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Short vs. Long Symptom Duration Prior to Remdesivir for Hospitalized Patients with COVID-19

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Background

- Remdesivir (RDV) has been a mainstay of COVID-19 therapy for hospitalized patients and non-hospitalized patients at high risk for progression.
- Impact of RDV timing in relationship to symptom-onset in hospitalized patients remains unclear, though early treatment is theorized to improve outcomes.
- Prior RCTs suggested an association between earlier initiation of RDV and shorter time to recovery.
- Though, varied definitions of "early" RDV treatment and inconsistent use of corticosteroids in early randomized and non-randomized trials limit findings of RDV benefits in a contemporary population.
- Furthermore, by measuring the timing of RDV initiation from symptom-onset instead of diagnosis-onset, we anticipate additional clarity on optimal timing of therapy as many patients present for testing in a delayed manner.

Purpose

- This study aimed to assess the clinical course and outcome of hospitalized adults with COVID-19 treated with RDV, stratified based on time to RDV administration from onset of COVID-19 symptoms.

Endpoints

- The primary outcome was **time to clinical recovery within 28 days**.
- Secondary outcomes were proportion of patients recovered and proportion discharged from the hospital within 10, 14, and 28 days; and mortality within 28 days.

Methods

- This was a **single-center retrospective study** of adult patients hospitalized for COVID-19 treated with RDV between July 2020 and July 2021.
- Patients were **excluded** if they:
  - transitioned to any RDV-related clinical trial,
  - received RDV at an outside facility with inaccessible records,
  - Were hospitalized primarily for reasons other than COVID-19,
  - had nosocomial onset of COVID-19, or
  - did not have information regarding onset of COVID-19 symptoms readily documented.
- Patients were reviewed by 2 independent investigators to determine disease course and outcomes.
- Patients were stratified based on time from symptom-onset to RDV initiation:
  - **Short-Symptom Duration (SDD): ≤7 days**
  - **Long-Symptom Duration (LSD): >7 days**
- The cutoff of 7 days was selected based on internal data and previously published data from our institution demonstrating this threshold as the median time to recovery.
- Disease severity and outcomes were classified on the first day of hospitalization, day of RDV initiation, and up to 28 days after RDV initiation according to the eight-category ordinal scale described in the ACTT-1 trial.
- The study protocol was approved by the Mass General Brigham Institutional Review Board (protocol 2021P000870) with a waiver of consent granted for review of medical records.
- Time to recovery was analyzed using the Kaplan-Meier method and the significance was tested by log rank tests. Cox's proportional hazards models were used to estimate hazard ratios (HR). Fisher's exact test was used to compare recovery rates between groups.
- Statistical analysis was performed using SAS version 9.4 (SAS, NC, USA) and the R programming language version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

- Of the 337 patients who met the inclusion criteria:
  - **178 (53%)** patients received RDV within **7 days** of symptom-onset
  - **159 (47%)** patients had symptoms for **>7 days** before RDV initiation
- Median symptom duration prior to RDV initiation across the entire cohort was 7 days (IQR 5-10).
- Most patients (89%) in both cohorts were partially- or unvaccinated at hospital admission.
- Finally, **91%** of patients in both **groups received dexamethasone in combination with RDV**.
- A 5-day course of RDV was used in the majority of patients in both groups, per institutional protocol.
- RDV was generally safe and well-tolerated with low rate of treatment-related discontinuation:
  - 14 (4%) patients stopped RDV earlier than planned due to adverse effects.

Results – continued

Figure 1: Time to Recovery After RDV Initiation

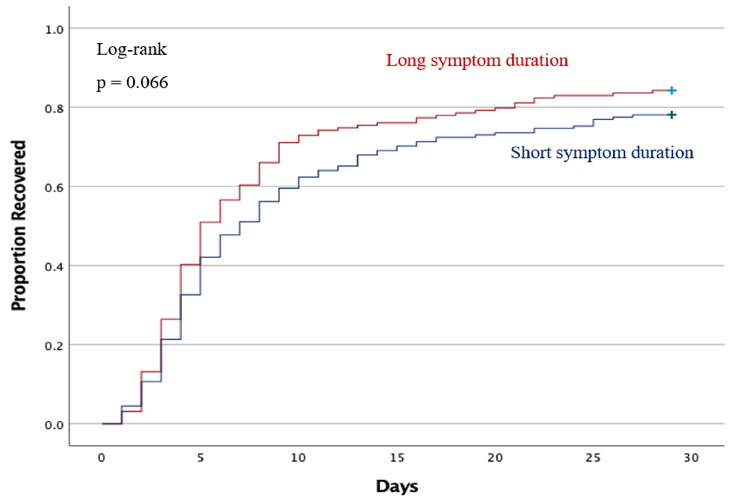
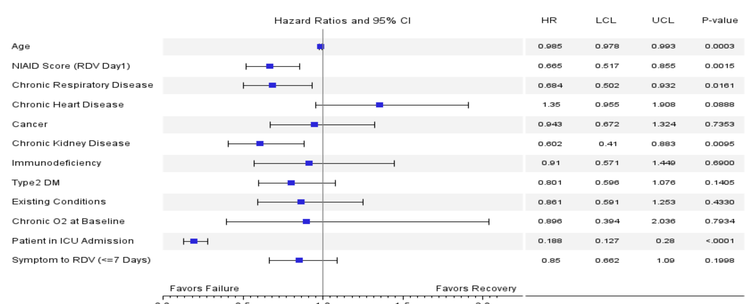


Table 1: Primary and Secondary Outcomes

	All patients (N=337)	Days from symptom-onset to RDV		
		≤7 days N (178)	>7 days N (159)	p-value
Primary Outcome				
Median Time to Recovery, Days (95% CI)				
All Patients	6 (5-7)	7 (5-9)	5 (4-6)	0.066
NIAID score 4	3 (2-4)	3 (2-4)	3 (2-4)	0.953
NIAID score 5	5 (4-6)	6 (4-8)	5 (4-6)	0.019
No ICU admission	4 (4-4)	5 (4-6)	4 (3-5)	0.015
Secondary Outcomes				
Recovery – n (%)				
Recovery by day 10	227 (67)	111 (62)	116 (73)	0.048
Recovery by day 14	244 (72)	123 (69)	121 (76)	0.175
Recovery by day 28	273 (81)	139 (78)	134 (84)	0.166
Hospital Discharge – n (%)				
Discharge by day 10	232 (68)	113 (63)	119 (75)	0.026
Discharge by day 14	248 (74)	125 (70)	123 (77)	0.173
Discharge by day 28	277 (82)	141 (79)	136 (86)	0.154
Mortality – n (%)				
Mortality by day 28	34 (10)	17 (10)	17 (11)	0.857

Figure-2: Time to Recovery Cox Regression



Discussion

- Most patients (**91%**) in this study were treated with a combination of RDV and **dexamethasone** as the standard of care for those requiring various levels of oxygen supplementation.
- Majority of patients presented between **January – July 2021**, prior to the Omicron wave.
- Patients presenting to the hospital earlier in their COVID-19 disease course were older and had more co-morbidities, both known to lengthen recovery time.
- Prior studies showed conflicting results with regards to timing of RDV initiation at inclusion in relationship to symptom- or positive test-onset, and are largely limited by:
  - varied definitions of "early" treatment,
  - inconsistent, or low, use of corticosteroids for those requiring oxygen supplementation, and
  - largely completed early in the pandemic timeline (i.e., prior to Delta and Omicron variants).

Limitations

- Retrospective nature and reliance on patient/family reporting of time of symptom-onset limit the findings, though this was confirmed by 2 independent study investigators.
- Degree and time course of COVID-19 inflammatory response were not assessed throughout the study period. At baseline both groups had similar inflammatory markers, as described by white blood cell count, absolute lymphocyte count, C-reactive protein, and D-Dimer.
- Impact of vaccination and prior COVID-19 infection were not fully evaluated in this study and may also have an impact on recovery time and benefit of early antiviral treatment.
- Study timeline largely preceded the Omicron variant wave in the U.S.A.

Conclusion

- **Long-symptom duration** (i.e., >7 days) prior to initiation of RDV therapy **was not associated with longer recovery time** or longer hospitalization after adjusting for confounders in the current study.

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Disclosures

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Abbreviations:
RDV: remdesivir
COVID-19: coronavirus disease 2019
RCT: randomized controlled trial
ACTT-1: adaptive Covid-19 treatment trial
IQR: interquartile range
HR: hazard ratio
NIAID: National Institute of Allergy and Infectious Diseases