http://links.lww.com/EDE/C15).[33–37] The goal of the approach is to create a cohort of patients with treatment patterns that reflect all cohort members being adherent to each arm of the target trial. For each protocol, a cohort was created by making a complete copy of the dataset including all eligible patients. Within each copied cohort, we followed patients until discharge, death, the outcome of interest, or the time at which their treatment was inconsistent with the copied cohort's protocol, whichever came first. Discharge dispositions of expired or transfer to hospice were considered in-hospital mortality events. We treated hospital discharges to home, a

skilled nursing facility, or a long-term care facility as competing events as such transfers indicate clinical improvement and preclude in-hospital mortality. We censored patients if they were transferred to another hospital or at the time their treatment deviated from the protocol. For example, a never remdesivir protocol deviation occurred at the time a patient-initiated remdesivir, and an early remdesivir protocol deviation occurred on day 3 following admission if the patient had not yet initiated remdesivir. On each day of follow-up, patients were weighted by the inverse of their estimated probability of being uncensored by that day to balance covariates between patients who did and did not follow the protocol. We estimated censoring probabilities with a Cox proportional hazards model that included calendar quarter; hospital size, setting (urban vs. rural), and type (teaching vs. non-teaching); census region; sex; age; all baseline conditions; time-updated medication use (dexamethasone, convalescent plasma, aspirin, biologic immunomodulators); oxygen support; and intensive care unit admission. Weighted Aalen–Johansen estimators estimated the cumulative risk and risk differences (RDs) of each outcome under each protocol. Standard errors were computed using a cluster bootstrap with 300 replications.[38] We conducted subgroup analyses in cohorts defined by the level of supplemental oxygen support on the day of admission. Due to the potential under-ascertainment of oxygen supplementation, we reclassified patients with pneumonia, ARDS, or acute respiratory failure and no record of oxygen at admission as receiving low-flow oxygen, as oxygen would be a component of standard care for those patients.

We conducted two sensitivity analyses. First, we repeated the analysis in patients with a principal diagnosis of COVID-19. Second, we reconducted the oxygen-stratified analysis without reclassifying oxygen supplementation. We also explored a post-hoc stratified analysis with admissions classified as occurring before or after 1 July 2021, to align with the delta variant becoming the dominant strain in the United States. All analyses were conducted in R version 4.1.3.

RESULTS

Study Population

Of 370,181 patients admitted to the hospital with COVID-19 present at admission between 1 May 2020 and 31 December 2021, 274,319 patients met the inclusion criteria and were included in the study (eAppendix; http://links.lww.com/EDE/C15).

Patient characteristics are presented in Table 1. The cohort was evenly divided between males (53%) and females (47%), and 46% were over age 65. Many patients had a history of hypertension (64%), diabetes (38%), obesity (30%), cardiovascular disease (27%), smoking (27%), or chronic kidney disease (15%). At admission, 55% had acute respiratory failure and 8% had SIRS. On the day of admission, 39% of patients received low-flow oxygen (after reclassification), 5% received high-flow oxygen, and 3% received MV/ECMO. Patients receiving supplemental oxygen or MV/ECMO at admission were more likely to have chronic comorbidities. Patients who received MV/ECMO on day 1 were more likely to have presented with SIRS and ARDS.

By day 30 of admission, 117,926 patients (43%) initiated remdesivir, with a median treatment duration of 6 days. Of these, 96,103 (81%) initiated on the first day of hospitalization, 14,318 (12%) initiated on the second day, and 7,505 (6%) initiated after the second day.

In-hospital Mortality

The crude and adjusted cumulative incidence of in-hospital mortality for each protocol are presented in **Figure 1** and **Table 2**. After adjustment, the 30-day risks of in-hospital mortality for each protocol were 13.2% (95% confidence interval [CI] = 13.0%, 13.4%) for the early remdesivir protocol, 16% (95% CI = 16%, 17%) for the no early remdesivir protocol, and 16.9% (95% CI = 16.5%, 17.4%) for the never remdesivir protocol. These correspond to RDs of −3% (95% CI = −4%, −3%; early remdesivir vs. no early remdesivir) and −4% (95% CI −4%, −3%; early remdesivir vs. never remdesivir). The risks and RDs were attenuated, though the confidence intervals still excluded the null, after restricting to the 180,638 (66%) patients with a principal diagnosis of COVID-19 (eAppendix; http://links.lww.com/EDE/C15). In the post-hoc analysis stratified by admission timing, the effect estimates were substantially larger in magnitude and confidence intervals excluded the null in the period before delta variant dominance and were nearly 0 in the period after (eAppendix; http://links.lww.com/EDE/C15).

The effect of remdesivir on mortality varied by the level of supplemental oxygen support at admission (Figure 2). The RDs comparing the early remdesivir and never remdesivir protocols were: −0.2% (95% CI = −1%, 0%) among no supplemental oxygen recipients, −4% (95% CI = −5%, −4%) among low-flow recipients, −8% (95% CI = −12%, −5%) among high-flow recipients, and −6% (95% CI = −10%, −3%) among MV/ECMO recipients. Without reclassifying patients with no oxygen support and pneumonia, ARDS, or acute respiratory failure as receiving low-flow oxygen, the RDs were −4% (95% CI = −5%, −4%) for those receiving no supplemental oxygen and −3% (95% CI = −4%, −2%) for those receiving low-flow oxygen.

Mechanical Ventilation or ECMO

The crude and adjusted cumulative incidences of MV/ECMO under each protocol are presented in **Figure 3** and **Table 3**. The adjusted 30-day cumulative incidences of MV/ECMO for each protocol were 11.2% (95% CI = 11.0%, 11.4%) for no remdesivir, 11% (95% CI = 10%, 11%) for no early remdesivir, and 11% (95% CI = 10%, 11%) for never remdesivir. The RDs were 1% (95% CI = 0%, 1%; early remdesivir vs. no early remdesivir) and 0.4% (95% CI = −0.1%, 0.8%; early remdesivir vs. never remdesivir). Stratified by

TABLE 1. Characteristics of Patients Hospitalized with COVID-19 at 333 Hospitals in the United States, 1 May 2020–31 December 2021[a]

	Overall, n = 274,319	No Oxygen,[b] n = 71,068	Low-flow Oxygen,[b] n = 180,248	High-flow Oxygen,[b] n = 14,912	MV/ECMO,[b] n = 8091
Age					
18–40	32,655 (12)	11,563 (16)	18,827 (10)	1,340 (9)	925 (11)
41–55	56,829 (21)	13,606 (19)	38,354 (21)	3,226 (22)	1,643 (20)
56–65	58,222 (21)	13,252 (19)	39,571 (22)	3,504 (23)	1,895 (23)
>65	126,613 (46)	32,647 (46)	83,496 (46)	6,842 (46)	3,628 (45)
Sex					
Female	128,284 (47)	35,088 (49)	83,368 (46)	6,603 (44)	3,225 (40)
Male	146,035 (53)	35,980 (51)	96,880 (54)	8,309 (56)	4,866 (60)
Region					
Midwest	19,740 (7)	4,562 (6)	13,815 (8)	828 (6)	535 (7)
Northeast	44,567 (16)	18,286 (26)	24,440 (14)	1,019 (7)	822 (10)
South	135,682 (49)	32,732 (46)	88,311 (49)	10,691 (72)	3,948 (49)
West	74,330 (27)	15,488 (22)	53,682 (30)	2,374 (16)	2,786 (34)
Hospital					
Hospital beds > 500	59,968 (22)	18,878 (27)	35,353 (20)	3,922 (26)	1,815 (22)
Teaching	103,675 (38)	31,765 (45)	62,565 (35)	5,944 (40)	3,401 (42)
Urban	250,952 (91)	64,047 (90)	165,836 (92)	13,711 (92)	7,358 (91)
Baseline medications					
Aspirin	23,596 (9)	6,558 (9)	15,467 (9)	922 (6)	649 (8)
Dexamethasone	104,121 (38)	13,679 (19)	82,729 (46)	4,649 (31)	3,064 (38)
Convalescent plasma	17,948 (7)	1,688 (2)	14,092 (8)	1,285 (9)	883 (11)
Biologics	4,488 (2)	196 (0)	3,217 (2)	647 (4)	428 (5)
Comorbidities					
Acute respiratory failure[c]	150,141 (55)	0 (0)	134,168 (74)	10,483 (70)	5,490 (68)
ARDS[c]	17,280 (6)	0 (0)	12,729 (7)	2,291 (15)	2,260 (28)
Autoimmune Disease	8,681 (3)	2,393 (3)	5,616 (3)	457 (3)	215 (3)
HIV/AIDS	1,866 (1)	699 (1)	1,029 (1)	87 (1)	51 (1)
Cancer	24,918 (9)	7,575 (11)	15,530 (9)	1,278 (9)	535 (7)
Cardiomyopathy	8815 (3)	2,509 (4)	5,213 (3)	638 (4)	455 (6)
Dementia	23602 (9)	7,595 (11)	14,430 (8)	975 (7)	602 (7)
Diabetes	104,818 (38)	24,677 (35)	69,966 (39)	6,423 (43)	3,752 (46)
Cardiovascular disease	73,763 (27)	18,840 (27)	46,995 (26)	5,064 (34)	2,864 (35)
Cerebrovascular disease	22,902 (8)	7,520 (11)	13,446 (7)	1,225 (8)	711 (9)
Chronic Kidney disease	40,418 (15)	10,643 (15)	25,847 (14)	2,540 (17)	1,388 (17)
Hypertension	17,4943 (64)	44,517 (63)	115,042 (64)	10,221 (69)	5,163 (64)
Liver disease	3,563 (1)	1,225 (2)	2,009 (1)	164 (1)	165 (2)
Pulmonary disease	30,473 (11)	5,928 (8)	21,253 (12)	2,203 (15)	1,089 (13)
Asthma	23,020 (8)	5,347 (8)	15,881 (9)	1,351 (9)	441 (5)
History of smoking	73,570 (27)	20,207 (28)	47364 (26)	4460 (30)	1,539 (19)
Myocarditis	468 (0)	109 (0)	285 (0)	31 (0)	43 (1)
Obese	81,967 (30)	14,033 (20)	59,470 (33)	5,855 (39)	2609 (32)
Pneumonia at admission[c]	105,021 (38)	0 (0)	94,625 (52)	6,173 (41)	4,223 (52)
SIRS	23,060 (8)	2,100 (3)	15,195 (8)	2,302 (15)	3,463 (43)

[a]All quantities are presented as N (%).
[b]Oxygen supplementation categories are mutually exclusive and based upon the highest level of oxygen support received by the patient at admission.
[c]Due to the reclassification of patients with pneumonia, acute respiratory failure, or ARDS at admission and no evidence of oxygen supplementation as having received low-flow oxygen, no patients with these conditions at admission could appear in the no oxygen group.

baseline oxygen support, the risk of MV/ECMO increased for those receiving no oxygen supplementation (after reclassification) under the early remdesivir protocol compared with both the no early remdesivir (RD: 0.9%; 95% CI = 0.6%, 1.3%) and never remdesivir protocols (RD: 0.9; 95% CI = 0.5%, 1.3%), but there was no effect estimated for other levels of oxygen use (Figure 4). After restricting to patients with a principal diagnosis of COVID-19, all risks decreased, but RDs were

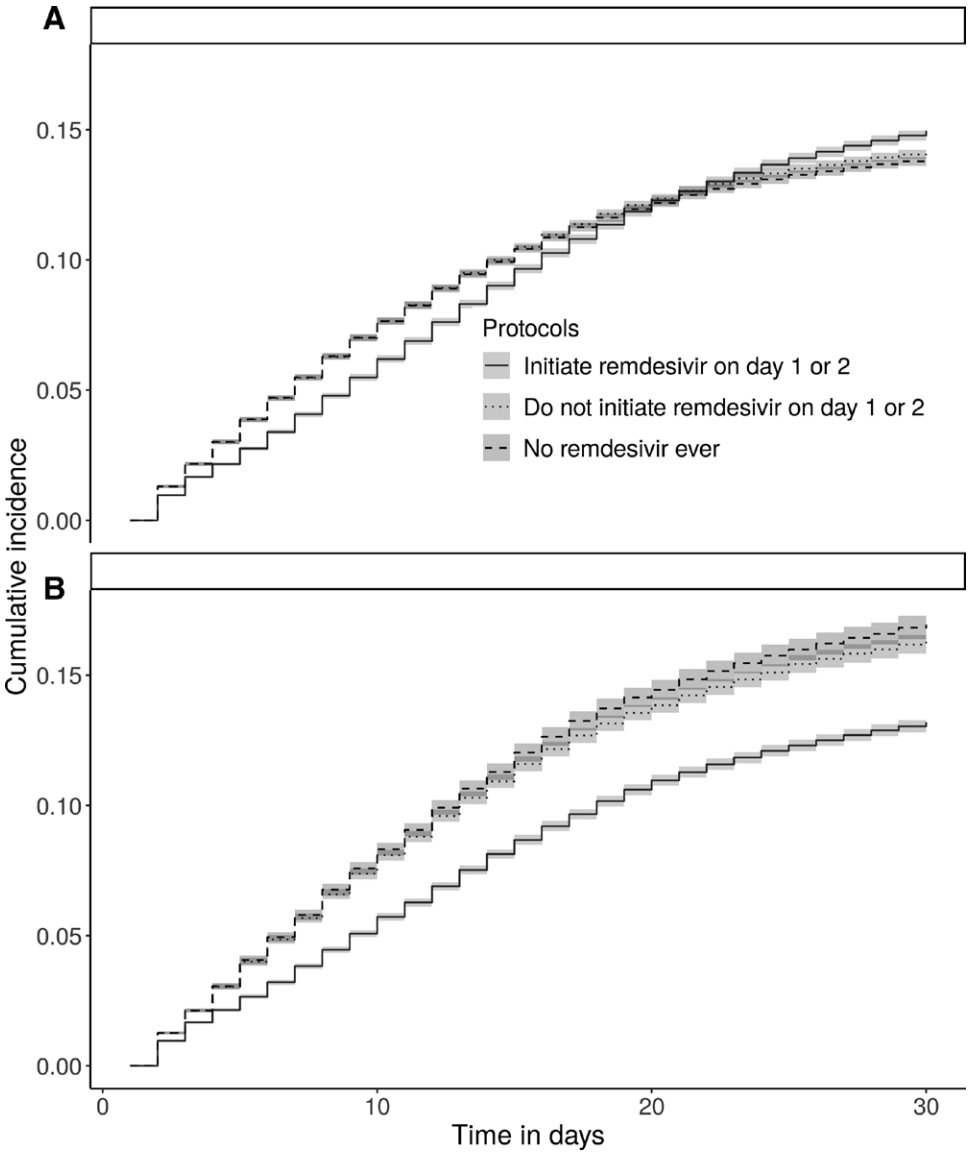

FIGURE 1. Cumulative incidence of in-hospital mortality under remdesivir-based treatment protocols among patients hospitalized with COVID-19 at 333 hospitals in the United States, 1 May 2020–31 December 2021. A, Crude cumulative incidence, all patients. B, Adjusted cumulative incidence, all patients.

similar and confidence intervals excluded the null (eAppendix; http://links.lww.com/EDE/C15). After stratifying into pre- and post-delta variant dominant periods, the effect estimates were close to 0 in the pre-delta period, while the effect estimates were larger in magnitude and confidence intervals excluded the null in the post-delta period (eAppendix; http://links.lww.com/EDE/C15).

DISCUSSION

Using chargemaster data from over 300 US hospitals, we estimated the effectiveness of remdesivir-based proto-cols for preventing MV/ECMO or, separately, death in hos-pitalized COVID-19 patients. Compared to a protocol that never uses remdesivir, initiating remdesivir within 2 days of admission reduced the 30-day risk of in-hospital mortality by 4%. When compared to a protocol that allows remdesivir only after 2 days of admission, initiating within 2 days of admission reduced in-hospital mortality at 30 days by 3%. This latter attenuated effect indicates that early initiation provides the greatest benefit.

These results are comparable to those from the randomized ACTT-1 (enrolled February 2020 to April 2020), which estimated a 29-day mortality RD of −4% comparing remdesivir to standard of care. We found the largest effect among those receiving high-flow oxygen (-8%), while ACTT-1 found the largest effect among those receiving low-flow (−7%). In ACTT-1, the estimated 29-day RD for MV/ECMO was −10% comparing remdesivir to placebo, with a substantially higher

TABLE 2. 30-Day Cumulative Incidence of In-hospital Mortality Under Remdesivir-based Treatment Protocols Among Patients Hospitalized with COVID-19 at 333 Hospitals in the United States, 1 May 2020–31 December 2021

Analysis	Protocol	Events	Person-time[a]	Rate	Unadjusted Risk (%)	Unadjusted RD[b] (%)	Adjusted Risk (%)	Adjusted RD[b] (%)
Overall	Remdesivir	20,450	1601	13	15.0 (14.8, 15.2)	Ref	13.2 (13.0, 13.4)	Ref
	No early remdesivir	22,590	1402	16	14.1 (14.0, 14.3)	0.82 (0.57, 1.1)	16.3 (15.9, 16.7)	−3.1 (−3.5, −2.7)
	Never remdesivir	20,942	1338	16	13.9 (13.7, 14.1)	1.1 (0.83, 1.3)	16.9 (16.5, 17.4)	−3.7 (−4.2, −3.2)
No oxygen,[c] no pneumonia, and no ARDS	Remdesivir	1,337	274	4.9	5.7 (5.4, 6.1)	Ref	5.0 (4.6, 5.5)	Ref
	No early remdesivir	2,666	388	6.9	4.8 (4.7, 5.0)	0.90 (0.53, 1.3)	5.1 (4.7, 5.5)	−0.065 (−0.63, 0.50)
	Never remdesivir	2,543	383	6.7	4.7 (4.5, 4.9)	1.0 (0.66, 1.4)	5.2 (4.7, 5.7)	−0.21 (−0.87, 0.44)
Low-flow oxygen[c]	Remdesivir	14,692	1163	13	14.7 (14.5, 15.0)	Ref	13.9 (13.6, 14.2)	Ref
	No early remdesivir	14,782	847	17	16.4 (16.1, 16.6)	−1.6 (−2.0, −1.3)	17.3 (16.9, 17.7)	−3.5 (−3.9, −3.0)
	Never remdesivir	13,419	793	17	16.2 (15.9, 16.4)	−1.4 (−1.8, −1.1)	18.0 (17.6, 18.5)	−4.2 (−4.7, −3.6)
High-flow oxygen[c]	Remdesivir	1,982	102	19	29 (28, 30)	Ref	23 (22, 25)	Ref
	No early remdesivir	2,167	97	22	24 (23, 25)	4.9 (3.5, 6.3)	31 (29, 33)	−7.4 (−10, −4.9)
	Never remdesivir	2,080	94	22	23.6 (22.7, 24.5)	5.3 (3.8, 6.7)	32 (29, 35)	−8.3 (−12, −5.0)
MV/ECMO[c]	Remdesivir	2,439	62	39	58 (57, 60)	Ref	54 (52, 56)	Ref
	No early remdesivir	2,975	69	43	58 (57, 59)	0.37 (−1.6, 2.4)	59 (57, 62)	−5.8 (−8.8, −2.8)
	Never remdesivir	2,900	68	43	58 (56, 59)	0.62 (−1.4, 2.6)	60 (57, 63)	−6.2 (−9.6, −2.8)

[a]Per 1000 person-days.
[b]RD = risk difference.
[c]Oxygen supplementation categories are mutually exclusive and based upon the highest level of oxygen support received by the patient at admission.

risk of the outcome in the placebo arm than we estimated under the never remdesivir protocol. Similar results were found in the CATCO trial (enrolled from August 2020 to April 2021).[22] The lower estimated incidence of MV/ECMO and reduced effect of remdesivir on MV/ECMO in our study likely reflects differences in patient case mix and evolving standards of care. In ACTT-1 and CATCO, more than 80% of those not receiving MV/ECMO at baseline were receiving oxygen support, compared with 45% in our study. Patients needing oxygen supplementation may be at a higher risk of requiring oxygen intensification, possibly contributing to the higher incidence and larger effects in ACTT-1 and CATCO.

Neither the DisCoVeRy[23] (enrolled from March 2020 to January 2021) nor the Solidarity[16] (enrolled from March 2020 to January 2021) trials found an effect of remdesivir on mortality. DisCoVeRy excluded patients without supplemental oxygen use, with elevated liver enzymes, or with severe chronic kidney disease, leading to a different patient population from our study. Further, neither DisCoVeRy nor Solidarity distinguished discharge to home or long-term care facility from hospital transfer, which could lead to reduced risk estimates. Lastly, almost 40% of Solidarity participants were hospitalized ≥2 days before randomization. The reduced estimates of in-hospital mortality may be due to effects being attenuated with later initiation.

An observational study investigating the effectiveness of remdesivir in patients hospitalized with COVID-19 between February 2020 and February 2021 found higher mortality risk estimates at 28 days compared with our study (remdesivir: 16%; controls: 20%).[39] Control patients, but not remdesivir initiators, were required to be hospitalized for at least 5 days. Like the ACTT trial, the study reported reduced mortality for those receiving remdesivir in the low-flow oxygen group (adjusted hazard ratio: 0.85) but not in the high-flow oxygen group. However, the minimum length of hospitalization requirement for the control patients may have biased the hazard ratio towards a null effect by underestimating the early risk among the controls.[40] Notably, on the difference scale, the study found the greatest effect of remdesivir was among those receiving high-flow oxygen (28-day RD: −5%).

Our study has several limitations, the primary of which is unmeasured confounding by important socioeconomic and clinical factors. For example, we were unable to adjust for race, access to care, or insurance status, all of which could affect the timing of hospital admission after symptom presentation and therefore the effectiveness of remdesivir.[41–43] Further, we could not investigate the impact of late admission due to not capturing the time of symptom onset. It is likely that remdesivir was less likely to be offered to those with longer intervals from symptom onset to admission and may not have experienced a benefit. Importantly, we were also unable to adjust for COVID-19 vaccination status, which could reduce mortality in high-risk patients and alter the population requiring inpatient care for COVID-19. The large difference between the unadjusted and adjusted results, which included reversal of the direction of the effects, indicates that treatment decisions are driven by prognostic patient characteristics.

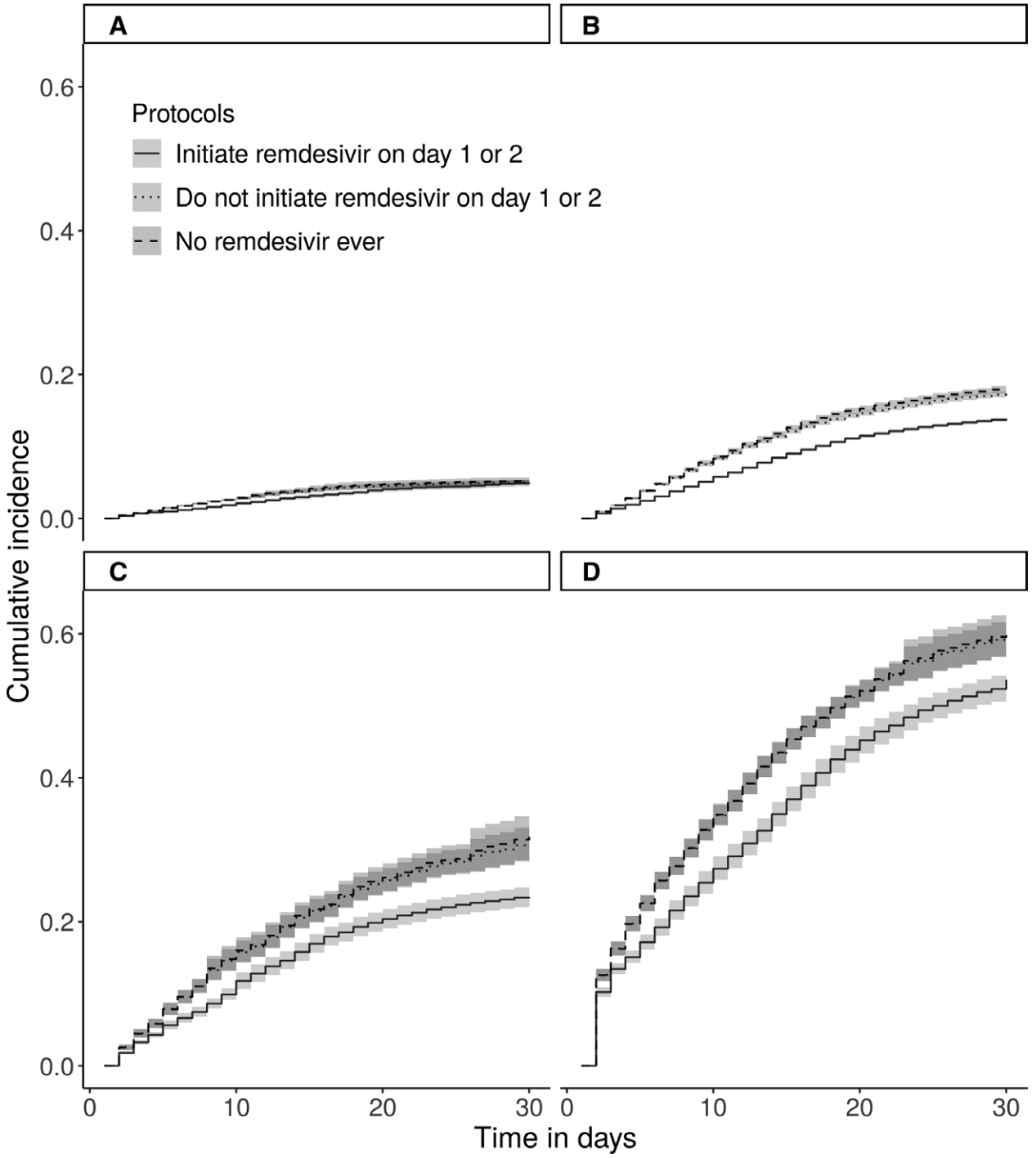

FIGURE 2. Cumulative incidence of in-hospital mortality by oxygen supplementation at admission under remdesivir-based treatment protocols among patients hospitalized with COVID-19 at 333 hospitals in the United States, 1 May 2020–31 December 2021. A, Adjusted cumulative incidence, patients with no supplemental oxygen use at admission. B, Adjusted cumulative incidence, patients with low-flow supplemental oxygen use at admission. C, Adjusted cumulative incidence, patients with high-flow supplemental oxygen use at admission. D, Adjusted cumulative incidence, patients on MV/ECMO at admission.

A second limitation is that our data are subject to measurement error. The data only included inpatient encounters, so we likely underestimated the prevalence of comorbidities. Additionally, the high prevalence of acute respiratory failure and ARDS, combined with the lower rate of baseline oxygen supplementation, indicates oxygen use was under-ascertained.

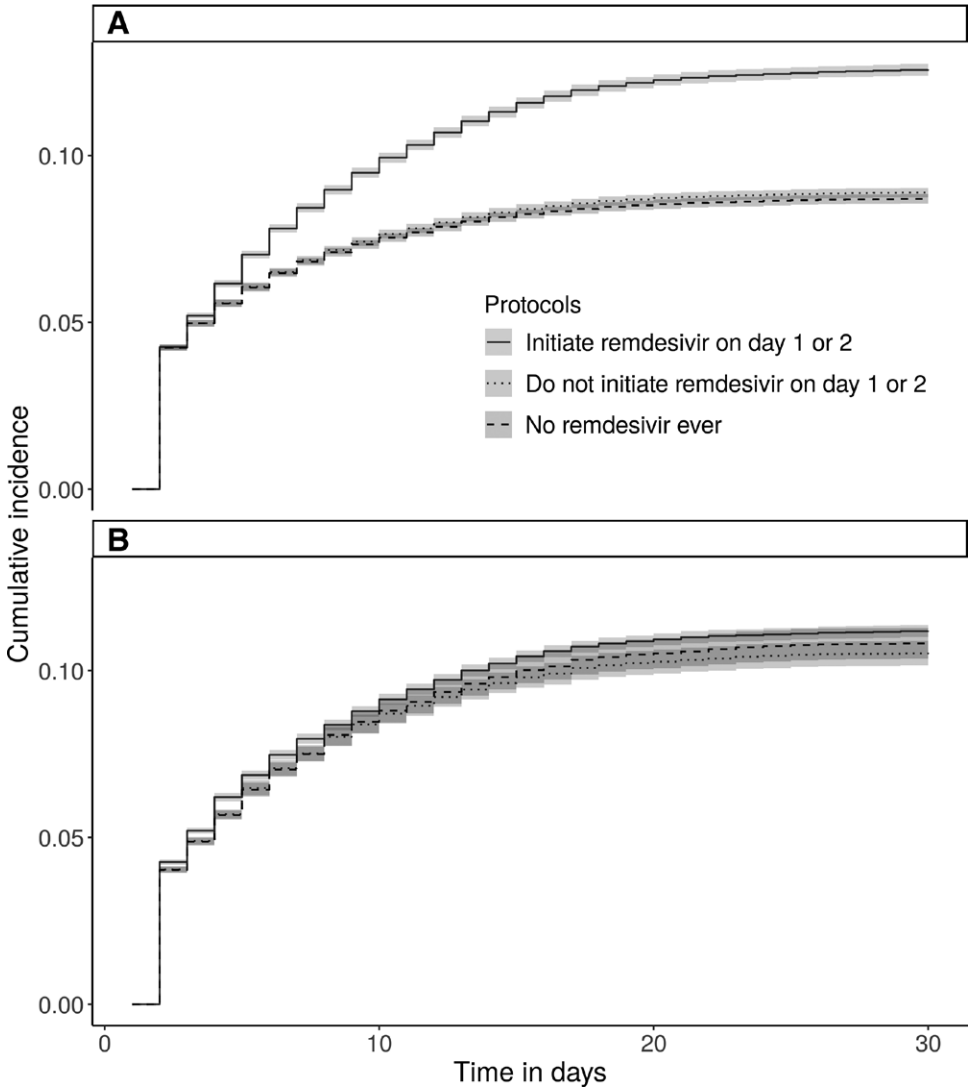

FIGURE 3. Cumulative incidence of MV/ECMO under remdesivir-based treatment protocols among patients hospitalized with COVID-19 at 333 hospitals in the United States, 1 May 2020–31 December 2021. A, Crude cumulative incidence, all patients. B, Adjusted cumulative incidence, all patients.

Though we reclassified those with ARDS, respiratory failure, or pneumonia and no evidence of baseline oxygen support as receiving low-flow oxygen, uncertainty remains regarding the true level of oxygen supplementation received. Third, we included all patients with a diagnosis of COVID-19, regardless of whether that was the primary reason for admission. If those with a secondary diagnosis of COVID-19 had a poorer prognosis, this may lead to overestimates of the effect of remdesivir, as treating COVID-19 would not prevent outcomes caused by unrelated conditions. After restricting to patients with a principal diagnosis of COVID-19, the estimated risks and effect estimates of mortality were attenuated, suggesting that patients with a non-COVID-19 principal diagnosis indeed had a poorer prognosis (eAppendix; http://links.lww.com/EDE/C15). Fourth, we did not investigate the impact of other treatments beyond adjusting for concomitant use, and we did not evaluate a specific remdesivir treatment duration, so our results cannot be used to inform optimal remdesivir regimens. Treatments have varied over the course of the pandemic, and while we only focused on the effect of remdesivir-based protocols, investigating the effects of protocols involving remdesivir in combination with other treatments may provide additional evidence to optimize patient care.

Finally, the standard of care, viral variants, and patient case mix may have been variable across the study period and across hospitals. Thus, our results may not generalize to settings with different distributions of standard of care and viral variants from those in our study. We further investigated this with a post-hoc analysis stratifying the study period into pre-delta variant and after, which found a strong

TABLE 3. 30-Day Cumulative Incidence of MV/ECMO Under Remdesivir-based Treatment Protocols Among Patients Hospitalized with COVID-19 at 333 Hospitals in the United States, 1 May 2020– 31 December 2021

Analysis	Protocol	Events	Person-time[a]	Rate	Unadjusted Risk (%)	Unadjusted RD[b] (%)	Adjusted Risk (%)	Adjusted RD[b] (%)
Overall	Remdesivir	23,193	1402	17	12.6 (12.4, 12.8)	Ref	11.2 (11.0, 11.4)	Ref
	No early remdesivir	14,968	1234	12	8.9 (8.8, 9.0)	3.7 (3.5, 3.9)	10.5 (10.2, 10.9)	0.67 (0.28, 1.1)
	Never remdesivir	14,315	1183	12	8.7 (8.6, 8.9)	3.9 (3.7, 4.0)	10.8 (10.4, 11.3)	0.37 (−0.10, 0.84)
No oxygen[c], pneumonia, or ARDS	Remdesivir	776	268	2.9	3.3 (3.0, 3.6)	Ref	2.3 (2.1, 2.7)	Ref
	No early remdesivir	665	381	1.7	1.2 (1.1, 1.3)	2.1 (1.8, 2.4)	1.4 (1.2, 1.6)	0.95 (0.60, 1.3)
	Never remdesivir	629	376	1.7	1.15 (1.06, 1.24)	2.1 (1.8, 2.4)	1.4 (1.2, 1.7)	0.89 (0.52, 1.3)
Low-flow oxygen[c]	Remdesivir	12,524	1043	12	10.9 (10.7, 11.1)	Ref	9.7 (9.5, 9.9)	Ref
	No early remdesivir	7,890	761	10	8.5 (8.3, 8.7)	2.4 (2.2, 2.7)	9.5 (9.2, 9.8)	0.19 (−0.17, 0.55)
	Never remdesivir	7,311	717	10	8.3 (8.1, 8.5)	2.6 (2.4, 2.8)	9.8 (9.4, 10.)	−0.075 (−0.48, 0.33)
High-flow oxygen[c]	Remdesivir	1,831	84	22	22 (21, 23)	Ref	17 (16, 18)	Ref
	No early remdesivir	989	86	12	10.6 (10.0, 11.3)	11 (10, 12)	16 (15, 18)	0.35 (−1.4, 2.1)
	Never remdesivir	951	84	11	10 (9.8, 11)	11 (10, 12)	16 (15, 18)	0.28 (−1.7, 2.3)

[a]Per 1000 person-days.
[b]RD = risk difference.
[c]Oxygen supplementation categories are mutually exclusive and based upon the highest level of oxygen support received by the patient at admission.

effect of remdesivir on mortality in the pre-delta variant and a nearly null effect in the delta period. This stratification also roughly corresponds to periods of time before and after vaccinations were widely available for the entire US population. These results could have important implications for evaluating the continuing usage of remdesivir in future variants, though the post-hoc nature of the analysis warrants caution in interpretation.

Though subject to limitations, our results add to the body of evidence on the effect of remdesivir treatment for hospitalized COVID-19 patients. As one of the largest and most geographically diverse studies of US patients hospitalized with COVID-19 to date, our findings are well generalizable to patients across the US and, when put in context with existing evidence, can better inform guidelines for use. Our results are consistent with the hypothesis that remdesivir is most beneficial when used early during a hospital admission, with the greatest benefit for those receiving high-flow oxygen support. Future work is needed to understand the effectiveness of COVID-19 treatment protocols in hospitalized patients with regard to continuously evolving patient populations and newly emerging viral variants.

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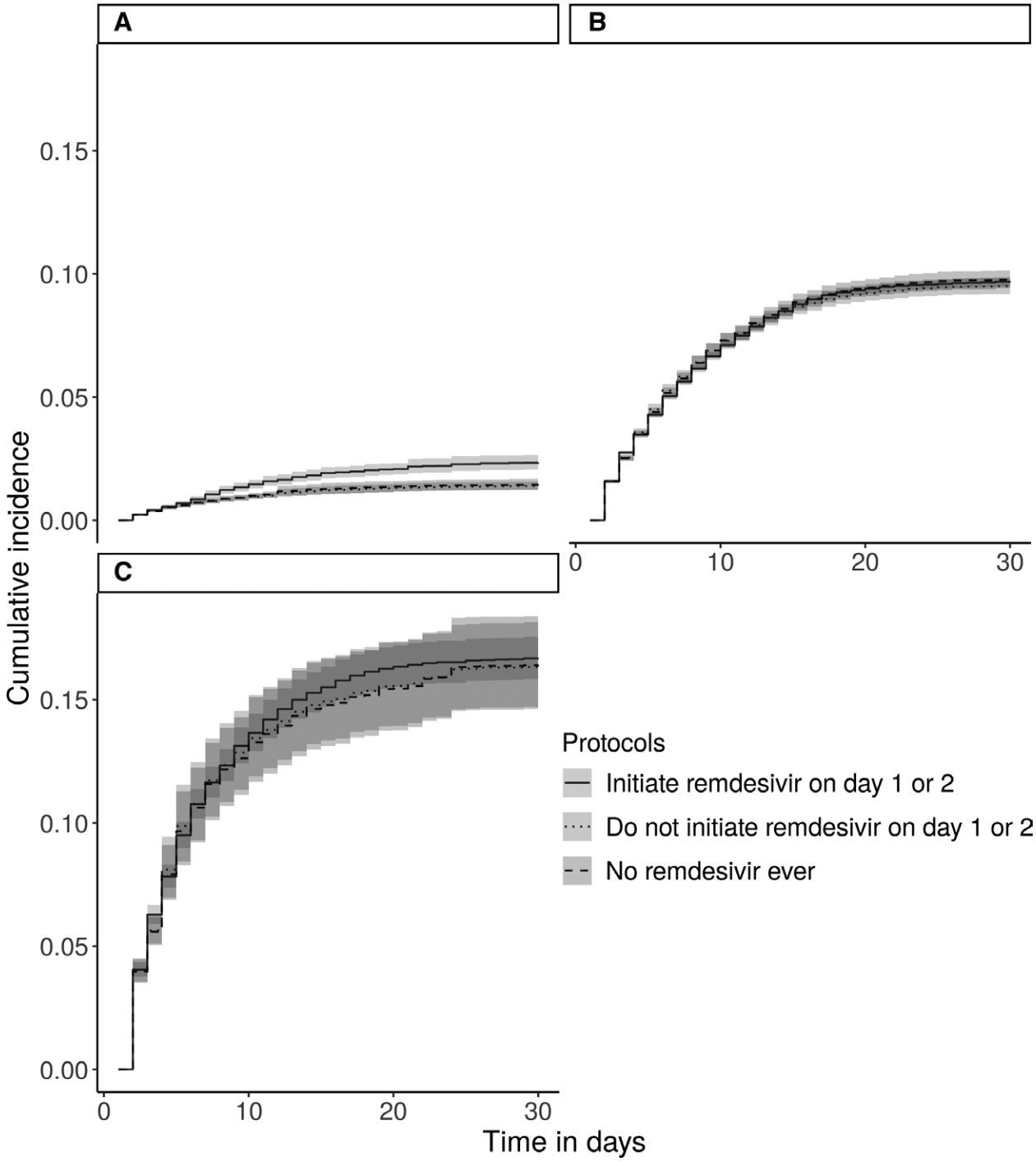

FIGURE 4. Cumulative incidence of MV/ECMO under remdesivir-based treatment protocols among patients hospitalized with COVID-19 at 333 hospitals in the United States, 1 May 2020–31 December 2021. A, Adjusted cumulative incidence, patients with no supplemental oxygen use at admission. B, Adjusted cumulative incidence, patients with low-flow supplemental oxygen use at admission. C, Adjusted cumulative incidence, patients with high-flow supplemental oxygen use at admission.

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