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Early Versus Late Versus No Remdesivir Initiation in Patients With Immunocompromising Conditions Hospitalised With COVID-19

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Conclusions

- Using a method that minimises bias from time-varying confounders, informative censoring, and immortal time bias, 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 late or no remdesivir
- This study underscores the importance of timely administration of remdesivir to improve clinical outcomes in this high-risk population

Plain Language Summary

- People with immunocompromising conditions are more vulnerable to severe COVID-19
- This study examined more than 97,000 people with immunocompromising conditions who were hospitalised with COVID-19 and found that those who started remdesivir treatment within 2 days of admission had a lower risk of dying compared with those who started treatment later or not at all
- These findings highlight the importance of early remdesivir administration to improve survival outcomes in people who are at high risk for severe COVID-19 due to immunocompromising conditions

Introduction

- People with immunocompromising conditions are at increased risk for severe COVID-19[1,2]
- Remdesivir (RDV) is a nucleotide analogue prodrug approved for the treatment of COVID-19 in nonhospitalised and hospitalised adult and paediatric patients[3]
- People with immunocompromising conditions hospitalised with COVID-19 who initiate RDV within 2 days of hospitalisation have a lower risk of all-cause mortality compared with those who do not initiate RDV[4]
  - — However, the impact of different timings of RDV initiation on its effectiveness in this high-risk population remains unknown

Objective

- To compare the effectiveness of early initiation of RDV (Days 1-2 of hospitalisation) with late initiation (Days 3-7 of hospitalisation) or no initiation for the prevention of in-hospital mortality in people with immunocompromising conditions hospitalised with COVID-19

Methods

- Data for this retrospective, observational cohort study were obtained from the HealthVerity database, which includes medical and pharmacy claims and hospital chargemaster data for patients in the United States
- The analysis included patients aged ≥12 years who were hospitalised between May 2020 and December 2023 with a primary diagnosis of COVID-19, had activity in the database (ie, ≥1 medical claim or chargemaster record) ≥12 months prior to hospitalisation and on the index date (date of admission = Day 1) with no single gap in enrolment of >30 days, and were diagnosed with an immunosuppressive condition prior to the index date
- Patients were categorised into treatment regimens based on the timing of RDV initiation after admission to the hospital:
  - — Days 1 to 2 (“early RDV”)
  - — Days 3 to 7 (“late RDV”)
  - — No evidence of RDV initiation during the follow-up period of up to 28 days (“no RDV”)
  - — A small number of patients were administered RDV after Day 7; these patients were excluded from this analysis
- A clone-censor-weight approach was used to estimate the adjusted cumulative incidence of 14- and 28-day in-hospital mortality for each treatment regimen, controlling for baseline and time-varying confounders, including oxygen support and glucocorticoids (**Table 1**)
  - — For each treatment regimen, the entire cohort was cloned or copied and, within each clone or copy, patients were followed until discharge, death, an outcome of interest, or until their actual RDV use (including non-use) deviated from their assigned regimen, whichever came first
  - — Inverse probabilities of censoring weights were used to address potentially informative censoring, accounting for factors affecting RDV treatment, timing, and clinical outcomes
  - — An inverse probability–weighted estimator was employed to estimate the cumulative risk of in-hospital mortality within each cohort copy
  - — 95% CIs were generated using a nonparametric cluster bootstrapping procedure with ≥300 replications
- Patient demographic and clinical characteristics and patterns of care were assessed using descriptive statistics

Results

- The study included a total of 97,587 patients, with 39,315 receiving early RDV, 4432 receiving late RDV, and 53,471 not receiving RDV (**Table 1**)
- Most patients were aged ≥65 years (67%) and 51% were female
- The most prevalent immunosuppressive conditions included solid malignancies (61%) and rheumatological/inflammatory conditions (44%)

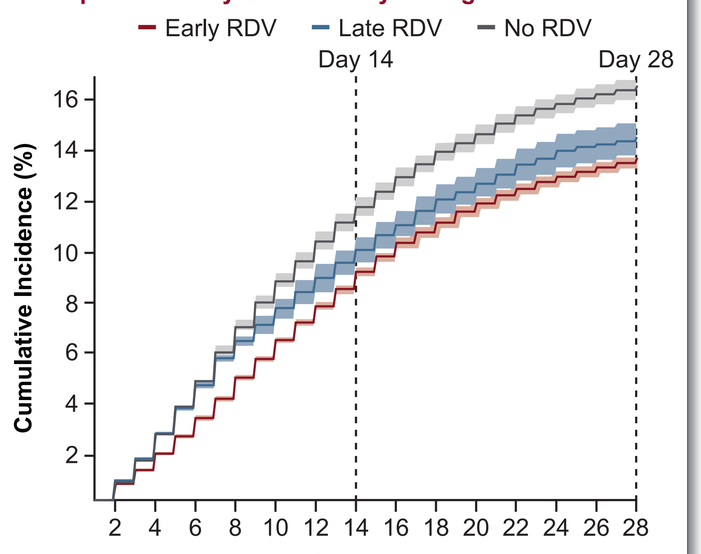
Table 1. Demographic and Clinical Characteristics by Timing of RDV Initiation

Characteristic, n (%)	Early RDV[a] (n = 39,315)	Late RDV[b] (n = 4432)	No RDV (n = 53,471)	Overall[c] (N = 97,587)
Age, years, median (Q1, Q3)[d]	71 (61, 79)	73 (64, 81)	72 (61, 81)	71 (61, 80)
Calendar time				
Pre-Delta	16,246 (41)	2576 (58)	24,288 (45)	43,363 (44)
Delta	7701 (20)	600 (14)	6573 (12)	14,913 (15)
Omicron	15,368 (39)	1256 (28)	22,610 (42)	39,311 (40)
Sex				
Female	19,754 (50)	2152 (49)	27,737 (52)	49,822 (51)
Male	19,561 (50)	2280 (51)	25,734 (48)	47,765 (49)
Baseline oxygen support[e]				
No oxygen	27,403 (70)	3348 (76)	40,517 (76)	71,552 (73)
Low-flow oxygen	6323 (16)	658 (15)	6507 (12)	13,523 (14)
High-flow oxygen	3973 (10)	289 (7)	4438 (8)	8729 (9)
Mechanical ventilation or ECMO	1616 (4)	137 (3)	2009 (4)	3783 (4)
Geographic region[d]				
Midwest	3125 (8)	368 (8)	7039 (13)	10,561 (11)
Northeast	8004 (20)	771 (17)	8361 (16)	17,200 (18)
South	19,389 (49)	2403 (54)	27,444 (51)	49,436 (51)
West	8797 (22)	890 (20)	10,627 (20)	20,390 (21)
Comorbidity				
Blood disorder	165 (<1)	11 (<1)	241 (<1)	418 (<1)
Cancer (excluding nonmelanoma skin cancer)	13,488 (34)	1607 (36)	18,201 (34)	33,429 (34)
Chronic kidney disease	9595 (24)	1333 (30)	17,390 (33)	28,451 (29)
Chronic liver disease	3699 (9)	392 (9)	5314 (10)	9441 (10)
Chronic lung disease	18,597 (47)	1998 (45)	24,999 (47)	45,776 (47)
Diabetes (type 1 or 2)	16,232 (41)	1970 (44)	23,939 (45)	42,324 (43)
Cardiovascular disease	30,426 (77)	3526 (80)	43,205 (81)	77,472 (79)
Alzheimer’s disease/dementia	3093 (8)	396 (9)	6046 (11)	9598 (10)
Obesity	13,076 (33)	1313 (30)	16,818 (31)	31,327 (32)
Stroke or cerebrovascular disease	6951 (18)	890 (20)	11,687 (22)	19,621 (20)
Substance use disorder	6241 (16)	688 (16)	9835 (18)	16,824 (17)
Tobacco use	13,319 (34)	1551 (35)	19,156 (36)	34,159 (35)
Disability[d,f]	17,730 (45)	2068 (47)	26,935 (50)	46,937 (48)
Mood disorder or schizophrenia	9431 (24)	1044 (24)	14,316 (27)	24,904 (26)
Tuberculosis infection	43 (<1)	6 (<1)	85 (<1)	134 (<1)
Immunosuppressive condition				
HIV/AIDS	610 (2)	75 (2)	852 (2)	1538 (2)
Haematological malignancy	2113 (5)	288 (6)	2506 (5)	4936 (5)
Other immune condition	3930 (10)	471 (11)	5987 (11)	10,424 (11)
Solid malignancy	24,506 (62)	2745 (62)	32,261 (60)	59,720 (61)
Organ transplant	2213 (6)	294 (7)	2919 (5)	5455 (6)
Rheumatological/inflammatory condition	16,704 (42)	1921 (43)	24,370 (46)	43,175 (44)
Baseline medication				
Oral antivirals (eg, nirmatrelvir/ritonavir, molnupiravir)	2 (<1)	1 (<1)	33 (<1)	36 (<1)
Glucocorticoids (eg, dexamethasone)[e]	24,319 (62)	1796 (41)	18,068 (34)	44,297 (45)
Biological immunomodulators (eg, tocilizumab, baricitinib, sarilumab, tofacitinib)	1486 (4)	36 (1)	627 (1)	2155 (2)
Antibody-based therapies (eg, convalescent plasma, monoclonal antibodies)	2183 (6)	68 (2)	658 (1)	2916 (3)
Other therapies (eg, anticoagulants, vasopressors)	12,601 (32)	1389 (31)	19,702 (37)	33,813 (35)

[a]“Early RDV” was defined as initiation of RDV on Days 1 to 2 of hospital admission.
[b]“Late RDV” was defined as initiation of RDV on Days 3 to 7 of hospital admission.
[c]Patients who received RDV on Days 8 to 28 (n = 369) were not included in this subgroup analysis.
[d]Baseline covariates included in the clone-censor-weight approach were age, geographic region, and disability.
[e]Time-varying covariates included in the clone-censor-weight approach were oxygen support, use of glucocorticoids, and interaction of oxygen support and glucocorticoids.
[f]Disability included attention-deficit/hyperactivity disorder, congenital malformation, learning disability, limitations with self-care or dependence for activities of daily living, spinal cord injury, and intellectual and developmental disabilities.
ECMO, extracorporeal membrane oxygenation; Q, quarter; RDV, remdesivir.

- The adjusted cumulative incidence of mortality at Day 14 and Day 28 was lowest in the early RDV group, followed by the late RDV group, and highest in the no RDV group (**Figure 1**)

Figure 1. Estimated Adjusted Cumulative Incidence of In-Hospital Mortality Over Time by Timing of RDV Initiation



Cumulative Incidence	Early RDV[a] (n = 39,315)	Late RDV[b] (n = 4432)	No RDV (n = 53,471)
Day 14, % (95% CI)	9.2 (8.9, 9.5)	10.1 (9.6, 10.6)	11.8 (11.5, 12.2)
Day 28, % (95% CI)	13.7 (13.3, 14.0)	14.5 (13.9, 15.3)	16.6 (16.2, 16.9)

[a]“Early RDV” was defined as initiation of RDV on Days 1 to 2 of hospital admission.
[b]“Late RDV” was defined as initiation of RDV on Days 3 to 7 of hospital admission.
RDV, remdesivir.

- The risk difference was greater for early versus no RDV than for early versus late RDV at both Days 14 and 28 (**Table 2**)
- Risk ratios of in-hospital mortality were stronger for early versus no RDV than for early versus late RDV at both Days 14 and 28

Table 2. Risk Differences and Risk Ratios of In-Hospital Mortality for the Late RDV Group and the No RDV Group Compared With the Early RDV Group

	Risk Difference, % (95% CI)		Risk Ratio (95% CI)	
	Day 14	Day 28	Day 14	Day 28
Early RDV[a] vs late RDV[b]	–0.89 (–1.49, –0.29)	–0.88 (–1.66, –0.10)	0.91 (0.86, 0.97)	0.94 (0.89, 0.99)
Early RDV[a] vs no RDV	–2.61 (–3.06, –2.17)	–2.90 (–3.39, –2.41)	0.78 (0.75, 0.81)	0.82 (0.80, 0.85)

[a]“Early RDV” was defined as initiation of RDV on Days 1 to 2 of hospital admission.
[b]“Late RDV” was defined as initiation of RDV on Days 3 to 7 of hospital admission.
RDV, remdesivir.

Limitations

- The large, diverse data source supports strong external validity, but the requirement for continuous health plan enrolment for 365 days and existing diagnoses for immunosuppressive conditions may limit generalisability to those with medical and pharmacy insurance in the United States
- The clone-censor-weight approach addresses known confounders but relies on correct specification, so unmeasured and poorly measured variables such as incomplete information on COVID-19 vaccine receipt, smoking, and obesity may cause residual confounding

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