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Remdesivir therapy for severe pediatric COVID-19 in Singapore: A single-center retrospective observational cohort study

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Abstract

Background and Aims: There is a paucity of information on remdesivir (RDV) use in severe pediatric coronavirus disease 2019 (COVID-19). We aimed to explore the effectiveness of RDV as the cumulative proportion of pediatric COVID-19 patients deescalated from Day 5 of high dependency or intensive care unit (HD/ICU).

Methods: All children ≤18 years admitted to Singapore's largest pediatric hospital from January 1, 2020 to March 18, 2022 were reviewed retrospectively. Patients were included if they were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on reverse transcriptase polymerase chain reaction, required oxygen, and HD/ICU care. The characteristics and outcomes of those who received RDV or not (no-RDV) were compared.

Results: We reviewed 15 children with a median age of 2.5 years (interquartile range [IQR]: 0.8–11.0), of which 7 (46.7%) received RDV. There was no difference in cumulative proportion of children deescalated from Day 5 of HD/ICU care in the RDV versus the no-RDV group (5/7, 70% vs. 7/8, 87.5%, $p = 0.57$). The RDV versus no-RDV group had higher disease severity, that is, WHO Ordinal Scale scores (median 6, IQR: 5–7 vs. 5, IQR: 4–5, $p = 0.03$), higher procalcitonin levels (ug/L) (median 4.31, IQR: 0.8–24.2 vs. 0.12, IQR: 0.09–0.26, $p = 0.02$), and longer HD/ICU care days (median 5, IQR: 4–9, vs. 1, IQR: 1–4, $p = 0.01$). There was no significant difference in hospitalization days. There were no adverse events directly attributable to RDV. None died from COVID-19 infection.

Conclusion: Our observational analysis was unable to detect any clear benefit of RDV in terms of reducing duration in HD/ICU. RDV was well-tolerated in children with severe COVID-19.

KEYWORDS

children, pediatric, remdesivir, SARS-CoV-2, severe COVID-19

Chia Yin Chong and Chee Fu Yung contributed equally to the study.

1 | BACKGROUND AND AIMS

Coronavirus disease 2019 (COVID-19) is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was declared a global pandemic by the World Health Organization (WHO) in March 2020.[1] Children represent approximately 10%–20% of COVID-19 cases, usually with milder clinical manifestations, but a small proportion can develop severe disease requiring oxygen support and intensive care management.[2,3]

Approaches to treating COVID-19 was initially experimental until remdesivir (RDV) showed promise in adult trials.[4,5] The CARAVAN study and other observational studies demonstrated that RDV was well-tolerated in hospitalized children.[6–10] Intravenous RDV was first approved by the Food and Drug Administration in October 2020 for COVID-19 treatment in adults and children ≥12 years of age and ≥40 kg[11] and later for Emergency Use Authorization in <12 years of age and ≥3.5 kg.[12] In Singapore, RDV was granted a conditional approval by our national regulatory authorities on June 10, 2020 to treat COVID-19 patients.[13]

There is a paucity of information especially from Asia on RDV use in severe pediatric COVID-19. Here, we described RDV use in our hospital and investigated its effectiveness in terms of the cumulative proportion of children with severe COVID-19 deescalated from high dependency or intensive care unit (HD/ICU) care by Day 5 in the RDV versus no-RDV group. RDV safety was evaluated by comparing the clinical and laboratory parameters between the two groups.

2 | METHODS

2.1 | Study design

This was a single-center retrospective observational cohort study. KK Women's and Children's Hospital (KKH) is an 830-bed tertiary-care hospital and the largest referral center for pediatric conditions in Singapore, with approximately 50,000 inpatient pediatric admissions yearly. KKH is the primary hospital for pediatric evaluation and isolation of COVID-19 in Singapore.

2.2 | Inclusion and exclusion criteria

We reviewed all children ≤18 years admitted to KKH from January 1, 2020 to March 18, 2022 with a positive test for SARS-CoV-2 on real-time reverse transcriptase polymerase chain reaction (rRT-PCR) from nasopharyngeal swabs and consulted for RDV treatment. Only those who met all three conditions were included: (1) severe COVID-19, (2) required oxygen supplementation, and (3) HD/ICU admission.

We defined severe COVID-19 as individuals with hypoxemia (oxygen saturation <95% at room air) requiring ICU/HD admission.[14] Severity of illness was classified using the WHO Ordinal Scale.[15] The 9 points of the scale are: 0—no clinical or virological evidence of infection; ambulatory—1: no activity limitation, 2: activity limitation; hospitalized—3: no oxygen therapy; 4: oxygen mask or nasal prongs; 5: noninvasive mechanical ventilation (NIMV) or high-flow nasal cannula; 6: intubation and invasive mechanical ventilation (IMV); 7: IMV + additional support such as vasopressors or extra-cardiac membranous oxygenation and 8: death.[15] Co-morbidity status included obesity (body mass index [BMI] > 30 kg/m^2 or ≥95th percentile), cardiac, respiratory, neurologic conditions, and obstructive sleep apnea.

De-escalation from HD/ICU care refers to patients assessed by the primary clinical team as clinically stable for general ward management where a higher level of respiratory, neurological and cardiovascular support is not required.

2.3 | Criteria for RDV use and safety monitoring

In KKH, all patients considered for RDV treatment are referred to our Pediatric Infectious Disease (ID) Services. Our service comprises of a team of pediatric ID physicians and pharmacists. Guidelines for RDV use in KKH were adapted from the National Institute of Health COVID-19 Treatment Guidelines, where RDV was considered for those hospitalized with severe COVID-19, or high-risk patients with mild to moderate COVID-19 early in disease course (<10 days).[16] Final decision for RDV treatment was made in consultation with the primary clinical team.

RDV was dosed and administered as follows[12]: ≥12 years, ≥40 kg: single 200-mg dose on Day 1, then daily 100-mg doses from Day 2. For those between 3.5 and 40 kg and age ≥28 days to 12 years, a single dose of 5 mg/kg on Day 1 was prescribed, followed by a daily dose of 2.5 mg/kg. Neonates <3.5 kg were given the same dose based on neonatal case series.[17] Baseline liver function tests (LFTs) and serum creatinine were done prior RDV use and monitored every 1–2 days. The RDV-group was placed on cardiac monitoring via electrocardiogram (ECG).

2.4 | Data collection

Patient demographics, characteristics, and relevant laboratory parameters, including SARS-CoV-2 PCR cycle threshold value, were collected using a standardized data collection form. All tests and treatments were performed at the discretion of the treating physicians. Duration of therapeutics were collected. Possible adverse events, if any, were reviewed.

2.5 | Outcomes

Our primary outcome to investigate RDV's effectiveness was the cumulative proportion of pediatric COVID-19 patients deescalated from HD/ICU care at Day 5. Secondary outcomes included days to temperature <38°C, HD/ICU care days, length of hospitalization, mortality, 30-day readmission and mortality. All information was obtained from individuals' electronic health records.

2.6 | Statistical analysis

For univariate analyses, categorical variables were compared using a χ^2 test or Fisher's exact test, where appropriate. Continuous variables were compared using a *t* test or Mann–Whitney *U* test, where appropriate. A *p* value was considered statistically significant if <0.05. All statistical analyses were performed using SPSS version 23 (IBM). Cumulative frequency curves of proportion of patients deescalated from HD/ICU care over time (days in HD/ICU care) in the RDV versus the no-RDV group were plotted.

This study was approved by the SingHealth Centralized Institutional Review Board (CIRB Ref: 2020/2094). All methods were carried out in accordance with relevant guidelines and regulations or Declaration of Helsinki. Written informed consent was waived in light of public health need and the COVID-19 pandemic.

3 | RESULTS

Fifteen children were included. Seven (46.7%) received RDV and eight (53.3%) did not receive RDV. There were nine (60.0%) boys. The median age was 2.5 (interquartile range [IQR]: 0.8–11.0) years. There were 10 (66.7%) children with co-morbidities, most commonly respiratory (asthma) ($n = 3$, 20%), neurology/neuromuscular ($n = 3$, 20%), obesity ($n = 3$, 30%), and obstructive sleep apnea ($n = 3$, 20%). Five (33.3%) had more than one co-morbidity. There were no significant differences in baseline characteristics in both groups in terms of age, BMI, ethnicity, proportion of boys, presence of co-morbidities and types. However, children in the RDV group trended toward older age (7.75 vs. 2.4 years old, $p = 0.46$).

3.1 | Clinical presentation, radiological findings and investigations

The majority (66.7%) presented with pulmonary COVID-19 (i.e., evidence of lower respiratory disease from examination and/or imaging) in both groups. This was followed by gastrointestinal manifestations (50%) in the no-RDV group (50%) versus neurological (42.9%) and cardiovascular manifestations (42.9%) in the RDV group. There was no significant difference in chest X-ray findings demonstrating significant findings such as consolidation between both groups (3, 37.5% vs. 3, 42.9% in the no-RDV vs. RDV group). Chest CT scan was not done in our cohort.

Children who were treated with RDV had more severe symptoms based on the WHO ordinal scale, versus those who did not (6, IQR: 5–7 vs. 5, IQR: 4–5; $p = 0.03$). More children in the RDV versus no-RDV group required invasive oxygen support (4, 57.1% vs. 0, $p = 0.03$) and fluid boluses (5, 71.4% vs. 0, $p = 0.007$). The RDV group also had higher procalcitonin values (ug/L) (4.31, IQR: 0.8–24.2 vs. 0.12, IQR: 0.09–0.26, $p = 0.02$). There was no significant difference in proportion of patients with raised LFTs and serum creatinine between both groups.

Characteristics of the seven children who received RDV are detailed in Table 2. RDV was initiated on median Day 1 (IQR: 1–2) of hospital admission and symptoms Day 3 (IQR: 2–6). The median

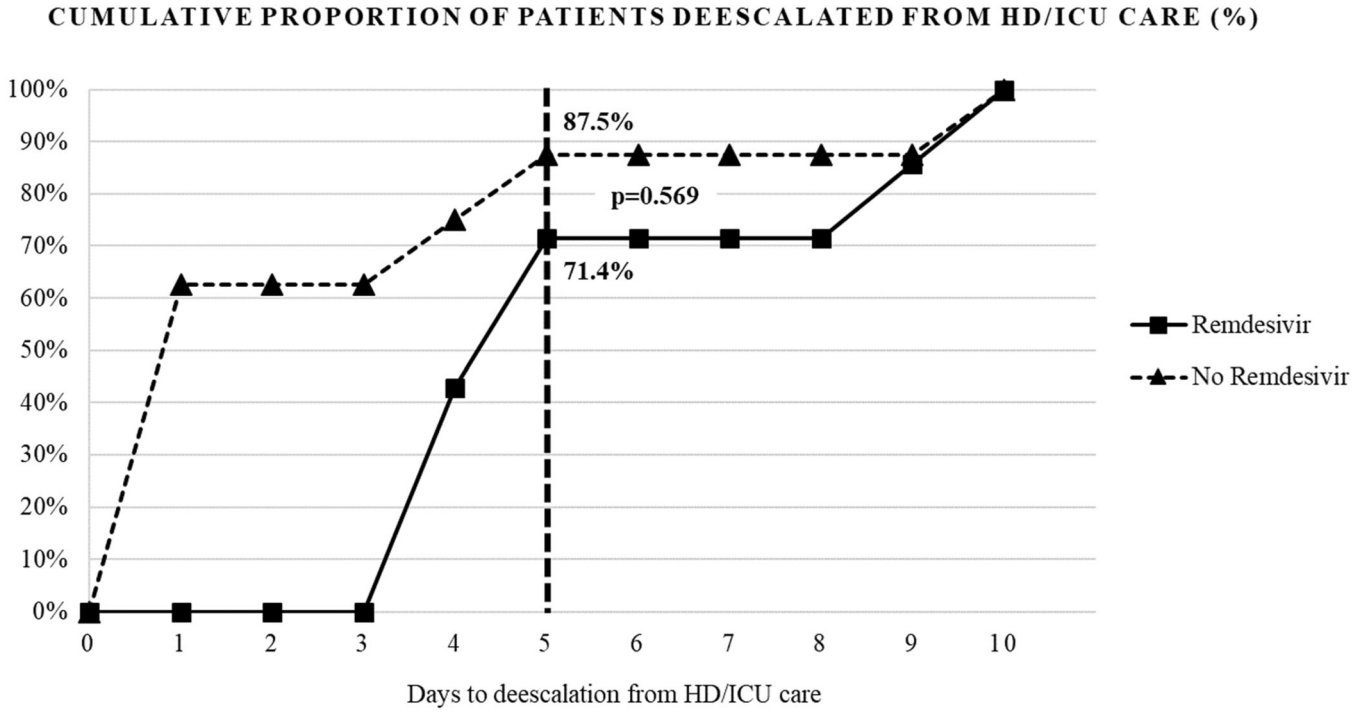

FIGURE 1 Comparison of percentage cumulative days to deescalation from high dependency/intensive care unit in children with or without remdesivir treatment.

TABLE 1 Comparison of clinical characteristics and outcomes of children who received and had not received remdesivir.

	All (*N* = 15)		No remdesivir (*N* = 8)		Received remdesivir (*N* = 7)		*p* Value
Demographics							
Male	9	(60.0)	6	(75.0)	3	(42.9)	0.32
Ethnicity							0.25
Chinese	6	(40.0)	4	(50.0)	2	(28.6)	0.61
Malay	7	(46.7)	4	(50.0)	3	(42.9)	>0.99
Others	2	(0.200)	0	(0.0)	2	(28.6)	0.20
Age[a] (years)	2.5	(0.8, 11.0)	2.4	(0.7, 9.9)	7.75	(1.75, 11)	0.46
Weight[a] (kg)	14.5	(7.9, 45.3)	13.3	(8.5, 39.6)	23	(7.89, 60)	0.61
Body mass index (BMI)[a]	19.8	(13.7, 28.3)	19.8	(12.8, 26.1)	21.3	(14.3, 32.8)	0.61
Co-morbidities present	10	(66.7)	5	(62.5)	5	(71.4)	>0.99
Number[a]	1	(0, 2)	1	(0, 2)	1	(0, 2)	0.96
Type							
Cardiac	2	(13.3)	1	(12.5)	1	(14.3)	>0.99
Respiratory	3	(20.0)	2	(25.0)	1	(14.3)	>0.99
Neurologic	3	(20.0)	1	(12.5)	2	(28.6)	0.57
Obesity	3	(20.0)	1	(12.5)	1	(14.3)	>0.99
Obstructive sleep apnea	3	(20.0)	1	(12.5)	2	(28.6)	0.57
Others[b]	2	(13.3)	2	(13.3)	0	(0.0)	0.47
Fully vaccinated with two doses of COVID-19 vaccine	2	(13.3)	1	(12.5)	1	(14.3)	>0.99
Clinical presentation							
Respiratory symptoms prior admission (days)[a]	2	(1, 3)	2.5	(1.3, 3)	2	(1, 3)	0.69
Fever prior admission (days)[a]	2	(1, 3)	2	(0.3, 2.8)	2	(1, 3)	0.78
Pulmonary COVID-19	10	(66.7)	6	(75.0)	4	(57.1)	0.61
Other system involvement	8	(53.3)	4	(50.0)	4	(57.1)	>0.99
Gastrointestinal	4	(26.7)	4	(50.0)	0	(0.0)	0.08
Neurological	3	(20.0)	0	(0.0)	3	(42.9)	0.08
Muscular	1	(6.7)	0	(0.0)	1	(14.3)	0.47
Cardiovascular	4	(26.7)	1	(12.5)	3	(42.9)	0.28
Laboratory parameters, radiological investigations and complications							
SARS-COV-2 Cycle threshold (CT), lowest[a]	16.8	(14.6, 20.7)	18.5	(13.8, 23.2)	16.8	(16.0, 18.4)	0.87
Days to CT ≥ 25,[a,d]	6	(5, 9)	8 (n = 3)	(6, 8)	5 (n = 4)	(5, 13)	0.40
C-reactive protein (mg/L), highest[a]	17.6	(5.8, 38.3)	13.5	(3.8, 26.1)	28.3	(8.1, 61.2)	0.23
Procalcitonin (ug/L), highest[a]	0.64	(0.13, 8.7)	0.12	(0.09, 0.26)	4.31	(0.8, 24.2)	0.02
Abnormal liver function							
ALT >5x ULN	2	(13.3)	1	(12.5)	1	(14.3)	>0.99
AST >5x ULN	1	(6.7)	0	(0.0)	1	(14.3)	0.47
Abnormal renal function	2	(13.3)	1	(12.5)	1	(14.3)	>0.99

TABLE 1 (Continued)

	All (*N* = 15)		No remdesivir (*N* = 8)		Received remdesivir (*N* = 7)		*p* Value
Chest X-ray consolidation	6	(40.0)	3	(37.5)	3	(42.9)	>0.99
Co-infection present[c]	5	(33.3)	3	(37.5)	2	(28.6)	>0.99
Management							
WHO Ordinal Severity Scale (highest)[a]	5	(4, 6)	5	(4, 5)	6	(5, 7)	0.03
Highest level of care							
High dependency (HD)	9	(60.0)	7	(87.5)	2	(28.6)	0.04
Intensive care (ICU)	6	(40.0)	1	(12.5)	5	(71.4)	0.04
HD/ICU care (days)[a]	4	(1, 5)	1	(1, 4)	5	(4, 9)	0.02
Reason(s) for HD/ICU admission							
Respiratory support	13	(86.7)	8	(100.0)	5	(71.4)	0.20
Cardiovascular support	2	(13.3)	0	(0.0)	2	(28.6)	0.20
Neurological deterioration	2	(13.3)	0	(0.0)	2	(28.6)	0.20
Oxygen requirements							
Low-flow oxygen	4	(26.7)	3	(37.5)	1	(14.3)	0.57
NIMV/high-flow	7	(46.7)	5	(62.5)	2	(28.6)	0.32
Invasive	4	(26.7)	0	(0.0)	4	(57.1)	0.03
Oxygen required (days)[a]	3	(2, 5)	2	(2, 5)	4	(3, 5)	0.40
Therapeutics							
Remdesivir use (RDV)	7	(18.9)					
Duration (days)[a]					4	(4, 5)	
Day of hospitalization					1	(1, 2)	
Day of symptoms					3	(2, 6)	
Adverse effects					0	0	
Steroid use	12	(80.0)	5	(62.5)	7	(100.0)	0.20
Steroid use (days)[a]	5	(1, 5)	3	(0, 5)	5	(3, 10)	0.07
Day of hospitalization	1	(1, 7)	1	(1, 7)	1	(1, 8)	0.88
Day of symptoms	3	(3, 9)	3	(3, 9)	3	(2, 9)	0.76
Reason(s) for steroid							
COVID-19 related	4	(26.7)	1	(12.5)	3	(42.9)	0.28
Non-COVID	8	(53.3)	4	(50.0)	4	(42.9)	>0.99
Bronchitis	3	(20.0)	3	(37.5)	0	(0.0)	0.20
Croup	4	(26.7)	1	(12.5)	3	(42.9)	0.28
Others[a]	2	(13.3)	0	(0.0)	2	(28.6)	0.20
Antibiotic use	11	(73.3)	5	(62.5)	6	(85.7)	0.57
Antibiotic (days)[a]	5	(0, 9)	5	(0, 9)	7	(3, 13)	0.46
Fluid bolus(es) required	5	(33.3)	0	(0.0)	5	(71.4)	0.007
Inotropic support	2	(13.3)	0	(0.0)	2	(28.6)	0.20

(Continues)

TABLE 1 (Continued)

	All (*N* = 15)		No remdesivir (*N* = 8)		Received remdesivir (*N* = 7)		*p* Value
Clinical outcomes							
Deescalation from HD/ICU care at Day 5	12	(80.0)	7	(87.5)	5	(71.4)	0.57
Days to temperature <38°C[a]	3	(1, 3)	3	(2, 6)	1	(1, 3)	0.12
Length of stay (days)[a]	6	(4, 10)	6	(3, 10)	6	(6, 18)	0.46
Mortality	0	(0.0)	0	(0.0)	0	(0.0)	>0.99
30-day all-cause readmission	0	(0.0)	0	(0.0)	0	(0.0)	>0.99
30-day all-cause mortality	0	(0.0)	0	(0.0)	0	(0.0)	>0.99

Note: All data *n* (%).

[a]Median, interquartile range.

[b]One patient each with: prematurity and beta-thalassemia trait, severe oropharyngeal dysphagia and reflux disease.

[c]RDV: hypotension (cortisol insufficiency), MIS-C (multisystem inflammatory syndrome in children).

[d]CT ≥ 25: institution's criteria for de-isolation/discharge.

[e]Co-infections: (a) Bacterial—non-RDV: MSSA and *Citrobacter freundii* (urine culture), RDV: Likely *Chlamydia trachomatis* pneumonia (presumed), (b) Viral—non-RDV, all 2: Rhinovirus/enterovirus, RDV: respiratory syncytial virus—all from respiratory virus multiplex PCR.

duration of RDV treatment was 4 days (IQR: 4–5). The youngest was a neonate (4 days old, patient #2) who required noninvasive ventilation support and ICU admission with the longest duration of RDV (7 days).

3.2 | Outcomes

Cumulative frequency curves of proportion of patients discharged over time (days in HD/ICU care) in the RDV versus the no-RDV group are compared in Figure 1. The cumulative proportion of patients deescalated from HD/ICU care at Day 5 in the RDV group was lower versus the no-RDV group but it was not statistically significant ($n = 5$, 71.4% vs. n = 7, 87.5%, $p = 0.57$) (Table 1). The RDV group had significantly longer median HD/ICU care days versus the no-RDV group (5 vs. 1 day, $p = 0.01$). All patients were eventually deescalated from HD/ICU care by Day 10 (Figure 1). Days to fever <38°C were (1 vs. 2 days, $p = 0.35$) and length of hospital stay (6 vs. 4.5 days, $p = 0.07$) were comparable in the RDV versus no-RDV group (Table 1). None of our patients died from COVID-19. There was no 30-day readmission or 30-day mortality in both groups (Table 1).

3.3 | RDV safety

There were no renal, cardiac, or liver side effects directly attributable to RDV therapy (Table 2). Patient #4 with existing idiopathic pulmonary arterial hypertension had asymptomatic bradycardia overnight but no prolonged QTc or heart block on ECG after 1 day of RDV and completed 4 days uneventfully. Patient #5 had normal LFTs before RDV but had seizures and worsening dystonia. On RDV Day 4, his alanine transaminase (ALT) and aspartate transaminase (AST) levels were both ≥5 times the upper limit of normal (ULN). Concurrently, he had elevated creatinine kinase levels (32,637 units/L) and lactate dehydrogenase (934 units/L); hence, the LFTs derangement was assessed to be contributed by rhabdomyolysis from seizures and dystonia, though the potential contribution of RDV was unclear. RDV was discontinued as he was afebrile with minimal oxygen requirements. His dystonia was controlled with improvement of creatinine kinase and LFTs on discharge. Patient #7 had mild transaminitis (ALT and AST < 5 times ULN) on admission but remained stable during RDV therapy.

4 | DISCUSSION

We describe 15 children admitted for severe COVID-19 requiring oxygen and HD/ICU admission during the COVID-19 pandemic in Singapore. We could not detect any clear benefit of RDV in terms of reducing duration in HD/ICU and overall hospitalization. All patients recovered eventually without adverse events directly attributable to RDV. There was no mortality.

There was a spectrum of severe COVID-19 clinical presentation in our cohort, but the majority were respiratory-related. Risk factors for pediatric severe COVID-19 have been described to include older age and co-morbidities such as obesity, respiratory conditions, and neurological disorders.[3,18] In contrast, our patients were younger with a median age of 2.5 years. Similarly, half of them had co-morbidities. However, there was no COVID-19 mortality in our cohort, although the mortality rate in severe pediatric COVID-19 has been reported to be <10%.[3,19] Children at high risk of severe COVID-19 require close monitoring with supportive HD/ICU care to prevent mortality. Interestingly, gastrointestinal symptoms (mainly vomiting) were predominantly observed in our no-RDV group who were also generally better. Shekerdemain et al.[19] speculated that

TABLE 2 Clinical details of seven children who received remdesivir.

Patient number	#1	#2	#3	#4	#5	#6	#7
Month of admission	November 2021	November 2021	February 2022	February 2022	February 2022	February 2022	March 2022
Demographics							
Sex/Ethnicity	Female/Malay	Female/Malay	Female/Malay	Female/Chinese	Male/Others	Male/Others	Male/Chinese
Age (years)	11	4 days	11	16	1.75	7.75	2.5
Weight (kg)	92.5	2.6	60	41.6	7.89	23	12.3
Co-morbidities	Obesity	None (Full term 41 weeks neonate, symmetrical small for gestational age)	Asthma, obstructive sleep apnea, eczema	Advanced idiopathic pulmonary arterial hypertension (PAH)	Dystonic cerebral palsy secondary to acute neonatal encephalopathy, severe oropharyngeal dysphagia, gastroesophageal reflux, laryngomalacia	Bilateral thalamic arterial venous malformation	None
Fully vaccinated	No	No	No	Yes	No	No	No
Laboratory parameters							
SARS-COV-2 CT count, lowest	20.5	16.4	18.4	16.8	18.3	14.6	16
Days to CT ≥ 25	5	16	5	5	N.A. (discharged)	N.A. (discharged)	N.A. (discharged)
Procalcitonin (ug/L), highest	0.16	6.42	50.34	NIL	15.54	0.98	2.2
C-reactive protein (mg/L), highest	61.2	38.3	135.8	4.7	28.3	8.1	11.8
Before RDV	61.2	3.7	66.5	4.7	28.3	8.1	NIL
After RDV	3.4	3.8	16.7	NIL	2.5	3.4	NIL
Abnormal parameters	None	None	Raised serum creatinine	Asymptomatic bradycardia	Raised LFTs and creatinine kinase levels	None	Raised LFTs
Pertinent chest X-ray findings	Confluent consolidation in the right mid-lower zones	Worsening of bilateral air space changes	Right lower zone opacity	Heart is enlarged. Lungs are clear.	Bilateral infiltrates	Mild peribronchial thickening in the perihilar regions	Subsegmental consolidation in the right upper lobe
Clinical management							
Reason(s) for HD/ICU admission	HD	ICU	ICU	ICU	HD	ICU	ICU

(Continues)

TABLE 2 (Continued)

Patient number	#1	#2	#3	#4	#5	#6	#7
	Respiratory support	Respiratory support	Encephalomyelitis, acute laryngitis	Respiratory support, PAH exacerbation	Respiratory support, dystonia	Meningoencephalitis, septic shock	Respiratory support
Days in HD/ICU	5	9	4	4	10	4	5
Other complications/ co-infections	None	Possible *Chlamydia trachomatis* pneumonia	MIS-C requiring anticoagulation	None	Rhabdomyolysis	Respiratory syncytial virus (RSV)	None
Maximum respiratory support	High flow (5 L face mask)	Invasive (PSIMV)	Invasive (PSIMV)	High flow (15 L nonrebreather mask)	Low flow (3 L nasal prongs)	Invasive (PSIMV)	Invasive (PSIMV)
Oxygen (days)	5	5	2	3	4	3	4
Maximum WHO ordinal severity score	5	6	6	7	4	7	6
Therapeutics							
Remdesivir (days)	5	7	4	4	4	3	5
Reasons for RDV initiation for severe COVID-19	Severe COVID-19 pneumonia requiring high flow oxygen, obesity	Severe COVID-19 pneumonia requiring NIV support and ICU admission	Severe acute COVID-19 infection with laryngitis and meningoencephalitis	Severe COVID-19 infection, requiring high flow oxygen, PAH	COVID19 pneumonia with O2 dependence	COVID-19 and RSV co-infection, early pneumonia, require intubation	Severe croup due to acute COVID-19
Steroid use (days)	5	8	21	10	2	3	5
Non-COVID-19 steroid indication	NIL	NIL	Croup, MIS-C	NIL	Croup	Hypotension, extubation	Croup
Antibiotic (days)	3	16	5	0	7	13	7
Outcomes							
Days to temperature <38°C	3	3	1	1	3	1	1
Length of stay (days)	6	18	7	4	19	6	6

Note: None had adverse effects directly attributable to RDV, or COVID-19 mortality.

Abbreviations: CT, cycle threshold; HD, high dependency; ICU, intensive care unit; LFT, liver function test; MIS-C, multisystem inflammatory syndrome in children; NIMV, noninvasive mechanical ventilation.

gastrointestinal symptoms may be associated with milder clinical presentations not typically requiring ICU admission, in contrast to the pooled analysis by Bolia et al.,[20] where diarrhea but not abdominal pain and nausea/vomiting correlated with disease severity. More studies to assess gastrointestinal symptoms as a predictor of COVID-19 severity in children would be useful.

In our study, there was no difference in cumulative proportion of patients deescalated from HD/ICU care at Day 5 between RDV and no-RDV groups. However, this was likely confounded by selection bias in terms of severity as those who received RDV in our cohort required more respiratory and hemodynamic support. This was similarly observed in children admitted to US ICU in Schuster et al.[21] Shekerdemian et al.'s cohort with COVID-19 in United States and Canadian ICU early in the pandemic also found that those who received COVID-19 therapies were older, had a higher proportion with medical complexity, required respiratory and/or vasopressor support, longer ICU and hospitalization duration compared with those without.[19] This was similar in our cohort, where the RDV group was older than the non-RDV group, though not statistically significant. Even though we could not discern a clear benefit in terms of reducing HD/ICU duration in our limited cohort, we could not rule out the possibility of a longer duration of higher acuity care and hospitalization if they did not receive early initiation of RDV therapy.

To date, RDV efficacy has not been evaluated in pediatric COVID-19 randomized trials. There was no comparator group in other observational pediatric RDV studies, of which their case-mix included mild disease, received other COVID-19 therapeutics, or focused on largely on the safety and tolerability profile of RDV.[7–10] Similarly, there are no randomized trials in adult COVID-19 patients. A single-blinded, non-randomized trial by Hegazy et al.[22] attempted to compare the efficacy and safety of antibodies cocktail (casirivimab and imdevimab), RDV, and favipravir in moderate, severe or critical COVID-19 disease. Use of antibodies cocktail demonstrated significantly less mortality (2%) versus RDV and favipravir (34% and 41%), respectively, though the patients were younger, with less co-morbidities and less severe COVID-19 symptoms. Other systematic reviews of COVID-19 therapeutics had varied findings, such as Vegivinti et al.[23] and Zhang et al.[24] which alluded to RDV possibly reducing time to recovery or discharge, but acknowledged that results were inconsistent across trials to draw concrete conclusions. However, RDV was initiated within 1–2 days of admission in our cohort, compared with most others where it was after a day and ranged widely.[7–10] It was interesting that our no-RDV group had good outcomes despite the presence of co-morbidities and requirement for oxygen support. They had lower WHO severity scale scores and lower procalcitonin levels. Larger studies are needed to evaluate the predictive value of these factors in guiding necessity of RDV therapy in this cohort.

There was no significant difference in proportion of patients who had raised liver enzymes and serum creatinine between those who received RDV and not. Although RDV has been implicated in transient mild-to-moderate transaminitis, it was consistent with COVID-19 and/or our patients' underlying medical conditions and could not be clearly attributed as treatment-related adverse events, similar to other cohorts.[9,10] In addition, though there are reports of sinus bradycardia associated with RDV therapy,[25] we could not ascertain if the occurrence in our patient was RDV-related as she had a pre-existing cardiac condition and RDV was completed without further issues. RDV seemed reasonably safe in our cohort.

4.1 | Limitations

The interpretation of our results is limited by the small cohort size and the lack of a randomized control group. Due to the limited sample size and differences in disease severity between the RDV and no-RDV groups, we cannot exclude Type 2 error and/or possibility of bias. However, we focused on a selected cohort of patients hospitalized with severe COVID-19 requiring oxygen, ICU/HD care and positive for SARS-CoV-2 on PCR testing. In contrast to most other cohorts, our patients did not receive other therapies which enabled us to attribute findings specifically to RDV.

We were not able to account for the impact or differences due to emergence of various COVID-19 variants since the onset of the pandemic. Our patients did not receive genotyping but 5 children were admitted while the Delta (B.1.167) variant was dominant prior January 2022, and 10 when Omicron (B.1.1.529) variant dominated.[26] The risks of severe COVID-19 in children regardless of variant exists and RDV remains active against both strains.[27]

5 | CONCLUSION

Children with severe COVID-19 requiring HD/ICU care and oxygen support can have good outcomes without RDV therapy. They tended to have lower WHO severity scale scores and lower procalcitonin levels. We were unable to detect any clear benefit of RDV in reducing HD/ICU stay, but we cannot exclude the risk of bias since severe cases were more likely to be treated with RDV. RDV therapy was safe for children with severe COVID-19 in our study.

AUTHOR CONTRIBUTIONS

Valerie Xue Fen Seah: Formal analysis; methodology; supervision; writing—original draft; writing—review and editing. **Rina Yue Ling Ong**: Formal analysis; writing—review and editing. **Kai Qian Kam**: Conceptualization; methodology; supervision; writing—review and editing. **Koh Cheng Thoon**: Writing—review and editing. **Natalie Woon Hui Tan**: Writing—review and editing. **Jiahui Li**: Writing—review and editing. **Karen Donceras Nadua**: Writing—review and editing. **Chia Yin Chong**: Conceptualization; methodology; writing—review and editing. **Chee Fu Yung**: Conceptualization; formal analysis; methodology; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the SingHealth Centralized Institutional Review Board (CIRB Ref: 2020/2094). All methods were carried out in accordance with relevant guidelines and regulations or Declaration of Helsinki. Written informed consent was waived by the SingHealth Centralized Institutional Review Board in light of public health need and the COVID-19 pandemic.

TRANSPARENCY STATEMENT

The lead author Valerie Xue Fen Seah, Chee Fu Yung affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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