

Immunocompromised patients hospitalized for COVID-19 in the United States: evolving patient characteristics and clinical outcomes across emerging variants

Essy Mozaffari¹, Aastha Chandak², Andre C. Kalil³, Chidinma Chima-Melton⁴, Mel Chiang⁵, EunYoung Lee¹, Rikisha Gupta¹, ChenYu Wang⁵, Robert L. Gottlieb⁶

¹Gilead Sciences, Foster City, CA; ²Certara, New York, NY; ³University of Nebraska Medical Center, Omaha, NE; ⁴UCLA Health, Torrance, CA; ⁵Gilead Sciences, Taipei, Taiwan; ⁶Baylor Scott & White Health and Baylor Scott & White Research Institute, Dallas, TX

Introduction

- Clinical management of COVID-19 has evolved rapidly over the course of the pandemic; patient outcomes have improved with advances in care and therapeutics¹⁻²
- Remdesivir (RDV) reduced time to recovery and improved clinical outcomes for COVID-19 patients in several randomized controlled trials^{3,4}; with additional evidence on effectiveness through real-world studies⁵⁻⁷
- However, there is limited information on effectiveness of COVID-19 therapies in immunocompromised patients, who are at higher risk of hospitalizations, complications, and mortality due to COVID-19⁸⁻¹¹

Objective

- The objective of this study, focused on routine clinical practice, was to:
 - Describe the patient characteristics and clinical outcomes and
 - Compare hospital all-cause mortality for RDV use vs. no RDV use among immunocompromised COVID-19 patients across dominant variants of concern (VOC) periods: pre-Delta, Delta and Omicron

Methods

Study design

- Data source:** PINC AI Healthcare Database (formerly Premier Healthcare Database)
- U.S. hospital-based, service-level, all-payer (Commercial, Medicare, Medicaid, others) database
- Covers ~25% of all US hospitalizations from 48 states
- Includes information on billed services and activities for each day of the hospitalization

Descriptive analysis:

- Retrospective cohort study
- Study period:** May 2020-April 2022
- Inclusion criteria:** Adult patients hospitalized with a primary diagnosis of COVID-19 (ICD-10: U07.1) and a secondary diagnosis of an immunocompromised condition during the study period
- VOC periods:** Pre-Delta (May 2020-Apr 2021), Delta (May-Nov 2021), Omicron (Dec 2021-Apr 2022) defined based on the dominant variants during these time periods

Comparative effectiveness analysis:

- Comparative effectiveness retrospective cohort study (Table 1)
- Study period:** December 2020-April 2022

Table 1. Study design

Inclusion criteria	✓	Age ≥18 years old
Primary discharge diagnosis of COVID-19 (ICD-10-CM: U07.1) flagged for being "present-on-admission"	✓	✓
Diagnosed with an immunocompromised condition: cancer, solid organ and hematopoietic stem cell transplant, hematologic malignancies, primary immunodeficiencies, asplenia, bone marrow failure/aplastic anemia, severe combined immunodeficiencies or HIV	✓	✓
Exclusion criteria	✗	
Pregnant	✗	
Had incomplete/erroneous data fields	✗	
Transferred from another hospital or hospice	✗	
Transferred to another hospital	✗	
Admitted for elective procedures	✗	
Discharged or died during the baseline period (first two days of hospitalization)	✗	

- All baseline variables (supplemental oxygenation, concomitant medications) were examined within the first two days of hospitalization
- Primary Endpoints:** 14-day and 28-day all-cause hospital mortality (defined as a discharge status of "expired" or "hospice")
- VOC periods:** Pre-Delta (Dec 2020-Apr 2021), Delta (May-Nov 2021), Omicron (Dec 2021-Apr 2022) defined based on the dominant variants during these time periods

Analysis

- Descriptive analyses for patient characteristics, supplemental oxygen requirement and clinical outcomes assessed for overall cohort and over time/by VOC periods
- For comparative analysis, stratified analyses were conducted for the VOC periods and levels of baseline supplemental oxygen, sample size permitting
- Propensity scores (PS) were estimated using separate logistic regression models for the different baseline supplemental oxygenation: no supplementary oxygen charges (NSOc), low-flow oxygen (LFO), high-flow/non-invasive ventilation (HFO/NIV), and invasive mechanical ventilation/extracorporeal membrane oxygenation (IMV/ECMO) with RDV use within first two days of admission as the outcome and key baseline and clinical factors as covariates
- Covariates used in PS calculation: Baseline demographics (age, gender, race, ethnicity, primary payer), comorbidities (obesity, COPD, diabetes mellitus, renal disease, cardiovascular disease, cancer), hospital characteristics (bed size, urban/rural, teaching, region of the hospital), admission month, admission from skilled nursing facility (SNF), intensive care unit (ICU)/General ward at baseline, severity level identified through level of oxygenation used at baseline, other indicators of severity based on admit diagnoses (respiratory failure, hypoxemia, sepsis, pneumonia), concomitant medications at baseline (corticosteroids, convalescent plasma, anticoagulants, tocilizumab, baricitinib)
- PS-Matching was conducted as specified in Figure 1
- Cox Proportional Hazards Model (adjusting for hospital-level random effects and key clinical covariates) was used to examine time to 14- and 28-day mortality
- Patients who did not have the outcome of interest or were discharged alive were censored at 14 and 28 days in the analyses

Figure 1. PS matching approach

Matching conducted separately in the 12 cohorts (3 VOC periods x 4 baseline supplemental oxygenation) using:

1:1 Preferential Same-Hospital Matching with replacement

1 PS-matching (caliper=0.2x s.d. of the logit of the PS) for patients with same age group, same supplemental oxygenation, same two/three-month blocks of admission month **within the same hospital**

| If unmatched in step 1

2 PS-matching (caliper=0.2x s.d. of the logit of the PS) for patients with same age group, same supplemental oxygenation, same two/three-month blocks of admission month **within another RDV-using hospital of same bed size**

Matched patients were not discharged within 3 days of RDV initiation to emulate ACTT-1 exclusion (which excludes anticipated discharges/transfers within 72 hrs)

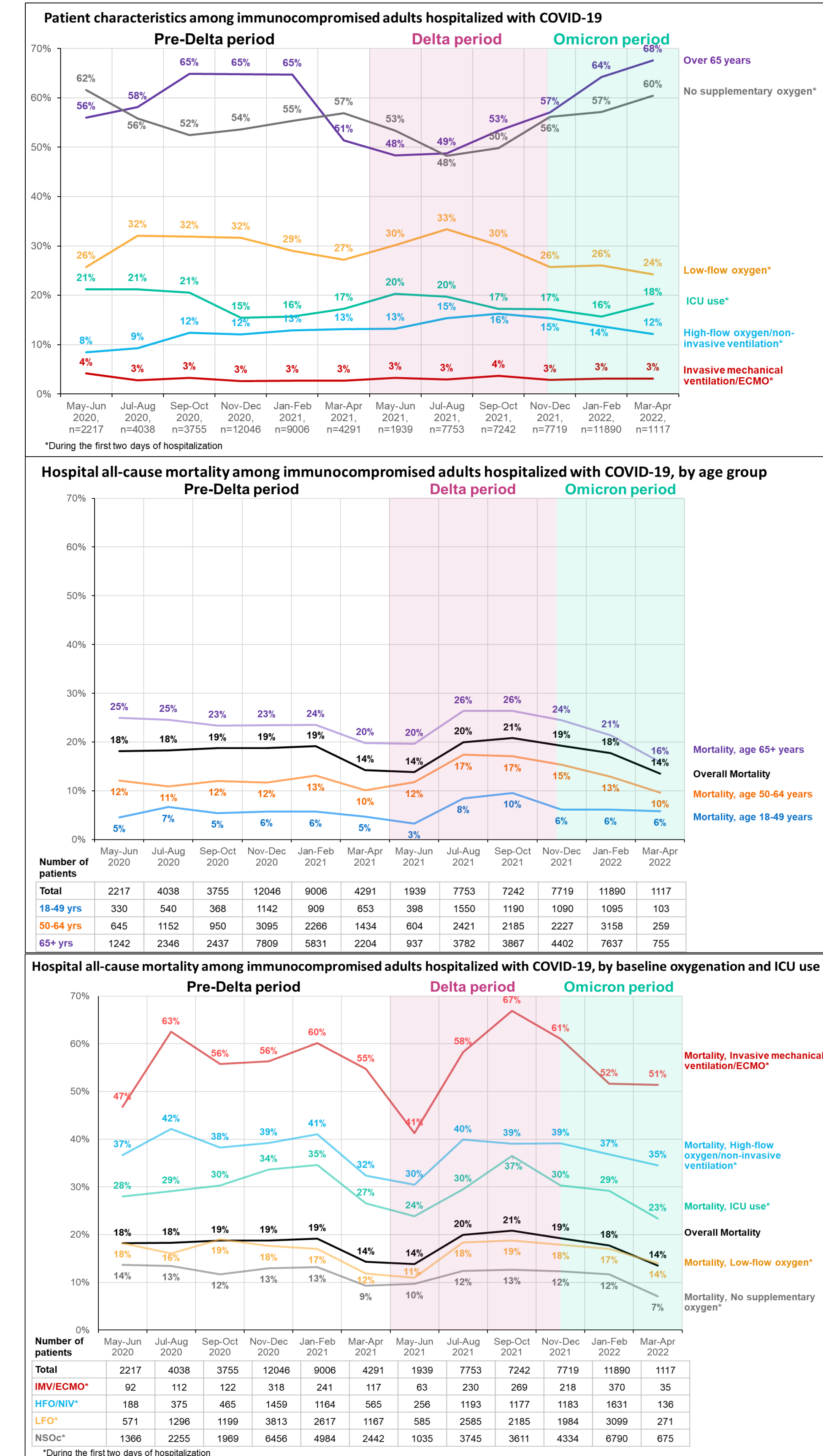
Matching with replacement: allowed for majority of the patients treated with RDV to be matched and included in the analysis despite a restricted matching criteria and higher % of RDV use in the study cohort; hence conclusions made are applicable to majority of the RDV patients

Results

Descriptive analysis

- 73,013 immunocompromised patients were hospitalized with a primary diagnosis of COVID-19 in 853 hospitals
- Median age 68 years (interquartile range [IQR]:58–77), 49% female
- Immunocompromised patients during Delta period (compared to pre-Delta):
 - Younger (median age 65 vs. 69; p<.0001)
 - Higher oxygen requirements upon admission: 15.5% vs. 11.9% on HFO/NIV and 3.2% vs. 2.8% on IMV/ECMO (p<.0001)
 - Higher mortality rates (19.6% vs. 18.2%; p<.0001)
- Patients during Omicron period (compared to Delta):
 - Older (median age 69 vs. 65; p<.0001)
 - Lower oxygen requirements upon admission: 14.1% vs. 15.5% on HFO/NIV and 25.8% vs. 30.8% on LFO (p<.0001)
 - Lower mortality rates (17.8% vs. 19.6%; p<.0001)
- From May 2020 to April 2022, overall mortality decreased from 18% to 14% with a peak at 21% in September and October 2021 (Delta period) (Figure 2)
- Mortality rates were the highest for older patients and for those with higher supplemental oxygen requirements (Figure 2)

Figure 2: Patient characteristics and hospital all-cause mortality among immunocompromised adults hospitalized with COVID-19



Comparative effectiveness analysis

- Comparative effectiveness analysis conducted in a subgroup of patients hospitalized between December 2020 to Apr 2022
- 51,123 immunocompromised adults hospitalized in 819 hospitals with a primary discharge diagnosis of COVID-19
- After applying inclusion/exclusion criteria, 32,835 patients from 755 hospitals included in the analysis:
 - 21,622 patients were treated with RDV in the first two days of hospitalization and
 - 11,213 patients were not treated with RDV
- After 1:1 matching with replacement (Figure 1):
 - 14,169 RDV patients were matched to 5,341 unique non-RDV patients (equivalent to 14,169 non-RDV patients based on matching with replacement)
- Post-matching balance was achieved across groups with different baseline supplemental oxygen and VOC periods with all covariates with a standardized difference absolute value of <.15
- In the matched cohort:
 - 59% were 65 years or older, 40.5% with no supplementary oxygen charges, 39% received LFO, 19% received HFO/NIV and 1.5% IMV/ECMO at baseline
 - 69% with primary immunodeficiencies, 27% severe combined immunodeficiencies, 22% cancer, 17% hematologic malignancies, 17% bone marrow failure/aplastic anemia, 8% solid organ or hematopoietic stem cell transplant, 4% with toxic effects of antineoplastics, 3% asplenia, and 1% HIV

Unadjusted analysis (PS-matched cohort)

- During Dec 2020-Apr 2022, **unadjusted mortality rate was significantly lower** for RDV patients compared to patients that did not receive RDV (log-rank test: p<.0001) (Figure 3)
- Lower mortality rate observed across all VOC periods** (log-rank test: p<.05) (Figure 3)

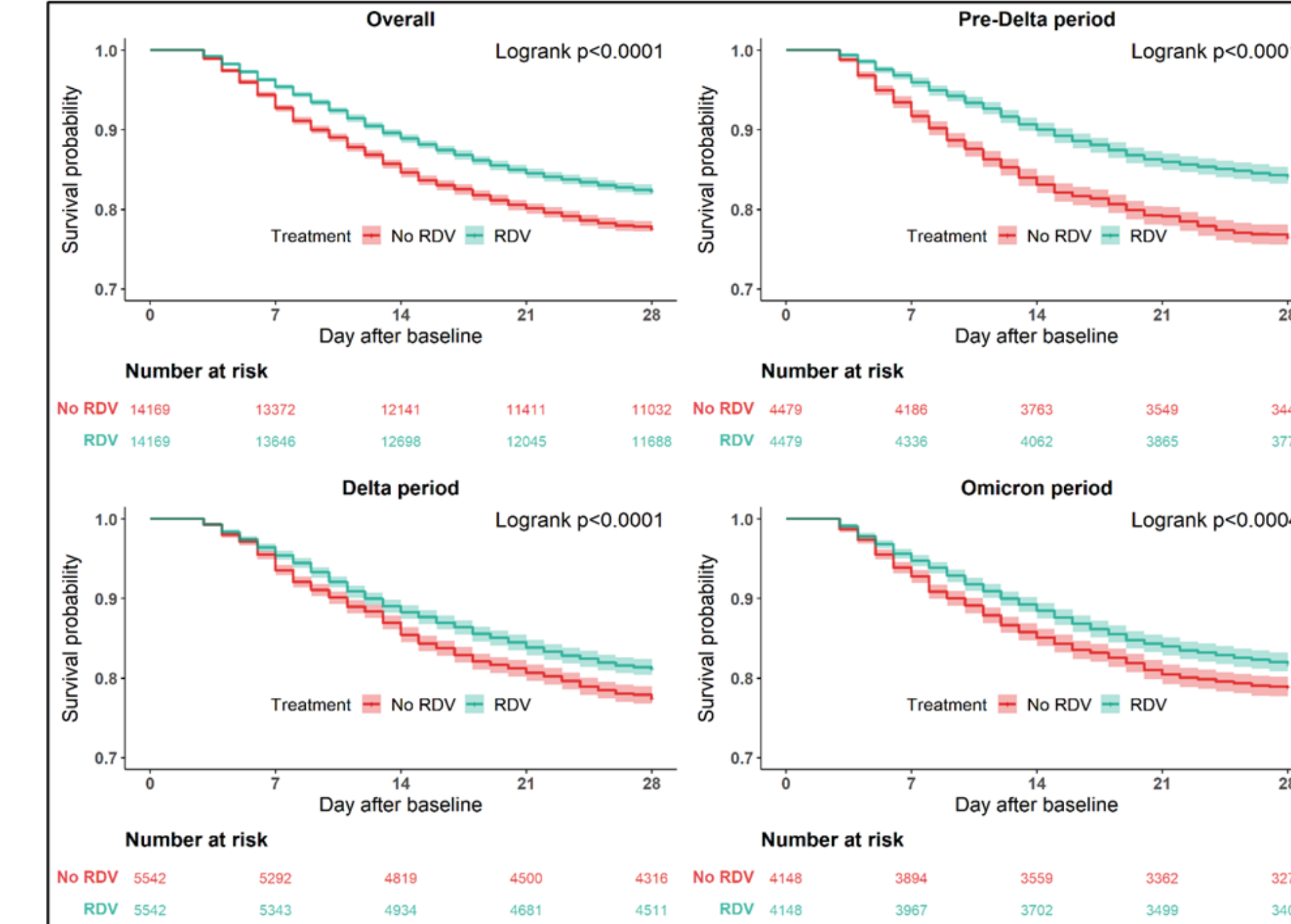
	14-day mortality		28-day mortality	
	RDV	Non-RDV	RDV	Non-RDV
Overall	11.9%	17.1%	18.8%	25.2%
Pre-Delta	10.5%	17.3%	16.7%	24.4%
Delta	13.2%	17.0%	21.4%	26.7%
Omicron	11.9%	17.0%	18.2%	24.6%

- This lower mortality rate was also observed for patients on NSOc and across all baseline supplemental oxygen requirements:

	14-day mortality		28-day mortality	
	RDV	Non-RDV	RDV	Non-RDV
NSOc	7.4%	10.4%	11.5%	14.5%
LFO	9.0%	15.3%	14.9%	22.2%
HFO/NIV	21.7%	24.3%	34.4%	37.3%
IMV/ECMO	30.4%	37.3%	47.0%	51.2%

NSOc: No supplementary oxygen charges; LFO: Low-Flow Oxygen; HFO/NIV: High-Flow Oxygen/Non-invasive ventilation; IMV/ECMO: Invasive Mechanical Ventilation/Extracorporeal Membrane Oxygenation

Figure 3. Kaplan-Meier curves



Note: Number of non-RDV patients are not of unique patients but weighted numbers since matching with replacement approach was used.

RDV, remdesivir

Adjusted analysis (PS-matched cohort)

- After adjusting for baseline and clinical covariates, 14-day and 28-day results showed that RDV had significantly lower mortality risk compared to non-RDV across all VOC periods (Figure 4)
- RDV had significantly lower mortality risk compared to non-RDV in subgroups of patients on NSOc and those on LFO, as sufficient sample size was available
 - Sample sizes in the HFO/NIV (n=5,432) and IMV/ECMO (n=434) subgroups were not sufficient to warrant statistical analyses, though directionally consistent results favoring RDV were observed
- In previously presented analysis, lower mortality risk associated with RDV vs. non-RDV was also consistently observed in an analysis of the overall cohort of patients with higher supplemental oxygen requirements of high-flow oxygen/non-invasive ventilation and invasive mechanical ventilation/ECMO as well as those with no supplementary oxygen charges¹²

Figure 4. 14- and 28- day mortality in immunocompromised patients across the COVID-19 variant periods (adjusted Cox Proportional Hazards model)

	N	aHR [95% CI]	P value
14-day mortality			
Overall	28,338	0.70 [0.62 - 0.78]	<.0001
Pre-Delta	8,958	0.59 [0.48 - 0.71]	0.0100
Delta	11,084	0.77 [0.65 - 0.92]	0.0035
Omicron	8,296	0.75 [0.63 - 0.90]	0.0020
28-day mortality			
Overall	28,338	0.75 [0.68 - 0.83]	<.0001
Pre-Delta	8,958	0.65 [0.56 - 0.76]	<.0001
Delta	11,084	0.79 [0.68 - 0.91]	0.0013
Omicron	8,296	0.84 [0.72 - 0.97]	0.0203

Favors RDV ← | → Favors Non-RDV

Note: Estimates adjusted for age, admission month, admission venue (ICU vs. general ward), and baseline treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab)
aHR: Adjusted Hazard Ratio; 95% CI: 95% Confidence Interval; RDV: remdesivir; ICU: intensive care unit

Conclusions

- With the changing dominant variants, patient characteristics and outcomes have evolved significantly for immunocompromised patients hospitalized for COVID-19
- Mortality rates varied by age group and supplemental oxygen requirements upon hospital admission across all variant time periods
- Despite the changing patient characteristics and outcomes, RDV initiation within the first two days of hospital admission remained associated with statistically significant reductions in mortality at 14- and 28 days in immunocompromised patients across all variants of concern periods studied through April 2022.
- Thus, RDV use has a clear and consistent benefit on important clinical outcomes in the immunocompromised cohort regardless of supplemental oxygen requirements across all VOC periods

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Disclosures:
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