Effectiveness of Early Remdesivir Initiation in Patients With Immunocompromising Conditions Hospitalized With COVID-19 by Variant Era, Severity of Immunosuppression, and Age

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Conclusions

- Using methods that reduce bias due to time-varying confounding, informative censoring, and immortal person-time, this study found that the risk of in-hospital mortality was lower for patients with immunocompromising conditions who received early remdesivir compared with those who received no remdesivir regardless of age, SARS-CoV-2 variant era, and severity of immunosuppression
- This study highlights the importance of timely remdesivir administration to improve survival outcomes in people with immunocompromising conditions who are hospitalized with COVID-19

Plain Language Summary

- People with immunocompromising conditions are more likely to develop severe COVID-19, and early treatment with remdesivir has been shown to reduce the risk of dying
- This study consistently found that early initiation of remdesivir after being hospitalized with COVID-19 was associated with a lower risk of dying across subgroups determined by age, SARS-CoV-2 variant era, and level of immunosuppression
- These findings confirm the importance of early remdesivir treatment for improving survival in people with immunocompromising conditions who are hospitalized with COVID-19

Introduction

- People with immunocompromising conditions are at greater risk of severe COVID-19 and COVID-19—related mortality^{1,2}
- Remdesivir (RDV) is a nucleotide analog prodrug approved for the treatment of COVID-19 in nonhospitalized and hospitalized adult and pediatric patients³
- People with immunocompromising conditions who initiate RDV within the first 2 days
 of hospitalization with COVID-19 have a lower risk of all-cause mortality compared
 with those who do not initiate RDV⁴

 However, the impact of early initiation of RDV in people with immunocompromising conditions by age, SARS-CoV-2 variant era, and severity of immunosuppression remains unknown

Objective

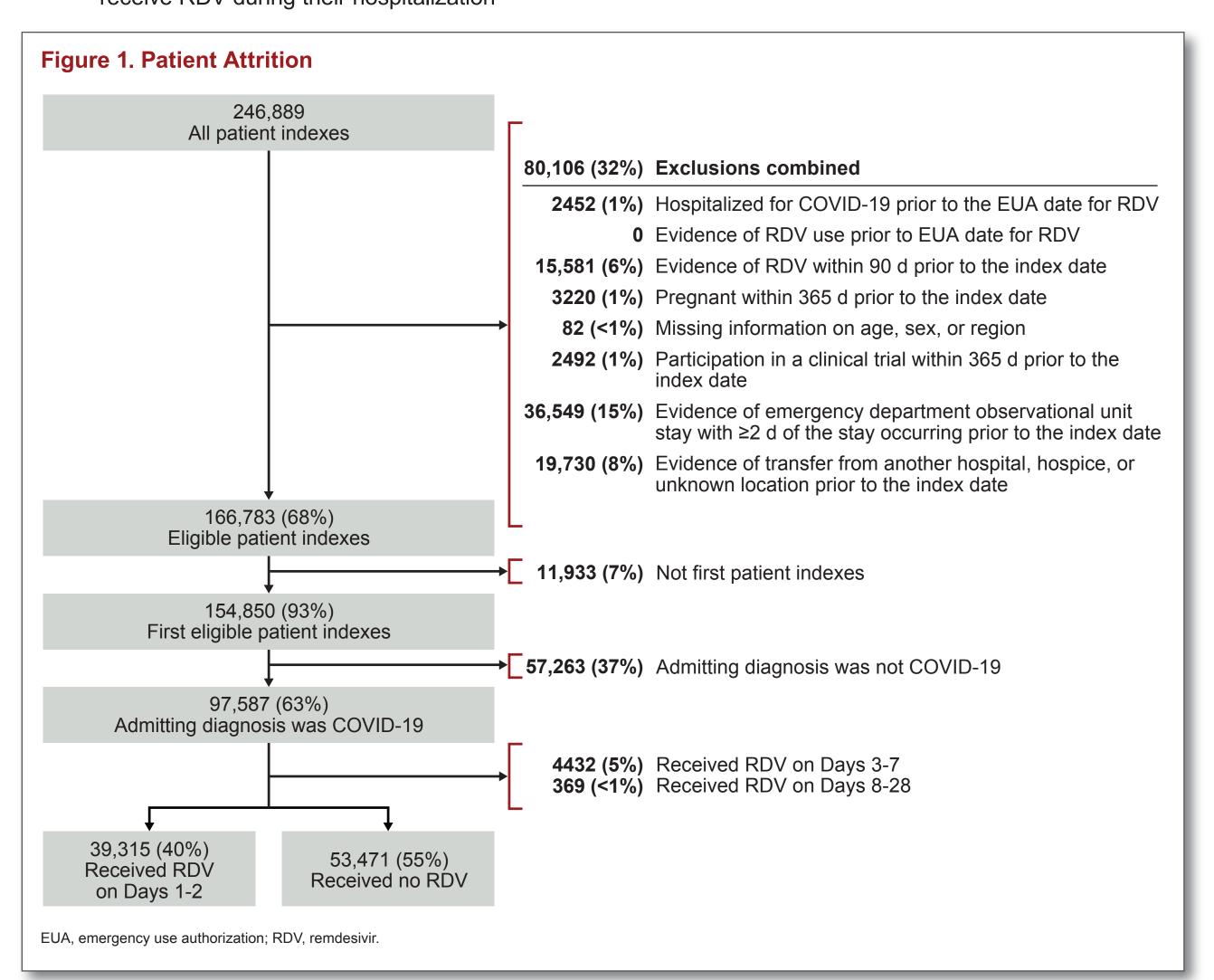
 To determine whether early initiation of RDV is associated with reduced mortality compared with no RDV treatment in subgroups of hospitalized COVID-19 patients with immunocompromising conditions stratified by age, SARS-CoV-2 variant era, and severity of immunosuppression

Methods

- This was a retrospective, observational cohort study that used HealthVerity data, which include linked US hospital chargemaster data and medical and pharmacy claims
- Patients with immunocompromising conditions aged ≥12 years who were hospitalized between May 2020 and December 2023 with a primary diagnosis of COVID-19 were included
- Immunocompromising conditions included HIV/AIDS, hematologic malignancy, other immune condition, solid malignancy, organ transplant, and rheumatologic/ inflammatory condition
- Patients who initiated RDV during the first 2 days of hospitalization (early RDV)
 were compared with those who had no evidence of RDV initiation during the 28-day
 follow-up period (no RDV)
- A clone-censor-weight approach was used to calculate risk ratios and risk differences for in-hospital mortality at 14 and 28 days after hospitalization, controlling for baseline and time-varying confounders
- Analyses were stratified by age group (12-64 or ≥65 years), variant era (Pre-Delta, Delta, or Omicron), and severity of immunosuppression (mild or moderate/severe)
- A test of homogeneity of the subgroup-specific risk differences at Day 28 was conducted using Cochran's Q test

Results

- Overall, 97,587 patients were eligible for the study (Figure 1)
- 4801 patients initiated RDV between Days 3 and 28 of their hospitalization; these patients were allowed to contribute person-time to the study, but the sample size was too small for inclusion in the current analysis
 39,315 patients initiated RDV during the first 2 days of their hospitalization, and 53,471 patients did not receive RDV during their hospitalization



- Demographic and clinical characteristics at admission for each subgroup are shown in Tables 1 through 3
 The most common immunosuppressive conditions across subgroups were solid malignancy and rheumatologic and inflammatory conditions
- Across all subgroups, greater proportions of patients in the early RDV group were on oxygen support and were on dexamethasone compared with the no RDV group at baseline

Table 1. Demographic and Clinical Characteristics at Admission by Age

	Age Category				
	12-	64 y	≥65 y		
	Early RDV (n = 13,227)	No RDV (n = 17,266)	Early RDV (n = 26,088)	No RDV (n = 36,205)	
Age, y, median (Q1, Q3)	56 (49, 61)	55 (47, 60)	77 (71, 93)	78 (72, 93)	
Sex, female, n (%)	7169 (54)	9369 (54)	12,585 (48)	18,368 (51)	
Comorbidities, n (%)					
Blood disorder	88 (1)	140 (1)	77 (<1)	101 (<1)	
Cancer (excluding nonmelanoma skin cancer)	2989 (23)	3836 (22)	10,499 (40)	14,365 (40)	
Chronic kidney disease	2083 (16)	4034 (23)	7512 (29)	13,356 (37)	
Chronic liver disease	1835 (14)	2622 (15)	1864 (7)	2692 (7)	
Chronic lung disease	5914 (45)	7868 (46)	12,683 (49)	17,131 (47)	
Diabetes (type 1 or 2)	5142 (39)	7385 (43)	11,090 (43)	16,554 (46)	
Cardiovascular disease	8836 (67)	12,121 (70)	21,590 (83)	31,084 (86)	
Alzheimer disease/dementia	134 (1)	354 (2)	2959 (11)	5692 (16)	
Obesity	5666 (43)	7081 (41)	7410 (28)	9737 (27)	
Stroke or cerebrovascular disease	1456 (11)	2553 (15)	5495 (21)	9134 (25)	
Substance use disorder	2732 (21)	4753 (28)	3509 (13)	5082 (14)	
Tobacco use	3868 (29)	5939 (34)	9451 (36)	13,217 (37)	
Disability	5085 (38)	7521 (44)	12,645 (48)	19,414 (54)	
Mood disorder or schizophrenia	3549 (27)	5321 (31)	5882 (23)	8995 (25)	
Tuberculosis infection	17 (<1)	30 (<1)	26 (<1)	55 (<1)	
Baseline oxygen support, n (%)					
No oxygen	9317 (70)	13,128 (76)	18,086 (69)	27,389 (76)	
Low-flow oxygen	1920 (14)	1922 (11)	4403 (17)	4585 (13)	
High-flow oxygen	1324 (10)	1408 (8)	2649 (10)	3030 (8)	
Mechanical ventilation or ECMO	666 (5)	808 (5)	950 (4)	1201 (3)	
Immunosuppressive condition, n (%)					
HIV/AIDS	443 (3)	655 (4)	167 (1)	197 (1)	
Hematologic malignancy	516 (4)	609 (4)	1597 (6)	1897 (5)	
Other immune condition	1689 (13)	2549 (15)	2241 (9)	3438 (9)	
Solid malignancy	6881 (52)	8315 (48)	17,625 (68)	23,946 (66)	
Organ transplant	1188 (9)	1648 (10)	1025 (4)	1271 (4)	
Rheumatologic/inflammatory condition	6102 (46)	8709 (50)	10,602 (41)	15,661 (43)	
Baseline medication, n (%)					
Oral antiviral (eg, nirmatrelvir/ritonavir, molnupiravir)	0	6 (<1)	2 (<1)	27 (<1)	
Glucocorticoid (eg, dexamethasone)	8425 (63)	5898 (34)	15,894 (61)	12,170 (34)	

Table 2. Demographic and Clinical Characteristics at Admission by Variant Era **Variant Era** Omicron Early RDV No RDV Early RDV No RDV Early RDV No RDV (n = 16,246) (n = 24,288) (n = 7701) (n = 6573) (n = 15,368) (n = 22,610)71 (60, 79) 71 (60, 80) 67 (56, 77) 68 (57, 78) 74 (64, 82) 74 (63, 82) Age, y, median (Q1, Q3) 7870 (48) | 12,537 (52) | 4082 (53) | 3442 (52) | 7802 (51) | 11,758 (52) Sex, female, n (%) Comorbidities, n (%) 107 (<1) 21 (<1) 23 (<1) 90 (1) 111 (<1) Cancer (excluding nonmelanoma skin cancer) 5204 (32) 8027 (33) 2375 (31) 2054 (31) 5909 (38) 8120 (36) 3856 (24) | 8057 (33) | 1438 (19) | 1842 (28) | 4301 (28) | 7491 (33) Chronic kidney disease Chronic liver disease 1503 (9) | 2378 (10) | 703 (9) | 687 (10) | 1493 (10) | 2249 (10) Chronic lung disease 7211 (44) | 10,990 (45) | 3158 (41) | 2881 (44) | 8228 (54) | 11,128 (49) 6913 (43) | 11,275 (46) | 2853 (37) | 2730 (42) | 6466 (42) | 9934 (44) Diabetes (type 1 or 2) 12,399 (76) 19,609 (81) 5483 (71) 5000 (76) 12,544 (82) 18,596 (82) Cardiovascular disease 496 (8) | 1592 (10) | 2690 (12) Alzheimer disease/dementia 8059 (33) | 2651 (34) | 2186 (33) | 4683 (30) | 6573 (29) Obesity 2607 (16) | 5096 (21) | 1084 (14) | 1228 (19) | 3260 (21) | 5363 (24) Stroke or cerebrovascular disease 1971 (12) | 3831 (16) | 1210 (16) | 1299 (20) | 3060 (20) | 4705 (21) Substance use disorder 4735 (29) | 7950 (33) | 2366 (31) | 2347 (36) | 6218 (40) | 8859 (39) Tobacco use 6472 (40) | 11,679 (48) | 2911 (38) | 2891 (44) | 8347 (54) | 12,365 (55) 3595 (22) | 6373 (26) | 1691 (22) | 1686 (26) | 4145 (27) | 6257 (28) Mood disorder or schizophrenia 12 (<1) | 41 (<1) | 10 (<1) | 7 (<1) | 21 (<1) | 37 (<1) **Tuberculosis** infection Baseline oxygen support, n (%) 10,944 (67) 18,006 (74) 5336 (69) 4850 (74) 11,123 (72) 17,661 (78) No oxygen 2907 (18) | 3303 (14) | 1154 (15) 749 (11) | 2262 (15) | 2455 (11) Low-flow oxygen High-flow oxygen 1999 (8) | 817 (11) | 656 (10) | 1560 (10) | 1783 (8) Mechanical ventilation or ECMO 980 (4) | 394 (5) | 318 (5) | 423 (3) | 711 (3) Immunosuppressive condition, n (%) 111 (2) 245 (2) 325 (1) HIV/AIDS 107 (1) 388 (5) 300 (5) 1031 (7) 1214 (5) Hematologic malignancy 718 (9) 719 (11) 1694 (11) 2509 (11) Other immune condition 10,118 (62) 14,448 (59) 4660 (61) 3896 (59) 9728 (63) 13,917 (62) Solid malignancy 1158 (5) 361 (5) 376 (6) 1221 (8) 1385 (6) Organ transplant Rheumatologic/inflammatory condition 6966 (43) | 11,141 (46) | 3256 (42) | 3018 (46) | 6482 (42) | 10,211 (45) Baseline medication, n (%)

Table 3. Demographic and Clinical Characteristics at Admission by Severity of Immunosuppression

10,984 (68) 8658 (36) 5417 (70) 2934 (45) 7918 (52) 6476 (29)

Oral antiviral (eg, nirmatrelvir/ritonavir,

Glucocorticoid (eg, dexamethasone)

ECMO, extracorporeal membrane oxygenation; Q1, first quartile; Q3, third quartile; RDV, remdesivir.

ECMO, extracorporeal membrane oxygenation; Q1, first quartile; Q3, third quartile; RDV, remdesivir

molnupiravir)

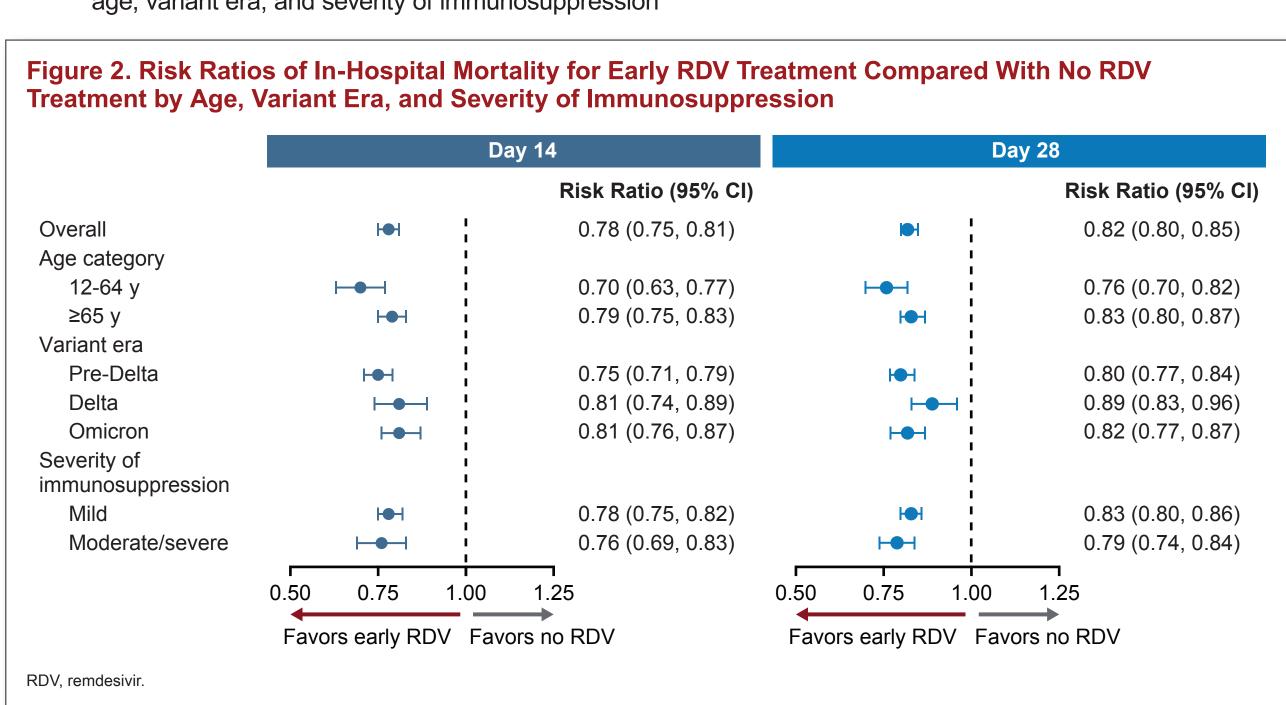
	Severity of Immunosuppression				
	M	ild	Moderate/Severe		
	Early RDV	No RDV	Early RDV	No RDV	
Age was disp (O1 O2)	(n = 32,344)	(n = 44,650)	(n = 6971)	(n = 8821)	
Age, y, median (Q1, Q3)	71 (61, 80)	73 (62, 82)	67 (58, 76)	68 (57, 77)	
Sex, female, n (%)	16,205 (50)	23,135 (52)	3549 (51)	4602 (52)	
Comorbidities, n (%)	404 (4)	100 (1)	0.4 (.4)	50 (4)	
Blood disorder	131 (<1)	189 (<1)	34 (<1)	52 (1)	
Cancer (excluding nonmelanoma skin cancer)	10,121 (31)	14,110 (32)	3367 (48)	4091 (46)	
Chronic kidney disease	7486 (23)	14,054 (31)	2109 (30)	3336 (38)	
Chronic liver disease	2753 (9)	4066 (9)	946 (14)	1248 (14)	
Chronic lung disease	14,324 (44)	19,807 (44)	4273 (61)	5192 (59)	
Diabetes (type 1 or 2)	13,189 (41)	19,924 (45)	3043 (44)	4015 (46)	
Cardiovascular disease	24,694 (76)	35,752 (80)	5732 (82)	7453 (84)	
Alzheimer disease/dementia	2708 (8)	5368 (12)	385 (6)	678 (8)	
Obesity	10,515 (33)	13,541 (30)	2561 (37)	3277 (37)	
Stroke or cerebrovascular disease	5626 (17)	9758 (22)	1325 (19)	1929 (22)	
Substance use disorder	4515 (14)	7508 (17)	1726 (25)	2327 (26)	
Tobacco use	10,011 (31)	15,004 (34)	3308 (47)	4152 (47)	
Disability	13,819 (43)	21,606 (48)	3911 (56)	5329 (60)	
Mood disorder or schizophrenia	7294 (23)	11,498 (26)	2137 (31)	2818 (32)	
Tuberculosis infection	29 (<1)	62 (<1)	14 (<1)	23 (<1)	
Baseline oxygen support, n (%)					
No oxygen	22,812 (71)	34,210 (77)	4591 (66)	6307 (71)	
Low-flow oxygen	5040 (16)	5201 (12)	1283 (18)	1306 (15)	
High-flow oxygen	3195 (10)	3638 (8)	778 (11)	800 (9)	
Mechanical ventilation or ECMO	1297 (4)	1601 (4)	319 (5)	408 (5)	
Immunosuppressive condition, n (%)	. ,	. ,		, , ,	
HIV/AIDS	246 (1)	339 (1)	364 (5)	513 (6)	
Hematologic malignancy	1122 (3)	1406 (3)	991 (14)	1100 (12)	
Other immune condition	2564 (8)	4124 (9)	1366 (20)	1863 (21)	
Solid malignancy	20,000 (62)	26,736 (60)	4506 (65)	5525 (63)	
Organ transplant	1122 (3)	1623 (4)	1091 (16)	1296 (15)	
Rheumatologic/inflammatory condition	14,134 (44)	20,742 (46)	2570 (37)	3628 (41)	
Baseline medication, n (%)	, (- /	, (-)	ζ- /		
Oral antiviral (eg, nirmatrelvir/ritonavir, molnupiravir)	1 (<1)	29 (<1)	1 (<1)	4 (<1)	
Glucocorticoid (eg, dexamethasone)	20,462 (63)	15,082 (34)	3857 (55)	2986 (34)	

• The cumulative incidence of in-hospital mortality by subgroup at Days 14 and 28 is shown in **Table 4**

Table 4. Cumulative Incidence of In-Hospital Mortality by Age, Variant Era, and Severity of Immunosuppression

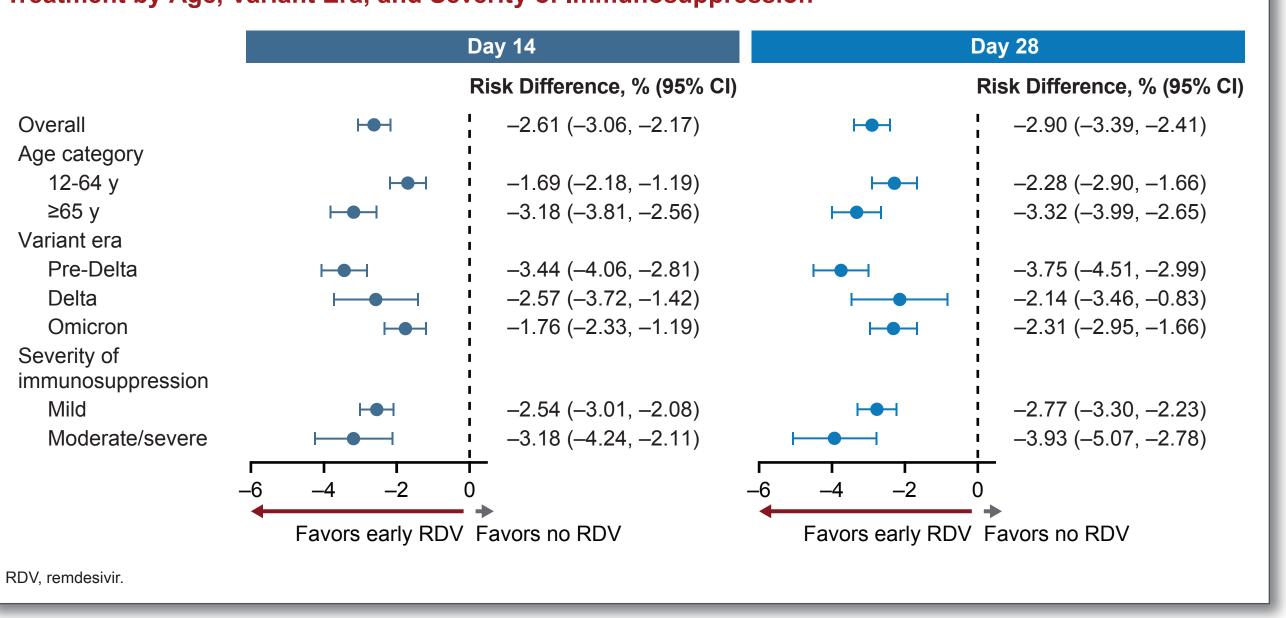
Cumulative Incidence, %	Day	Day 14		Day 28	
	Early RDV	No RDV	Early RDV	No RDV	
Overall	9.22	11.84	13.66	16.56	
Age category					
12-64 y	3.89	5.58	7.13	9.41	
≥65 y	11.78	14.96	16.79	20.11	
Variant era					
Pre-Delta	10.07	13.50	15.23	18.98	
Delta	11.13	13.70	17.87	20.01	
Omicron	7.62	9.38	10.37	12.68	
Severity of immunosuppression					
Mild	9.06	11.60	13.44	16.21	
Moderate/severe	9.96	13.13	14.60	18.52	

Overall, initiation of RDV during the first 2 days of hospitalization was associated with a 22% decreased risk of in-hospital mortality at Day 14 and an 18% decreased risk at Day 28 compared with no initiation of RDV (Figure 2)
 — Similarly, in-hospital mortality risk was lower with early RDV treatment when the population was stratified by age, variant era, and severity of immunosuppression



- In the overall population, initiation of RDV during the first 2 days of hospitalization was associated with 2.61% and 2.90% absolute reductions in the risk of in-hospital mortality at Days 14 and 28, respectively, compared with no initiation of RDV (Figure 3)
- The risk difference ranged from –1.69% to –3.93% across all subgroups at Days 14 and 28

Figure 3. Risk Differences of In-Hospital Mortality for Early RDV Treatment Compared With No RDV Treatment by Age, Variant Era, and Severity of Immunosuppression



- At Days 14 and 28, the risk ratio of in-hospital mortality for early RDV treatment versus no RDV treatment was stronger for patients aged 12 to 64 years compared with those aged ≥65 years (**Figure 2**)
- The risk difference was greater for patients aged ≥65 years compared with those aged 12 to 64 years at Day 14 (**Figure 3**); the effect of early RDV treatment on in-hospital mortality compared with no RDV treatment was significantly stronger in patients aged ≥65 years at Day 28 based on the test of homogeneity (*P* = 0.021 on the risk difference scale)
- The risk ratio of in-hospital mortality for early RDV treatment versus no RDV treatment was similar across variant eras (Figure 2)
- The risk difference was greater for patients hospitalized during the Pre-Delta era compared with those hospitalized during the Omicron era at Days 14 and 28 (**Figure 3**); the effect of early RDV treatment on in-hospital mortality compared with no RDV treatment was significantly different across variant eras at Day 28 (*P* = 0.009 on the risk difference scale)
- The risk difference of in-hospital mortality for early RDV treatment versus no RDV treatment was greater among patients with moderate/severe immunosuppression relative to patients with mild immunosuppression (**Figure 3**); the effect of early RDV treatment on in-hospital mortality compared with no RDV treatment was greater in patients with moderate/severe immunosuppression at Day 28, although this was not statistically significant (*P* = 0.068 on the risk difference scale)

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Disclosures: MB, **VS**, **CN**, **MA**, and **APC** are stockholders and employees of Gilead Sciences, Inc. **KH**, **NR**, and **RWF** are employees of and own equity in Target RWE. **MAB** served as a scientific advisory committee member for Amgen, Brigham and Women's Hospital, Gilead Sciences, Inc., Kite Pharma, and the National Institute of Diabetes and Digestive and Kidney Diseases; received consulting fees/equity from Target RWE; and received equity from Accompany Health and VitriVax.