

ORIGINAL PAPER

Remdesivir use in hospitalized children with COVID-19: hepatic and systemic safety

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ABSTRACT

Introduction: Safety data regarding remdesivir in pediatric populations remain limited, particularly for those with complex comorbidities. This study evaluated the hepatic and systemic safety of remdesivir in hospitalized children with COVID-19 by comparing treated patients to a control group receiving no antiviral therapy.

Material and methods: This single-center, retrospective case-control study included 76 hospitalized children: 42 children treated with remdesivir and 34 controls. Clinical and laboratory parameters, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, creatinine, and C-reactive protein were assessed at baseline and at peak during hospitalization. Clinical severity was evaluated using the World Health Organization clinical progression ordinal scale. To isolate treatment-emergent hepatotoxicity, patients presenting with baseline transaminase elevations $> 2 \times$ the upper limit of normal (ULN) were excluded from hepatic sub-analyses.

Results: The treated group was significantly older (median 12.3 vs. 2.3 years; $p < 0.001$) and required longer hospitalization (median 10 vs. 5 days; $p < 0.001$). Baseline disease severity was comparable ($p = 0.173$), though all patients requiring mechanical ventilation were in the treated cohort. Peak ALT and AST values were significantly higher in the remdesivir group (ALT: 51.0 vs. 22.5 U/L, $p = 0.006$; AST: 47.0 vs. 38.0 U/L, $p = 0.033$). Treatment-emergent ALT elevation $> 2 \times$ ULN occurred in 19.0% of treated patients vs. 5.9% of controls ($p = 0.039$). However, all elevations were transient and not associated with clinically significant hepatic dysfunction or treatment discontinuation. No significant differences were observed in bilirubin or creatinine levels between groups. Mortality (7.1%) occurred only among critically ill patients with severe comorbidities and was not attributed to remdesivir toxicity.

Conclusions: Remdesivir is associated with transient, manageable elevations in liver enzymes but demonstrates a favorable safety profile in hospitalized children. These findings support its use in pediatric COVID-19 management, even among those with significant underlying comorbidities.

KEY WORDS:

COVID-19, remdesivir, hepatotoxicity, pediatrics.

INTRODUCTION

Although COVID-19 mortality in children remains low compared to adults, the disease has exerted a substantial burden on the pediatric population. During the first two years of the pandemic, COVID-19 accounted for

1.4% of all pediatric deaths in England, with the highest mortality rates observed in children under five years and those with significant underlying comorbidities, particularly neurological and immunocompromising conditions [1]. In the United States, COVID-19 emerged as the eighth leading cause of death among individuals

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aged 0–19 years between August 2021 and July 2022, and was the primary cause of death from infectious or respiratory diseases in this demographic [2]. Children with medical complexities, including chronic lung disease, neurological disorders, cardiovascular disease, and malignancies, face a significantly increased risk for severe COVID-19 requiring intensive care unit admission [3–6]. Remdesivir, a nucleoside analog RNA polymerase inhibitor, remains an established antiviral option for selected pediatric patients at increased risk of severe COVID-19. It is Food and Drug Administration (FDA)-approved for the treatment of COVID-19 in pediatric patients from birth to 18 years of age (weighing ≥ 1.5 kg) in both hospitalized and high-risk non-hospitalized settings [7, 8]. Remdesivir functions as an adenosine triphosphate analog that competes for incorporation into nascent viral RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase [8–10]. Once incorporated, the active triphosphate metabolite causes delayed chain termination at the +3 position, effectively halting viral replication [8, 10, 11].

Despite its increasing use in clinical practice, pediatric safety data for remdesivir remain limited. The Food and Drug Administration approval was largely extrapolated from adult clinical trials and supported by a single, small open-label phase 2/3 trial of 53 hospitalized children [8, 12, 13]. While early reports indicate high recovery rates and a favorable safety profile, transient transaminase elevation has emerged as the most frequently reported laboratory abnormality [13–15]. This study evaluates the safety profile of remdesivir in a cohort of 42 hospitalized pediatric patients compared to a control group of 34 untreated children, providing clinicians with practical data relevant to the clinical management of SARS-CoV-2 infections in this vulnerable population.

MATERIAL AND METHODS

This single-center, retrospective case-control study evaluated 76 pediatric patients hospitalized with laboratory-confirmed SARS-CoV-2 infection between October 2020 and February 2024. The cohort consisted of 42 patients who received at least one dose of remdesivir and a control group of 34 patients who received no antiviral therapy. Inclusion criteria were age ≤ 18 years and a positive SARS-CoV-2 status confirmed *via* reverse transcription-polymerase chain reaction or rapid antigen testing. Clinical data were extracted from the hospital's secure electronic health records. Collected variables included patient demographics, pre-existing risk factors, clinical symptoms at presentation, and respiratory support requirements.

Remdesivir administration followed national recommendations and FDA criteria for hospitalized pediatric patients (aged ≥ 28 days, weighing ≥ 3 kg). Qualification required a positive SARS-CoV-2 test combined

with either a severe clinical presentation at admission or chest computed tomography findings of ground-glass opacities. Driven by clinical severity and uncontrolled underlying comorbidities, intravenous treatment was prioritized within the first 5–7 days of symptom onset using weight-based dosing guidelines. Patients weighing ≥ 40 kg received a 200 mg loading dose on day 1 followed by 100 mg daily; those weighing 3–40 kg received 5 mg/kg on day 1 followed by 2.5 mg/kg daily. The intended 5-day course could be abbreviated or extended up to 10 days based on clinical response, discharge, or mortality.

Laboratory parameters were evaluated at baseline and at their peak during hospitalization. In addition to hepatic markers (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and inflammatory markers (C-reactive protein [CRP]), bilirubin and creatinine levels were assessed when available to evaluate hepatic and renal dysfunction. Because laboratory testing was not uniformly available for all patients, analyses were performed using available data.

Hepatotoxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Transaminase elevations were defined relative to the laboratory upper limit of normal (ULN; 40 U/l), with Grade 3 elevation defined as $> 5 \times$ ULN (> 200 U/l). To better assess treatment-emergent effects, a prespecified sub-analysis excluded patients with significant baseline transaminase elevations ($> 2 \times$ ULN).

Descriptive statistics were used to summarize the data. Categorical variables are presented as frequencies and percentages. Continuous variables were assessed for normality using the Shapiro-Wilk test and are presented as medians with interquartile ranges (IQR). Comparisons between groups were performed using the Mann-Whitney *U* test, χ^2 test, or Fisher's exact test, as appropriate (Table 1). A *p*-value < 0.05 was considered statistically significant. All analyses were performed using Jamovi (Version 2.3).

RESULTS

A total of 76 pediatric patients were included in the study: 42 who received remdesivir and 34 controls. In the treated group, 36 patients (85.7%) completed the full 5-day course, while 6 patients had abbreviated therapy (range 1–4 days) due to discharge or mortality.

Patients treated with remdesivir were significantly older than controls (median age 12.3 years [IQR 4.1–15.6] vs. 2.3 years [IQR 0.9–6.2]; $p < 0.001$) (Table 1). Male sex predominated in both groups (66.7% vs. 64.7%). Comorbidities were present in 42.9% of treated patients and 35.3% of controls ($p = 0.638$), most commonly neurological and oncological disorders (Table 2).

Most children presented with moderate-to-severe disease. The most frequent symptoms were fever (87.8%), cough (70.7%), dyspnea (31.7%), and asthenia (26.8%).

TABLE 1. Comparison of clinical characteristics and laboratory parameters between groups

Parameters	Overall (N = 76)	Treated patients (n = 42)	Controls (n = 34)	p-value*
Demographics				
Gender (female/male), n (%)	26/50 (34/66)	14/28 (33/67)	12/22 (35/65)	1.000
Age [years], median (IQR)	6.16 (1.7–13.8)	12.32 (4.1–15.6)	2.30 (0.9–6.2)	< 0.001
Clinical severity				
Oxygen therapy (any), n (%)	39 (51.3)	24 (57.1)	15 (44.1)	0.356
Mechanical ventilation, n (%)	6 (7.9%)	4 (9.5%)	2 (5.9)	0.686
Length of stay [days], median (IQR)	8.0 (5.5–11.0)	10.0 (8.0–13.8)	5.0 (3.0–8.0)	< 0.001
WHO ordinal scale at admission, n (%)	4.0 (3.0–4.0)	4.0 (3.0–4.0)	3.0 (3.0–4.0)	0.173
Inflammatory markers				
Admission CRP [mg/l], median (IQR)	17.09 (3.5–46.0)	23.77 (7.1–47.9)	13.21 (2.2–44.0)	0.447
Peak CRP [mg/l], median (IQR)	34.78 (6.1–63.9)	37.39 (11.6–53.1)	29.41 (3.4–118.1)	0.742
Liver function (U/l)				
Admission AST, median (IQR)	34.0 (28.0–44.0)	31.0 (26.5–43.5)	38.0 (29.0–44.0)	0.345
Peak AST, median (IQR)	42.0 (31.3–65.5)	47.0 (35.5–78.5)	38.0 (30.0–44.0)	0.033
Admission ALT, median (IQR)	21.0 (12.5–34.5)	19.0 (11.0–38.0)	22.0 (15.3–32.8)	0.377
Peak ALT, median (IQR)	30.0 (18.0–75.0)	51.0 (25.8–88.5)	22.5 (15.5–41.3)	0.006
Outcomes				
Mortality, n (%)	3 (3.9)	3 (7.1)	0 (0.0)	0.112
Recovery/discharge, n (%)	73 (96.1)	39 (92.9)	34 (100)	0.822

ALT – alanine aminotransferase, AST – aspartate aminotransferase, CRP – C-reactive protein, IQR – interquartile range

P-values were calculated using Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Bold values indicate statistical significance ($p < 0.05$).

Supplemental oxygen was required in 57.1% of the remdesivir group and 44.1% of controls ($p = 0.356$); mechanical ventilation was required in 9.5% of treated patients. Initial clinical severity was assessed using the 7-point World Health Organization (WHO) clinical progression ordinal scale. There was no statistically significant difference between groups at admission (median 4.0 in treated patients vs. 3.0 in controls; $p = 0.173$). However, the most severe cases (WHO scores 6–7) occurred exclusively within the remdesivir group, representing 9.5% of the treated cohort compared to 0% of the control group. At admission, median CRP levels did not differ significantly between the treated and control groups (23.77 vs. 13.21 mg/l, $p = 0.447$), indicating a comparable baseline inflammatory status. Median hospital stay was longer in the remdesivir group (10.0 days [IQR 8.0–13.8] vs. 5.0 days [IQR 3.0–8.0]; $p < 0.001$) (Table 1).

Elevated baseline ALT was observed in 16 patients (9 treated, 7 controls), including 4 with ALT $> 2 \times$ ULN (2 in each group); levels decreased during hospitalization in all four. To isolate treatment-emergent hepatotoxicity, patients with baseline ALT $> 2 \times$ ULN were excluded from the subsequent analysis. After excluding these patients, any ALT elevation during hospitalization occurred in 26 children (19 treated patients vs. 7 controls; $\chi^2 = 9.33$, $p = 0.002$), while ALT $> 2 \times$ ULN occurred in 8 treated patients and

2 controls ($\chi^2 = 4.27$, $p = 0.039$). The highest ALT recorded was 201 U/l ($> 5 \times$ ULN) in one treated child.

Baseline AST > 40 U/l was present in 26 patients (14 treated patients, 12 controls), including 8 with AST $> 2 \times$ ULN, who were excluded from subsequent analysis. Among the remaining cohort ($n = 58$; 30 treated patients, 28 controls), any AST elevation during hospitalization occurred in 28 children (18 treated children vs. 10 controls; $\chi^2 = 2.52$, $p = 0.113$), and AST $> 2 \times$ ULN occurred in 4 treated patients and no controls ($\chi^2 = 2.20$, $p = 0.138$). The highest AST recorded was 686 U/l in a treated patient.

Despite these biochemical abnormalities, no clinically significant hepatic dysfunction or treatment discontinuation occurred. Bilirubin was available in 20 children (13 treated patients, 7 controls) and showed no significant between-group differences; elevated values were noted in 1 treated patient and 2 controls. Creatinine was available in 47 patients (29 treated patients, 18 controls); elevated values occurred in 2 treated patients and 1 control, with no clinically significant renal dysfunction.

Remdesivir was well tolerated, with no clinically significant adverse events, such as bradycardia or infusion reactions. Mild gastrointestinal symptoms (abdominal pain, loss of appetite, or diarrhea) were reported in four children during the treatment period; however, as these are com-

TABLE 2. Risk factors for severe SARS-CoV-2 infection in children

Category	Overall (N = 76), n (%)	Treated patients (n = 42), n (%)	Controls (n = 34), n (%)	p-value*
Oncological and hematological disorders	10 (13.2)	4 (9.5)	6 (17.6)	0.328
Neuromuscular disorders and neurodisability	5 (6.6)	3 (7.1)	2 (5.9)	1.000
Genetic syndromes and congenital disorders	7 (9.2)	4 (9.5)	3 (8.8)	1.000
Chronic respiratory support [^]	5 (6.6)	5 (11.9)	0 (0.0)	0.061
Prematurity and neonatal conditions	2 (2.6)	0 (0.0)	2 (5.9)	0.197
Immunodeficiency and recurrent infections	3 (3.9)	1 (2.4)	2 (5.9)	0.584
Autoinflammatory syndromes (e.g., PFAPA)	1 (1.3)	1 (2.4)	0 (0.0)	1.000
Recent surgery	1 (1.3)	1 (2.4)	0 (0.0)	1.000
Other infection (e.g., RSV)	1 (1.3)	0 (0.0)	1 (2.9)	0.447
No comorbidities reported	31 (40.8)	16 (38.1)	15 (44.1)	0.644
Other/unclassified conditions	8 (10.5)	5 (11.9)	3 (8.8)	0.725

* p-values calculated using Fisher's exact test.

[^] Includes tracheostomy and home ventilation.

n/N (%) represents the number of patients with the condition out of the total in that group.

mon manifestations of pediatric SARS-CoV-2 infection, a definitive distinction between remdesivir toxicity and the natural course of COVID-19 could not be established.

The overall recovery rate was 96.1%. Mortality occurred in 3 patients (7.1%) in the treated group and no patients in the control group ($p = 0.112$). All three deaths occurred in critically ill patients with severe pre-existing comorbidities and were considered by the clinical team to be associated with the severity of the primary disease rather than remdesivir toxicity.

DISCUSSION

Remdesivir remains an important treatment option for COVID-19, particularly in children at increased risk of severe disease. Remdesivir is generally well tolerated, with reported adverse effects including elevated liver enzymes and gastrointestinal symptoms (Table 2).

Our study examined the safety of remdesivir use in 42 pediatric patients compared to a control group of 34 untreated children. Hepatic safety remains the primary concern regarding remdesivir use in children. While we observed a higher frequency of ALT and AST elevations in the treated group compared to controls ($p = 0.039$ for ALT $> 2 \times$ ULN), these elevations were transient and clinically manageable. This finding is consistent with the phase 2/3 trial by Ahmed *et al.* [13], which reported that while transaminase elevations occur, they rarely necessitate treatment discontinuation. A notable finding was the normalization trend observed in patients with marked transaminase elevations. For example, the patient with a peak AST of 686 U/l showed a decline toward baseline values by discharge without concomitant bilirubin elevation or signs of synthetic hepatic failure. This pattern suggests that such elevations may be transient in the context of acute illness. Additionally, after excluding patients with baseline

ALT or AST $> 2 \times$ ULN, treatment-emergent significant elevations remained uncommon, supporting a generally favorable hepatic safety profile. Crucially, the statistical significance of the ALT shift persisted even after this exclusion. This suggests that the observed difference is likely treatment-emergent rather than solely baseline-driven.

Regarding systemic tolerability, renal abnormalities were rare, with creatinine elevations observed in only two treated patients. Non-laboratory adverse events were infrequent; while some studies report higher rates of nausea or bradycardia, we observed only mild gastrointestinal symptoms in four children, mirroring the favorable side-effect profile described by Goldman *et al.* [16]. Crucially, because these signs closely overlap with the typical clinical presentation of pediatric COVID-19, they likely reflect viral pathogenesis rather than true drug-induced toxicity, meaning transient gastrointestinal distress rarely warrants antiviral discontinuation.

While baseline WHO ordinal scale scores were statistically comparable between groups ($p = 0.173$), the remdesivir cohort included all patients requiring high-flow oxygen or mechanical ventilation. This higher concentration of severe cases likely accounts for the significantly longer hospital stay observed in the treated group.

The mortality rate in our treated cohort (7.1%) was not statistically significant compared to controls ($p = 0.112$) and occurred exclusively in critically ill patients with severe oncological or neurological comorbidities. This aligns with findings by Ahmed *et al.* [13] and Kautsch *et al.* [17] in a Polish pediatric cohort, both demonstrating that mortality in fragile pediatric subsets is driven entirely by advanced primary disease severity rather than drug-induced toxicity.

Evaluating a distinct survival benefit in children remains inherently limited by low baseline event rates. Because pediatric COVID-19 mortality is exceedingly

rare compared to adults, individual cohort studies are typically underpowered to demonstrate a statistically significant reduction in death rates. This statistical reality is highlighted in larger multi-center data, such as the propensity-score-matched analysis by Shoji *et al.* [18], which observed that while remdesivir significantly accelerated clinical recovery, it did not demonstrate a statistically significant shift in 30-day mortality. Consequently, the clinical utility of remdesivir in vulnerable pediatric populations is more accurately measured by surrogate markers of stabilization, including the prevention of disease progression and avoiding escalation to mechanical ventilation.

Our study has two primary limitations. First, a statistically significant age discrepancy was observed between the cohorts; however, current literature does not suggest that age is an independent risk factor for remdesivir-induced hepatotoxicity. Second, due to this baseline imbalance and the limited sample size, the study was not powered to perform a formal evaluation of clinical efficacy. Consequently, the analysis remained focused on safety, where the available data were most robust.

CONCLUSIONS

This study provides evidence that remdesivir is a safe and well-tolerated therapeutic option for hospitalized pediatric patients with COVID-19, including those with complex underlying comorbidities. We demonstrated that while remdesivir is associated with more frequent transaminase elevations compared to untreated controls, these biochemical shifts are transient and do not result in clinically significant hepatic dysfunction or necessitate treatment discontinuation.

With a 92.9% treatment completion rate and no serious drug-related adverse events, our findings reinforce the favorable safety profile of remdesivir in the pediatric population. Although mortality occurred in a small subset of the treated cohort, these outcomes were driven by the severity of the primary disease and underlying comorbidities rather than the antiviral intervention. While acknowledging the age differences between groups and the retrospective study design, these findings support remdesivir as a generally safe component of clinical management in vulnerable children with COVID-19.

DISCLOSURES

1. Institutional review board statement: This study was approved by the Ethics Committee of the Bioethics Committee (approval decision no. APK.002.398.2020, dated: 26.11.2020).
2. Assistance with the article: The authors thank the healthcare personnel involved in the care of pediatric patients during the COVID-19 pandemic.
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4. Conflicts of interest: None.

5. Patient consent: Written informed consent was obtained from the patients' legal guardians for publication of this study..

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